Clinical Diagnosis and Management of Dystonia

Edited by
Thomas T Warner
Susan B Bressman

informa healthcare
Clinical Diagnosis and Management of Dystonia
Clinical Diagnosis and Management of Dystonia

Edited by

THOMAS T WARNER PhD FRCP
Department of Clinical Neurosciences
Institute of Neurology, University College London
and Royal Free Hospital
National Hospital for Neurology and Neurosurgery
London, UK

SUSAN B BRESSMAN MD
Department of Neurology
Beth Israel Medical Center and
Albert Einstein College of Medicine
New York, NY, USA
Contents

List of Contributors vii
Preface xi

1. Diagnosis of dystonia
   Howard L Geyer and Susan B Bressman 1

2. Epidemiology of dystonia
   Meike Kasten, Anabel R Chade, and Caroline M Tanner 15

3. Overview of the genetic forms of dystonia
   Thomas T Warner and Susan B Bressman 27

4. Pathophysiology of dystonia
   Su Kanchana and Mark Hallett 35

5. Functional imaging in primary dystonia
   Maren Carbon-Correll, Kotaro Asanuma and David Eidelberg 45

6. DYT1 dystonia
   Laurie J Ozelius and Susan B Bressman 53

7. Other primary generalized dystonias
   Antonio E Elia, Anna Rita Bentivoglio, Enza Maria Valente, and Alberto Albanese 65

8. Cervical dystonia
   Cynthia L Comella 73

9. Cranial dystonia
   Dirk Dressler and Fereshte Adib Saberi 81

10. Writer’s cramp, limb dystonia, and other task-specific dystonias
    Jörg Müller and Werner Poewe 97

11. Laryngeal dystonia
    Christy L Ludlow 111

12. Dystonia-plus syndromes
    Thomas Gasser, Friedrich Asmus, and Christoph Kamm 121
CONTENTS

13. Secondary and heredodegenerative dystonia
   Yvette M Bordelon and Steven J Frucht 131

14. Drug-induced and tardive dystonia
   Mark J Edwards and Kailash P Bhatia 149

15. Paroxysmal dyskinesias
   Pablo Mir, Susanne A Schneider and Kailash P Bhatia 159

16. Psychogenic dystonia
   Martin Cloutier, Tamara Pringsheim, and Anthony E Lang 171

17. Drug therapy of torsion dystonia
   Paul Greene 183

18. Botulinum toxin
   Ronald Tintner and Joseph Jankovic 189

19. Surgery for dystonia
   Joachim K Krauss and Thomas J Loher 209

20. Role of the physiotherapist
   Jean-Pierre Bleton 223

21. Role of the specialist dystonia nurse
   Marianne King 233

22. Dystonia and quality of life
   Stefan J Cano and Thomas T Warner 241

23. Dystonia rating scales
   Stefan J Cano and Thomas T Warner 249

Index 261
Contributors

Fereshte Adib Saberi MD
Department of Neurology
Klinikum Nord
Hamburg
Germany

Alberto Albanese MD
Fondazione IRCCS Istituto Neurologico Carlo Besta
Università Cattolica del Sacro Cuore
Milan
Italy

Kotura Asanuma MD
Center for Neurosciences
Feinstein Institute for Medical Research
North Shore – Long Island Jewish Health System
Manhassett, NY
USA

Friedrich Asmus MD
Hertie-Institute for Clinical Brain Research
Department of Neurodegenerative Diseases
University of Tübingen
Tübingen
Germany

Anna Rita Bentivoglio MD
Istituto di Neurologia
Università Cattolica del Sacro Cuore
Rome
Italy

Kailash P Bhatia MD DM MRCP
Sobell Department of Motor Neuroscience and Movement Disorders
Institute of Neurology
University College London
London
UK

Jean-Pierre Bleton PT
Physiotherapy Unit
Neurology Department
Raymond Garin Center
Sainte-Anne Hospital
Paris
France

Yvette M Bordeon MD PhD
Department of Neurology
David Geffen School of Medicine at UCLA
Reed Neurological Research Institute
Los Angeles, CA
USA

Susan B Bressman MD
Department of Neurology
Beth Israel Medical Center and
Albert Einstein College of Medicine
New York, NY
USA

Stefan J Cano PhD
Neurological Outcome Measures Unit
Institute of Neurology
University College London
London
UK

Maren Carbon MD
Center for Neurosciences
Feinstein Institute for Medical Research
North Shore – Long Island Jewish Health System
Manhassett, NY
USA
LIST OF CONTRIBUTORS

Anabel R Chade MD
Centro Neurologico Hospital Frances
Buenos Aires
Argentina

Martin Cloutier MD FRCPC
Hopital Charles-Lemoyne
Service de Neurologie
Greenfield Park, QC
Canada

Cynthia L Comella MD
Department of Neurological Sciences
Rush University Medical Center
Chicago, IL
USA

Dirk Dressler MD
Department of Neurology
Rostock University
Rostock
Germany

Mark J Edwards
Sobell Department of Motor Neuroscience and Movement Disorders
Institute of Neurology
University College London
London
UK

David Eidelberg MD
Center for Neurosciences
Feinstein Institute for Medical Research
North Shore – Long Island Jewish Health System
Department of Neurology
North Shore University Hospital
Manhasset, NY
New York University School of Medicine
New York, NY
USA

Antonio E Elia
Fondazione IRCCS Istituto Neurologico Carlo Besta
Università Cattolica del Sacro Cuore
Milan
Italy

Steven J Frucht MD
Columbia University Medical Center
Department of Neurology
The Neurological Institute
New York, NY
USA

Thomas Gasser MD
Hertie-Institute for Clinical Brain Research
Department of Neurodegenerative Diseases
University of Tübingen
Tübingen
Germany

Howard L Geyer MD PhD
Department of Neurology
Albert Einstein College of Medicine
Montefiore Medical Center
Bronx, New York, NY
USA

Paul Greene MD
Associate Professor of Clinical Neurology
Dystonia Clinical Research Center
Neurological Institute
Columbia-Presbyterian Medical Center
New York, NY
USA

Mark Hallett MD
Human Motor Control Section
National Institute of Neurological Disorders and Stroke
Bethesda, MD
USA

Joseph Jankovic MD
Parkinson's Disease Center and Movement Disorders Clinic
Baylor College of Medicine Department of Neurology
Houston, TX
USA

Christoph Kamm MD
Hertie-Institute for Clinical Brain Research
Department of Neurodegenerative Diseases
University of Tübingen
Tübingen
Germany

Su Kanchana MD PhD
Division of Neurology, Department of Neuroscience
Lehigh Valley Hospital and Health Network
Allentown, PA
USA

Meike Kasten MD
Klinik für Psychiatrie and Psychotherapie
Lübeck
Germany
Marianne King  
Dystonia Nurse Specialist  
PNRU  
Sharoe Green Hospital  
Fulwood, Preston  
UK

Joachim K Krauss MD  
Professor and Chairman  
Department of Neurosurgery  
Medical University Hannover, MHH  
Hannover  
Germany

Anthony E Lang MD FRCPC  
University Health Network  
Toronto Western Hospital  
Department of Medicine  
Division of Neurology  
University of Toronto  
Toronto, Ontario  
Canada

Thomas J Loher MD  
Department of Neurology  
University of Berne  
Salem Spital  
Berne  
Switzerland

Christy L Ludlow PhD  
Laryngeal and Speech Section  
National Institute of Neurological Disorders and Stroke  
Bethesda, MD  
USA

Jörg Müller MD  
Department of Neurology  
Medical University Innsbruck  
Innsbruck  
Austria

Laurie J Ozelius PhD  
Albert Einstein College of Medicine  
Department of Genetics and Genomic Sciences  
Mount Sinai School of Medicine  
New York, NY  
USA

Werner Poewe MD  
Department of Neurology  
Medical University Innsbruck  
Innsbruck  
Austria

Tamara Pringsheim MD  
University Health Network  
Toronto Western Hospital  
Department of Medicine  
Division of Neurology  
University of Toronto  
Toronto, Ontario  
Canada

Caroline M Tanner MD PhD  
Director, Clinical Research  
The Parkinson’s Institute  
Sunnyvale, CA  
USA

Ronald Tintner  
Parkinson’s Disease Center and Movement Disorders Clinic  
Department of Neurology  
Baylor College of Medicine  
Houston, TX  
USA

Enza Maria Valente  
Institute C.S.S. Mendel  
Rome  
Italy

Thomas T Warner PhD FRCP  
Department of Neurosciences  
Institute of Neurology  
Royal Free Hospital  
National Hospital for Neurology and Neurosurgery  
University College London  
London  
UK
Preface

It is almost 100 years since the first clinical descriptions were made of cases of dystonia. In the ensuing century, the study of this protean movement disorder has undergone a turbulent evolution, with dramatic shifts in the views regarding its causation and phenomenology. Having been considered for a considerable period of time as a psychological or psychiatric disorder, the dystonias are now recognized to be, in the majority of cases, an organic neurological disorder.

The time, therefore, is fitting to take stock of our knowledge of the various conditions that we now recognize as dystonias. This is the primary aim of this volume. We have drawn together a series of monographs from world leaders in the field of dystonia. We hope that this book will lead the reader through the phenomenology and etiology of dystonia, to then describe specific forms. The final chapters summarise various medical and surgical treatment strategies for dystonia, including paramedical input, and the book concludes on how we can measure dystonia and its effects on quality of life.

By nature, a collection of chapters by numerous authors will contain some repetition, but we hope this has been kept to a minimum and, where it exists, is important for the issues being discussed.

We are very grateful for all the authors who contributed during the prolonged gestation of this book, and for the support they have given. The same applies to the families of the editors and publishers! Finally, both editors have benefited from working with two supreme clinical neurologists, whose contribution to the study of dystonia has been immense: the late David Marsden in London and Stanley Fahn in New York. Their energy and clinical skills in dissecting out the clinical and anatomical basis of dystonia has been inspirational.

We hope that this book will further encourage young neurologists and neuroscientists to focus their energies in the area of dystonia to take forward our understanding of this movement disorder in the next 100 years.

Tom Warner
Susan Bressman
INTRODUCTION

Dystonia is a movement disorder characterized by patterned, directional, and sustained muscle contractions that produce abnormal, often twisting, postures or repetitive movements. Dystonia can result from a wide variety of causes, and clinicians must endeavor to elucidate its etiology in every patient in order to tailor optimal counseling and therapy for each individual. Although our understanding of the basic pathophysiologic mechanisms that give rise to this condition remains incomplete, thanks to advances in fields as disparate as neuroimaging and molecular genetics, modern diagnostic testing permits a specific diagnosis to be applied in many patients with dystonia. This chapter will present one diagnostic approach to patients with dystonia.

IDENTIFYING DYSTONIA

An important first step in diagnosing dystonia is recognizing abnormal movements as dystonic. Dystonic contractions tend to exhibit consistent directionality, and are patterned, repeatedly involving the same muscle groups; this latter feature differentiates dystonia from disorders such as chorea in which it is often impossible to predict which muscles will move next. The movements typically cause twisting of body parts, as connoted by the term torsion dystonia; in body parts that do not permit twisting, such as the jaw, there is consistent directionality (e.g. jaw opening or closing). Movements are usually more sustained (i.e. of longer duration) than other hyperkinesias, such as myoclonus. Although dystonia may result in jerking movements that mimic tremor, dystonic ‘tremor’ exhibits a directional preponderance (i.e. relatively forceful jerks in one direction alternate with slower movements in the opposite direction) which distinguishes it from the sinusoidal oscillations of true tremor. Unlike tics, dystonia is not preceded by an urge to perform the movement, nor is it associated with relief once the movement is executed. During dystonic movements, agonist and antagonist muscles contract simultaneously.1

Typically, dystonia is aggravated by voluntary movement, and in action dystonia, the dystonic movements are present only with voluntary movement. When dystonia is elicited exclusively by particular actions, it is called task-specific dystonia; examples include writer’s cramp, which affects the arm and hand muscles involved in writing, and the embouchure dystonia of the orobucal muscles observed in woodwind and brass musicians. Activation of dystonic movements by actions in remote parts of the body is called overflow; examples include leg dystonia while writing and axial dystonia induced by talking. More rarely, voluntary activity actually suppresses the dystonia; such paradoxical dystonia is more common in dystonia involving facial and oromandibular muscles. For example, talking or chewing may suppress eye closure in blepharospasm or jaw opening in oromandibular dystonia. Many patients discover a tactile or proprioceptive sensory trick (geste antagoniste) that minimizes the dystonia; for instance, a patient with head tilt due to cervical dystonia may lightly touch the chin to keep the head straight. Like many movement disorders, dystonia is worsened by fatigue and emotional stress, and the movements usually abate with relaxation or sleep.

A number of conditions that can produce abnormal postures resembling dystonia should be considered in the differential diagnosis. Causes of such pseudodystonia include disorders of the central and peripheral nervous systems as well as non-neurologic conditions. Tonic seizures can produce sustained twisting movements, and should be considered when symptoms are paroxysmal. Head tilt can result from vestibulopathy, trochlear nerve palsy, or a mass lesion in the posterior fossa or retropharyngeal space. Head tilt may also develop in patients (typically young boys) with hiatal

1 Diagnosis of dystonia

Howard L Geyer and Susan B Bressman
hernia and gastroesophageal reflux (Sandifer syndrome). Apraxia of eyelid opening or ptosis of any etiology can be mistaken for blepharospasm. Stiff-person syndrome causes sustained contraction of axial and proximal limb muscles, and may be etiologically related to Satayoshi syndrome, a childhood disorder with painful muscle contractions, malabsorption, and alopecia. Neuromuscular causes of sustained muscle contraction include neuromyotonia (Isaac syndrome), myotonic disorders, and rarely inflammatory myopathies. Carpopedal spasms can result from tetany due to hypocalcemia, hypomagnesemia, or alkalosis. Orthopedic and rheumatologic processes affecting bones, ligaments, or joints can also result in abnormal postures.

**CLASSIFICATION OF DYSTONIA**

Classifying a patient’s dystonia along each of several dimensions aids greatly in prognosis and guides the diagnostic work-up and selection of therapy (Table 1.1). These dimensions include anatomic distribution of involved body areas, age at onset, and etiology of the dystonia.

**Anatomic distribution**

In focal dystonia, the abnormal movements involve a single body region, whereas segmental dystonia affects two or more contiguous body parts. When dystonia is multifocal, two or more non-contiguous body areas are involved. Hemidystonia affects one side of the body. Generalized dystonia involves the legs (or one leg and the trunk) plus at least one other area of the body.

Cervical dystonia is the most common type of focal dystonia. Various abnormal head positions can occur, including torticollis (horizontal rotation), laterocollis (lateral tilting), anterocollis (flexion), and retrocollis (extension), depending on the particular combination of neck muscles involved. For example, torticollis may result from dystonic contraction of the ipsilateral splenius capitis and contralateral sternocleidomastoid muscles. Although pain is not a common finding in most forms of dystonia, approximately 75% of patients with cervical dystonia experience neck pain. Like dystonia elsewhere, contractions vary in their duration, so that neck movements may be relatively tonic or more clonic. Clonic repetitive jerking of the head may resemble tremor, but unlike true tremor usually exhibits a directional preponderance. One maneuver that may help identify a directional preponderance is to observe the resultant position when the patient is asked to ‘relax and let the head (or other involved body region) go in the direction it wants’. Another method is to ask the patient to slowly move the head in various directions and then observe for a ‘null point’ or a direction in which the jerking is quieted; alternatively, one may also seek to identify a direction in which the jerking is more forceful.

Less prevalent than cervical dystonia are focal dystonias involving cranial muscles. Spasmodic dysphonia is dystonia of the vocal cords; abnormal adduction, which causes a strained, strangled voice, is more common than abduction, in which the voice sounds whispering and breathy. Patients with blepharospasm have abnormal contraction of the orbicularis oculi; mild cases are characterized by increased rate and flurries of blinking, whereas in more severe cases forceful eye closure may interfere with vision. In oromandibular dystonia, there is abnormal activity in lower facial, tongue, jaw, and pharyngeal muscles that can interfere with speaking or swallowing. Brachial dystonia is a form of focal dystonia involving the arm and hand.
dystonia that may be primarily, or exclusively, present with writing (writer’s cramp); it is probably more common than usually recognized.

Segmental dystonia can involve the cranial muscles, as in the combination of blepharospasm and oromandibular dystonia, sometimes called Meige syndrome. In craniocervical dystonia, another type of segmental dystonia, the cranial musculature is involved together with neck muscles. Writer’s cramp spreads from the dominant to the contralateral arm in 15% of patients, at which point it is considered segmental (bibrachial) dystonia. Hemidystonia is not typical of primary dystonia; it almost invariably implies that the dystonia is secondary to another cause, most commonly stroke, trauma, or perinatal injury. Dystonia may be generalized at onset or may begin as focal or segmental dystonia and subsequently spread to become generalized.

The anatomic distribution of dystonia carries some prognostic value: complete remissions may occur in patients with cervical dystonia, but remissions occur very rarely in generalized dystonia and are usually partial.

Age at onset

The age at onset of primary dystonia is bimodally distributed, with modes at 9 years (early onset) and 45 years (late onset) and a nadir at 27 years. Age at onset is closely related to anatomic distribution. Early-onset dystonia usually starts in a leg or arm, and less commonly starts in the neck, vocal cords, or other cranial muscles. Late-onset primary dystonia commonly affects the neck or cranial muscles and is less likely to begin in a limb; onset in the leg is especially unlikely. Additionally, age at onset is also an important consideration in prognosis: most early-onset patients beginning with leg or arm dystonia progress to involve more than one limb and about 50% eventually generalize, whereas late-onset primary dystonia tends to remain focal or segmental.

Generalized dystonia beginning in adulthood is far more likely to be secondary (or psychogenic) than to be primary dystonia.

Etiology

Although it is not possible to identify the cause of dystonia in every patient, every effort should be made to do so, in order to individualize more specific therapy and counseling. One etiologic classification system identifies two broad categories: primary, or idiopathic, dystonia; and secondary, or symptomatic, dystonia (see Table 1.1).

Primary dystonia

In primary dystonia, dystonia is the only neurologic abnormality present, except for the occasional occurrence of tremor (resembling essential tremor) or, especially in DYT1 dystonia (see below), occasional myoclonic jerks involving dystonic muscles. Findings such as parkinsonism, ataxia, ocular motor abnormalities, weakness, spasticity, seizures, or dementia suggest that dystonia is secondary. In primary dystonia there are no structural brain abnormalities and no inborn errors of metabolism identifiable with conventional investigations. The majority of primary dystonias are focal or segmental in distribution, with onset in adulthood. Approximately 10% of patients with primary dystonia have generalized dystonia, usually starting in childhood or adolescence.

For many types of primary dystonia a genetic etiology is known or suspected, although a family history of dystonia cannot always be elicited. Four primary dystonia loci have been mapped, and for one locus (DYT1) the gene product has been identified. Table 1.2 lists loci for genetic forms of primary and some secondary dystonias. About 90% of generalized primary dystonia in Ashkenazi Jews and up to 50% of generalized primary dystonia in other populations is due to deletion of a GAG triplet from the DYT1 gene located at chromosome 9q34. This mutation results in loss of a glutamic acid residue from the translated protein torsinA, a member of the AAA+ family of proteins (chaperone-like ATPases associated with the assembly, operation, and disassembly of protein complexes). DYT1 dystonia is inherited in autosomal dominant fashion with reduced penetrance of 30%. Because all affected patients possess the same mutation, screening for this form of dystonia is relatively easy and is now commercially available.

DYT1 dystonia has a mean age at onset of 12.5 years but the range is broad (3–64 years); in 94% of cases, symptoms begin in a limb. In about two-thirds of patients there is progression to generalized or multifocal dystonia, while in the remainder dystonia remains focal or segmental, usually as writer’s cramp or bibrachial dystonia. Progression usually occurs within 5 years of onset, but can occur later.

The other familial primary dystonias whose genes have been mapped are less common. These include DYT6 (dystonia with variable expression in Mennonite/Amish families), DYT7 (focal dystonia in a northwestern German family), and DYT13 (craniocervicobrachial dystonia in an Italian family), all of which are inherited in autosomal dominant fashion with reduced penetrance. Genetic testing for these dystonias is not currently commercially available.
<table>
<thead>
<tr>
<th>Disease</th>
<th>Dystonia type</th>
<th>Pattern of inheritance</th>
<th>Chromosome region</th>
<th>Gene locus</th>
<th>Protein</th>
<th>Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oppenheim's torsion dystonia</td>
<td>PTD</td>
<td>Autosomal dominant</td>
<td>9q34</td>
<td>DYT1</td>
<td>TorsinA</td>
<td>17,18</td>
</tr>
<tr>
<td>Early-onset (unconfirmed)</td>
<td>PTD</td>
<td>Autosomal recessive</td>
<td>Not mapped</td>
<td>DYT2</td>
<td>Not identified</td>
<td>19</td>
</tr>
<tr>
<td>Lubag (X-linked dystonia-parkinsonism)</td>
<td>Heredo-</td>
<td>X-linked recessive</td>
<td>Xq13.1</td>
<td>DYT3</td>
<td>Multiple transcript system</td>
<td>20</td>
</tr>
<tr>
<td>dysenerative dystonia</td>
<td>degenerenti</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whispering dystonia (one family only)</td>
<td>PTD</td>
<td>Autosomal dominant</td>
<td>Not mapped</td>
<td>DYT4</td>
<td>Not identified</td>
<td>21</td>
</tr>
<tr>
<td>Dopa-responsive dystonia</td>
<td>Dystonia-plus</td>
<td>Autosomal dominant</td>
<td>14q22.1</td>
<td>DYT5</td>
<td>GTP cyclohydrodase I</td>
<td>22,23</td>
</tr>
<tr>
<td>Craniocecal dystonia (Mennonite/Amish)</td>
<td>PTD</td>
<td>Autosomal dominant</td>
<td>8p21-q22</td>
<td>DYT6</td>
<td>Not identified</td>
<td>24</td>
</tr>
<tr>
<td>Familial torticollis</td>
<td>PTD</td>
<td>Autosomal dominant</td>
<td>18p</td>
<td>DYT7</td>
<td>Myofilibrillogenesis regulator 1</td>
<td>25</td>
</tr>
<tr>
<td>Paroxysmal dystonic choreoathetosis (non-</td>
<td>Paroxysmal</td>
<td>Autosomal dominant</td>
<td>2q33-q35</td>
<td>DYT8</td>
<td>Not identified</td>
<td>26</td>
</tr>
<tr>
<td>kinesigenic) (Mount–Rebak)</td>
<td>dystonia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paroxysmal dyskinesias with spasticity</td>
<td>Paroxysmal</td>
<td>Autosomal dominant</td>
<td>1p21</td>
<td>DYT9</td>
<td>Not identified</td>
<td>27</td>
</tr>
<tr>
<td>Paroxysmal kinesigenic dyskinesia</td>
<td>Paroxysmal</td>
<td>Autosomal dominant</td>
<td>16p11.2-q12.1</td>
<td>DYT10</td>
<td>Not identified</td>
<td>28</td>
</tr>
<tr>
<td>Myoclonus-dystonia</td>
<td>Dystonia-plus</td>
<td>Autosomal dominant</td>
<td>7q21-q23</td>
<td>DYT11</td>
<td>α-sarcoglycan</td>
<td>29</td>
</tr>
<tr>
<td>Rapid-onset dystonia-parkinsonism</td>
<td>Dystonia-plus</td>
<td>Autosomal dominant</td>
<td>19q13</td>
<td>DYT12</td>
<td>Na⁺/K⁺-ATPase α3</td>
<td>30</td>
</tr>
<tr>
<td>Craniocecalobrachial</td>
<td>PTD</td>
<td>Autosomal dominant</td>
<td>1p36</td>
<td>DYT13</td>
<td>Not identified</td>
<td>31,32</td>
</tr>
<tr>
<td>Dopa-responsive dystonia</td>
<td>Dystonia-plus</td>
<td>Autosomal dominant</td>
<td>14q13</td>
<td>DYT14</td>
<td>Not identified</td>
<td>33</td>
</tr>
<tr>
<td>Myoclonus-dystonia</td>
<td>Dystonia-plus</td>
<td>Autosomal dominant</td>
<td>18p11</td>
<td>DYT15</td>
<td>Not identified</td>
<td>34</td>
</tr>
</tbody>
</table>

PTD = primary torsion dystonia.
**Secondary dystonia**

When dystonia is secondary to a hereditary neurologic disorder or an exogenous insult, neurologic abnormalities in addition to dystonia are likely to be present. An important exception is dystonia resulting from dopamine receptor-blocking agents (acute dystonic reaction and tardive dystonia), which usually consists of dystonia only. Some clues suggesting that a patient’s dystonia is secondary rather than primary are listed in Table 1.3. Secondary dystonias can be further classified (see Table 1.1).

**Dystonia-plus syndromes**

One subcategory of secondary dystonia comprises the dystonia-plus syndromes. These are inherited conditions in which dystonia is accompanied by other neurological abnormalities, but (like in the primary dystonias) there is no evidence of brain degeneration. Dystonia-plus syndromes include dopa-responsive dystonia, myoclonus-dystonia, and rapid-onset dystonia-parkinsonism.

A highly treatable condition, dopa-responsive dystonia (DRD) must always be considered in the differential diagnosis of dystonia. It typically presents in early or mid-childhood with gait dysfunction, and girls are affected more commonly than boys. Classically, symptoms worsen over the course of the day and improve with sleep.22 Parkinsonism (including rigidity, bradykinesia, stooped posture, and loss of postural reflexes) may develop, making juvenile parkinsonism an important consideration in the differential diagnosis.38 Because increased tone and hyperreflexia are often present and ankle clonus may be found (although Babinski signs are uncommon), DRD may be misdiagnosed as cerebral palsy.39 DRD can present in adulthood as focal dystonia40–42 or parkinsonism.43,44

Classic cases of DRD are caused by heterozygous mutations in the GTP-cyclohydrolase I (GCH1) gene located at chromosome 14q22.1-q22.2 (classified as DYT5).23 Inheritance of DRD is autosomal dominant, with reduced penetrance that apparently is sex-influenced (higher in girls).45 The mutations severely impair the activity of GCH1, the enzyme which catalyzes the rate-limiting step in the synthesis of tetrahydrobiopterin (BH4); BH4 is a necessary cofactor for tyrosine hydroxylase, the enzyme which catalyzes the conversion of tyrosine to levodopa in the rate-limiting step of dopamine biosynthesis.23 Over 100 mutations have been identified and de novo mutations appear to be common, making genetic testing complex and expensive.42,45

Whereas most DRD is due to heterozygous GCH1 mutations, rarer DRD variants result from homozygous or compound heterozygous mutations in the GCH1 gene46 or in genes encoding tyrosine hydroxylase47–49 or other enzymes involved in pterin metabolism.50 Patients with these defects are often more severely affected, and their dystonia may be less salient than features due to deficiency of nonepinephrine and serotonin, including hypotonia, hypokinesia, oculogyric crises, ptosis, miosis, seizures, and drooling.

Myoclonus-dystonia is a rare dystonia-plus syndrome with prominent myoclonic jerks, usually affecting the arms, neck, and trunk more than the legs. The dystonia, which is usually mild, most commonly manifests as writer’s cramp or torticollis. Symptoms typically begin in

---

**Table 1.3 Clues suggesting that dystonia is secondary**

- History of exogenous insult or exposure (e.g. drug exposure, head trauma, encephalitis, perinatal hypoxia)
- Dystonia at rest (rather than with action) at onset
- Atypical site for age at onset (e.g. leg onset in an adult, cranial onset in a child)
- Early onset of speech abnormality
- Hemidystonia
- Presence of abnormalities other than dystonia on neurologic examination or general medical examination:
  - e.g. parkinsonism, ataxia, dementia, seizures, myoclonus, visual loss, optic atrophy/other ophthalmoscopic abnormalities, ocular motor abnormalities, deafness, dysarthria, dysphagia, weakness, hypotonia, muscle atrophy, neuropathy, hyperreflexia, dysautonomia, Kayser–Fleischer ring, hepatosplenomegaly, characteristic rash or odor, evidence of malabsorption
- Non-physiologic findings suggesting a psychogenic basis (e.g. false weakness, false sensory loss, inconsistent or incongruous movements)
- Abnormality on brain imaging
- Abnormality in laboratory evaluation
childhood or early adolescence. Many patients, especially those with a positive family history, have a mutation in the ε-sarcoglycan gene (SGCE) on chromosome 7q21 (classified as DYT11). Myoclonus-dystonia due to SGCE mutation is inherited in autosomal dominant fashion but there is imprinting (i.e. penetrance is reduced and is dependent on the parent transmitting the gene mutation); most patients inherit the mutation from the father. The symptoms characteristically respond to alcohol.

In rapid-onset dystonia-parkinsonism, another rare dystonia-plus syndrome, dystonia and parkinsonism often begin suddenly during adolescence or early adulthood and progress over hours to weeks, after which the symptoms usually stabilize. Inheritance is autosomal dominant. The responsible gene, which maps to chromosome 19q13 (classified as DYT12), was recently identified; it codes for Na+/K+ ATPase α3, a catalytic subunit of the sodium-potassium pump.

Degenerative neurologic disorders  Inherited causes of dystonia include numerous conditions in which there is histopathologic evidence of brain degeneration; many of these are autosomal recessive disorders resulting from inborn errors of metabolism, but dystonia is also associated with various autosomal dominant, X-linked, and mitochondrially inherited disorders (Table 1.4). Neuroimaging is frequently abnormal in these heredodegenerative conditions. Dystonia is thought to result from disrupted basal ganglia function and/or impaired dopamine synthesis. In many of these disorders, other abnormalities may be more prominent than the dystonia; these may include mental retardation, seizures, optic atrophy, gaze paresis ataxia, and neuropathy. Since some of these conditions can respond to specific interventions (e.g. anti-copper therapy for Wilson’s disease) or dietary restriction or supplementation, a specific diagnosis should always be sought.

Wilson’s disease is a degenerative disorder with autosomal recessive inheritance that can produce secondary dystonia; as a treatable condition, it should be considered in the differential diagnosis. It results from mutations in the ATP7B gene on chromosome 13q14.3-q21.1 which produce a defect in copper metabolism, leading to the insidious development of neurologic, psychiatric, and/or hepatic dysfunction. Because over 200 different mutations have been reported, genetic testing is of limited feasibility. When onset is in childhood, Wilson’s disease usually presents with hepatic dysfunction, but in adult-onset disease, neurologic presentation is most typical. Dystonia can be generalized, segmental, or multifocal, but cranial involvement is characteristic; Wilson described the typical ‘sardonic’ smile in his original 1912 monograph. Other common neurologic abnormalities include tremor (classically ‘wing-beating’),

<table>
<thead>
<tr>
<th>Table 1.4 Etiologies of secondary dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dystonia-plus syndromes</strong></td>
</tr>
<tr>
<td>Dopa-responsive dystonia</td>
</tr>
<tr>
<td>Myoclonus-dystonia</td>
</tr>
<tr>
<td>Rapid-onset dystonia-parkinsonism</td>
</tr>
<tr>
<td><strong>Hereditary conditions associated with neurodegeneration</strong></td>
</tr>
<tr>
<td>Autosomal dominant:</td>
</tr>
<tr>
<td>Huntington’s disease</td>
</tr>
<tr>
<td>Machado–Joseph disease (SCA3)</td>
</tr>
<tr>
<td>Other SCA subtypes (SCA2, SCA6, SCA17)</td>
</tr>
<tr>
<td>Familial basal ganglia calcification (Fahr’s disease)</td>
</tr>
<tr>
<td>Dentatorubral-pallidolusian atrophy</td>
</tr>
<tr>
<td>Neuroferritinopathy</td>
</tr>
<tr>
<td>Frontotemporal dementia</td>
</tr>
<tr>
<td>Neuronal intranuclear inclusion disease</td>
</tr>
<tr>
<td>(inheritance not well-established)</td>
</tr>
<tr>
<td>Autosomal recessive:</td>
</tr>
<tr>
<td>Juvenile Parkinson’s disease (parkin)</td>
</tr>
<tr>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Aceruloplasminemia</td>
</tr>
<tr>
<td>Pantothenate kinase-associated neurodegeneration (formerly Hallervorden–Spatz syndrome)</td>
</tr>
<tr>
<td>Neuroacanthocytosis</td>
</tr>
<tr>
<td>Ataxia with vitamin E deficiency</td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
</tr>
<tr>
<td>Ataxia with oculomotor apraxia</td>
</tr>
<tr>
<td>Sulfite oxidase (molybdenum cofactor) deficiency</td>
</tr>
<tr>
<td>Triosephosphate isomerase deficiency</td>
</tr>
<tr>
<td>Guanidinoacetate methyltransferase deficiency</td>
</tr>
<tr>
<td>Infantile bilateral striatal necrosis</td>
</tr>
<tr>
<td>Cockayne’s disease</td>
</tr>
<tr>
<td>Lysosomal storage disorders:</td>
</tr>
<tr>
<td>GM1 gangliosidosis</td>
</tr>
<tr>
<td>GM2 gangliosidosis (hexosaminidase A deficiency)</td>
</tr>
<tr>
<td>Niemann–Pick type C (juvenile dystonia lipidosis)</td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
</tr>
<tr>
<td>Krabbe’s disease</td>
</tr>
<tr>
<td>Neuronal ceroid lipofuscinosis</td>
</tr>
<tr>
<td>Amino and organic acid disorders:</td>
</tr>
<tr>
<td>Glutaric acidemia type I</td>
</tr>
<tr>
<td>Homocystinuria</td>
</tr>
<tr>
<td>Propionic acidemia</td>
</tr>
<tr>
<td>Methylmalonic aciduria</td>
</tr>
<tr>
<td>Fumarase deficiency</td>
</tr>
<tr>
<td>Hartnup disease</td>
</tr>
</tbody>
</table>

(Continued)
Diagnosis of Dystonia

7

dysarthria, dysphagia, drooling, ataxia, and dementia. In addition to brain and liver (cirrhosis, acute hepatitis) involvement, numerous systemic findings may occur, including renal, endocrine, and cardiac abnormalities. In addition to Kayser–Fleischer rings (see below), which do not produce symptoms, ophthalmologic findings may include sunflower cataracts. As treatment can alleviate symptoms and prevent progression, especially if instituted early, the diagnosis of Wilson’s disease should be considered in all patients with onset of dystonia prior to 50 years of age.

Another important hereditary condition causing dystonia is juvenile parkinsonism due to mutations in the parkin gene. In this autosomal recessive condition, parkinsonism usually begins before the age of 40 years and is associated with dystonia at onset, hyperreflexia, slow progression, and dyskinesias occurring early in the course of levodopa treatment. The dystonia often predominates in the lower limbs, but the hands, neck, and trunk may also be involved. Symptoms typically

Table 1.4 (Continued)

X-linked recessive:
- Lubag (X-linked dystonia-parkinsonism)
- Lesch–Nyhan syndrome
- Deafness–dystonia–optic atrophy syndrome
  (Mohr–Tranebjaerg syndrome)
- Pelizaeus–Merzbacher disease
- Rett’s syndrome

Mitochondrial:
- Leber’s hereditary optic neuropathy
- Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS)
- Myoclonic epilepsy with ragged-red fibers (MERRF)
- Leigh’s syndrome (subacute necrotizing encephalomyelopathy)

Acquired/exogenous causes

Toxins:
- Medications:
  - Dopamine receptor-blocking agents
  - Antiepileptic agents
  - Levodopa
  - Dopamine agonists
  - Calcium channel blockers (cinnarizine, flunarizine)
- Carbon monoxide
- Carbon disulfide
- Cyanide
- Manganese
- Methanol
- Wasp sting

Perinatal cerebral injuries:
- Cerebral palsy
- Kernicterus

Vascular lesions:
- Stroke
- Arteriovenous malformation
- Antiphospholipid syndrome

Infection:
- Encephalitis
- Subacute sclerosing panencephalitis
- Human immunodeficiency syndrome/acquired immunodeficiency syndrome (HIV/AIDS)
- Abscess
- Brain tumors
- Paraneoplastic syndrome

Demyelination:
- Multiple sclerosis
- Pontine myelinolysis

Trauma:
- Head trauma
- Cervical cord injury
- Peripheral injury (including complex regional pain syndrome)

Structural:
- Atlanto-axial subluxation
- Klippel–Feil syndrome
- Syringomyelia
- Arnold–Chiari malformation

Parkinson’s disease and other parkinsonisms associated with dystonia

Parkinson’s disease
- Progressive supranuclear palsy
- Corticobasal ganglionic degeneration
- Multiple system atrophy

Other movement disorders exhibiting dystonic phenomenology

Tic disorders
- Familial paroxysmal kinesigenic dyskinesias
- Familial paroxysmal non-kinesigenic dyskinesias
- Episodic ataxia syndromes

(Continued)
Parkinson’s disease may be a dystonic phenomenon.62,63 The camptocormia (forward flexion of the thoracolumbar spine) that occurs in patients with areas as well. The camptocormia (forward flexion of the thoracolumbar spine) that occurs in patients with areas as well. The camptocormia (forward flexion of the thoracolumbar spine) that occurs in patients with areas as well.

Dystonia can occur in association with other movement disorders. It frequently accompanies Parkinson’s disease, often occurring as painful foot dystonia when levodopa levels are low, but it may affect other body areas as well. The camptocormia (forward flexion of the thoracolumbar spine) that occurs in patients with Parkinson’s disease may be a dystonic phenomenon.62,63 Parkinson’s-plus syndromes are even more strongly associated with dystonia than is idiopathic Parkinson’s disease. In one study, 59% of patients with corticobasal degeneration had dystonia, mostly involving the arms.64 In another series, dystonia was present in 46% of patients with progressive supranuclear palsy, most commonly manifesting as limb dystonia or blepharospasm.65,66 Whereas the prevalence of dystonia in multiple system atrophy has been reported to be as high as 46% (mostly anterocollis and unilateral limb dystonia),67 other authors have found frequencies closer to 12%.68

Spinocerebellar ataxia, especially type 3 (SCA3), can be associated with dystonia. A recent series found the prevalence of dystonia to be 10% of 80 patients with SCA3,69 while another series reported dystonia in 23% of 61 patients.70 Also known as Machado–Joseph disease, SCA3 is the most common hereditary ataxia with autosomal dominant inheritance in the United States, constituting 21% of 149 families with dominantly inherited ataxia in one series.71 It results from expansion of CAG repeats in the ATXN3 gene on chromosome 14q24.3-q31, and the likelihood of dystonia is correlated with increasing repeat length.70 Presentation is often in the third or fourth decade and begins with speech and gait dysfunction, typically followed by ophthalmoparesis, dysarthria, dysphagia, and ataxia. Other characteristic features include bulging eyes, perioral fasciculations, and peripheral neuropathy. Dystonia is highly variable in presentation72,73 and may even respond to levodopa therapy.74,75 Dystonia also may occur in SCA17,76 but is uncommon in other forms of spinocerebellar ataxia.

Patients with other movement disorders can also exhibit movements that resemble dystonia but are not generally categorized as dystonia. For example, tics can be dystonic in appearance when they are slow and sustained. Similarly, paroxysmal and episodic disorders can produce dyskinetic postures resembling dystonia.77

Toxic causes of dystonia are most commonly iatrogenic, induced by medications prescribed for psychosis, gastrointestinal complaints, or other indications. Manganese intoxication may result in a dystonic-parkinsonian syndrome,78 and severe exposure can lead to dystonic posturing of the limbs and trunk, as well as focal dystonia such as blepharospasm, grimacing, torticollis, and oculogyric crisis.79,80 Other toxins associated with dystonia include carbon monoxide,81 cyanide,82,83 carbon disulfide,84 and methanol.85,86 Dystonia has been reported following a wasp sting.87

Dystonia can result from acquired brain lesions such as tumors, infections (e.g. abscess, encephalitis), strokes, vascular malformations, trauma, and demyelination. Structural lesions producing dystonia are most commonly located in basal ganglia and thalamus (and, for blepharospasm, in rostral brainstem).88,89 Lesions of the parietal lobe have also been reported.90,91 In a series of 25 patients with cervical dystonia secondary to lesions of the central nervous system, cerebellum and brainstem were the areas most commonly involved, followed by basal ganglia and cervical spinal cord.92 Perinatal insults such as asphyxia or kernicterus may be associated with the development of dystonia, onset of which may be delayed by years.93,94 Dystonia may develop following peripheral trauma, and may be particularly likely when complex regional pain syndrome is present, but whether peripheral injury truly plays a causal role in producing dystonia remains controversial.95–100 Sometimes classified as a subtype of secondary dystonia, psychogenic dystonia deserves particular mention. In one unpublished series, psychogenic dystonia was the third most common cause of secondary dystonia (after tardive dystonia and birth injury), accounting for 14% of classifiable secondary dystonias.101 A psychogenic origin of dystonia should be suspected when manifestations vary over time, remit upon distraction or when socially convenient, or are inconsistent with normal physiologic patterns.

**DIAGNOSTIC EVALUATION**

The diagnosis of dystonia, like that of all neurologic disorders, relies most firmly upon a thorough history and a complete physical and neurologic examination; these usually permit presumptive classification of the...
dystonia as primary or secondary, which in turn guides the subsequent evaluation.

**Primary dystonia**

If the history and examination demonstrate no neurologic abnormalities other than dystonia, there is no history suggesting an acquired insult (including drug exposure), and there are no features suggesting a secondary cause (see Table 1.3), a primary dystonia can be postulated. However, the possibility of DRD should always be considered and, when appropriate, excluded (see below).

In patients with onset of primary dystonia prior to 26 years of age, DYTI testing is a reasonable initial investigation, as this test correctly identifies 100% of clinically ascertained carriers. We also consider DYTI testing in patients with later onset who have an affected relative with an early age at onset. If the GAG deletion is detected, DYTI dystonia is confirmed and no further diagnostic work-up is necessary.

If the GAG deletion is not present, a primary dystonia is still possible; unfortunately, at this time, genetic testing for primary dystonias other than DYTI is not commercially available. It is likely that additional gene tests will become available in the future. The website http://www.geneclinics.org is a useful resource for up-to-date information about genetic testing.

When DYTI testing is negative (or is not indicated due to onset at age 26 or later), subsequent investigation emphasizes the exclusion of secondary etiologies (including dystonia-plus syndromes) with greater certainty. In most cases a trial of levodopa to exclude DRD is warranted (see below). Magnetic resonance imaging (MRI) of the brain should be performed to exclude structural lesions as well as signal abnormalities suggestive of a metabolic disorder.

**Secondary dystonia**

The work-up for secondary dystonia may proceed if the evaluation for a suspected primary dystonia is negative, or may be launched ab initio when clinical features suggest a secondary cause for the dystonia.

Although the differential diagnosis of secondary dystonia (see Table 1.4) appears daunting, it can often be narrowed considerably on the basis of age at onset, family history, and presence of other features such as developmental delay, ataxia, or spasticity. Consultation with geneticists and specialists in metabolic disorders is often invaluable. When dystonia follows an exogenous insult with an appropriate temporal interval, further work-up may not be necessary.

MRI of the brain is critical in assessing secondary dystonia. Imaging may reveal a structural lesion (e.g. stroke, arteriovenous malformation, tumor, or abscess) in a brain region associated with dystonia. Caudate atrophy should prompt consideration of Huntington’s disease or neuroacanthocytosis. In Wilson’s disease there may be abnormalities involving the putamen, thalamus, and brainstem, including the ‘face-of-the-giant-panda’ sign, comprising hyperintensity in the midbrain tegmentum sparing the red nucleus, preserved signal intensity in the lateral substantia nigra pars reticulata, and hypointensity of the superior colliculus. Pan-}

othenate kinase-associated neurodegeneration (PKAN, formerly Hallervorden–Spatz syndrome) is classically associated with the ‘eye-of-the-tiger’ sign: i.e. pallidal hypointensity with relative hyperintensity in the anteromedial globus pallidus on T2-weighted MRI. Basal ganglia calcification may signify Fahr’s disease. Diffuse signal abnormality in the white matter raises the possibility of a leukodystrophy. Other metabolic conditions with characteristic MRI patterns include neuroferritinopathy, glutaric aciduria, and methylmalonic aciduria. Positron emission tomography is not currently in widespread use in the evaluation of dystonia but may assume a more important role as its utility is further elucidated. In addition to brain imaging, MRI of the cervical spine may be helpful in assessing patients with cervical or brachial dystonia, as it may disclose a lesion such as a tumor, syrinx, or demyelinating plaque.

Along with neuroimaging, the investigation of secondary dystonia also includes ruling out treatable conditions that can cause dystonia, chiefly DRD and Wilson’s disease. Methods currently available for the clinical diagnosis of DRD include empiric treatment with levodopa; measurement of tetrahydrobiopterin, neopterin, and dopamine metabolites in cerebrospinal fluid (CSF); phenylalanine loading; and measurement of BH4 levels and GCH1 activity in fibroblasts or lymphocytes. Chronic oral levodopa replacement at a low dose usually results in a return to normal or near-normal motor function that is sustained over time. We offer a therapeutic trial of levodopa to patients with onset of dystonia in childhood or adolescence, as well as to adult-onset patients with any features suggesting DRD (e.g. parkinsonism, diurnal variation, hyperreflexia). We begin with half a tablet of carbidopa/levodopa 25/100 daily, slowly increasing the dose over several weeks. While a daily dose of 600 mg of levodopa is occasionally required, most patients with DRD will respond to a dose of 300 mg/day or less. Because other forms of dystonia may demonstrate some response to levodopa, improvement with empiric treatment is not specific for DRD; however, it is very sensitive, and if a patient responds to levodopa, treatment should usually be continued.
Another tool for diagnosing DRD is lumbar puncture for measurement of neopterin and biotin in CSF; reduced levels of neopterin appear to be specific for DRD due to GCH1 deficiency. A less invasive test involves demonstration of elevated phenylalanine levels, decreased tyrosine levels, and elevated phenylalanine/tyrosine ratios in serum following oral phenylalanine loading. This test detects GCH1 deficiency because biotin is a necessary cofactor for phenylalanine hydroxylase, which catalyzes the hydroxylation of phenylalanine to tyrosine, and because DRD patients have normal baseline levels of phenylalanine and tyrosine. The sensitivity and specificity of this test are still being clarified. Reduced activity of GCH1 and decreased neopterin and biotin levels have been demonstrated in lymphoblasts and cultured skin fibroblasts; these findings may prove useful for diagnosis, and prenatal diagnosis may even be possible if these techniques can be applied to amniocytes.

Genetic testing for DRD is available through a few commercial laboratories (listed at www.geneclinics.org). Single-strand conformation polymorphism/sequence analysis of all six exons of the gene reveals a mutation in about 50–60% of clinically diagnosed cases, but this methodology may miss large heterozygous deletions and multiplications. A recent study in which sequence analysis was supplemented with quantitative duplex polymerase chain reaction identified mutations in the GCH1 gene in 87% of DRD patients identified with rigorous inclusion criteria, but such high sensitivity has not been replicated. A negative result, especially when only sequence analysis is performed, does not exclude the diagnosis of DRD. As always, it is essential that patients and families meet with an experienced genetic counselor before and after testing so that they understand the implications of a positive or negative result.

Another treatable cause of dystonia, Wilson’s disease should be considered in patients whose dystonia begins prior to age 50 years. Treatment options include dietary modification, chelating agents, and agents that reduce copper absorption from the gastrointestinal tract. As described above, MRI of the brain may suggest the diagnosis. Serum ceruloplasmin is a reasonable initial screening test for Wilson’s disease, but is not sufficiently sensitive (85% in one study) or specific. Slit-lamp examination for Kayser–Fleischer rings (due to deposition of copper in Descemet’s membrane) is nearly (but not quite) 100% sensitive in patients with neurologic Wilson’s disease. As urinary copper may be elevated, measurement of 24-hour urinary copper is sometimes helpful. Liver biopsy is probably the most sensitive diagnostic modality; in one study in which hepatic copper content was measured in 15 patients with neurologic Wilson’s disease, the concentration was greater than 250 μg/g in 14 patients and greater than 50 μg/g in all patients. Genetic testing, including mutation analysis of the ATP7B gene and sequence analysis/mutation scanning of select exons, is available on a limited basis, but the sensitivity of this testing depends on the patient’s ethnicity and the particular mutations sought and exons examined. In practice, we rely on slit-lamp examination, 24-hour urinary copper, and serum ceruloplasmin level to screen for Wilson’s disease; if these are normal and clinical suspicion is high (due to concomitant hepatic dysfunction, psychiatric or cognitive abnormalities, or suggestive family history), we may consider liver biopsy.

When neuroimaging is normal and there is no evidence for DRD or Wilson’s disease, additional laboratory investigations may be helpful. Routine blood tests such as complete blood count, electrolytes, glucose, calcium, magnesium, coagulation profile, and kidney, liver, and thyroid function are usually supplemented by erythrocyte sedimentation rate, antinuclear antibody screen, and syphilis screen. More specialized testing may be indicated as well, as dictated by the clinical presentation. Features such as chorea, orolingual dystonia, seizures, and abnormal behavior and cognition might suggest the diagnosis of neuroacanthocytosis; serum creatine phosphokinase (CPK) should be measured and a peripheral blood smear performed to assess for acanthocytes. Adult-onset chorea may reflect neuroferritinopathy, and serum ferritin may be helpful in making this diagnosis. Ataxia due to vitamin E deficiency can be diagnosed by demonstrating low serum levels of this vitamin. Ataxia-telangiectasia should be suspected when ataxia accompanies recurrent infections and conjunctival telangiectasias, and may be confirmed by low serum levels of immunoglobulins and elevated α-fetoprotein. A history of thrombotic events or fetal loss may bespeak the antiphospholipid syndrome, and should prompt testing for anticardiolipin antibodies and related studies. Quantitative analysis of amino acids in serum and urine and of organic acids in urine is useful in assessing for amino acidopathies and organic acidopathies. Measurement of lysosomal enzymes in leukocytes may disclose a lysosomal storage disease. Testing for the human immunodeficiency virus is indicated when appropriate. Genetic testing is available for some of the hereditary conditions causing dystonia (e.g. Huntington’s disease, juvenile parkinsonism due to the parkin mutation, and some spinocerebellar ataxias), and undoubtedly mutational analysis for more conditions will be offered in the future. Lactate and pyruvate can be measured in blood and CSF when a mitochondrial disorder is considered. Pterins and neurotransmitter metabolites can also be assayed in CSF.
In some cases, electrophysiologic testing modalities such as nerve conduction studies/electromyography, evoked potentials, and electroencephalography can provide useful information, but these rarely lead to a specific diagnosis. Occasionally, definitive diagnosis may require tissue biopsy. As mentioned above, liver biopsy for measurement of hepatic copper may be needed to confirm the diagnosis of Wilson’s disease. Bone marrow of patients with Niemann–Pick disease type C usually contains foam cells and sea-blue histiocytes. Fibroblasts obtained by skin biopsy can be used for lysosomal enzyme screening in suspected storage diseases, as well as for filipin staining and low-density lipoprotein-induced cholesterol esterification in Niemann–Pick type C. Muscle biopsy can be useful; abnormalities consistent with mitochondrial myopathy (such as ragged red fibers) suggest a mitochondrial disorder. Brain biopsy may reveal intraneuronal inclusions but is not a common component of the diagnostic evaluation of dystonia.

APPLYING THE DIAGNOSIS

The ultimate goal of a precise diagnosis of dystonia is the optimization of treatment for each patient. At the current time, most patients with dystonia are treated with symptomatic therapies such as oral medications, chemodenervation with botulinum toxin, and surgical procedures that are not highly specific for the particular cause of the individual's dystonia. Nevertheless, timely assignment of a specific diagnosis allows better genetic counseling, more reliable estimation of prognosis, and design of more meaningful clinical trials. As our understanding of these complex and challenging disorders grows, individualized therapies directed at specific dystonia syndromes will undoubtedly emerge.

REFERENCES

12 CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA


INTRODUCTION

Epidemiology is the investigation of the distribution and determinants of a disease or condition in a population. Dystonia is the third most common movement disorder, yet little is known regarding its population distribution and causes. Barriers to good studies include its relative rarity, the lack of disease registries such as exist for cancer, and the widespread belief that a substantial proportion of cases may not seek medical attention or are misdiagnosed. Deficiencies in epidemiologic knowledge limit progress in identifying treatments, prevention, or cures for this disabling disorder. In this chapter, we provide an overview of the epidemiology of dystonia, beginning with a short review of epidemiologic concepts as they apply to dystonia. Subsequent sections review what is known regarding the frequency and distribution of dystonia and its determinants. Because much remains to be done in this area, we conclude by identifying important directions for future work.

Although dystonic syndromes can be classified in many ways (see Chapter 1), the traditional grouping into two broad categories, based on etiology, of primary and secondary dystonia is followed in this chapter.1 Primary dystonia (also called primary torsion dystonia, PTD) is distinguished from most secondary dystonias by the absence of signs and symptoms other than dystonia or dystonic tremor. Dystonia may also be characterized by age of onset (early vs late onset), site of symptoms (focal, segmental, generalized), or specific cause.

EPIDEMIOLOGIC CONCEPTS IMPORTANT TO THE STUDY OF DYSTONIA

A complete consideration of the principles of neuroepidemiology is beyond the scope of this chapter, but may be found in several textbooks.2-4 A brief discussion of some key aspects is presented here. Published estimates of the frequency of dystonia suggest that dystonia is a rare disease. Whether this is a correct assessment has been questioned by some, and the final answer will require further research investigations. The uncertainty stems from several characteristics of dystonia that make epidemiologic investigations particularly challenging. First, the term dystonia covers a clinically and etiologically heterogeneous set of disorders. All of the epidemiologic studies of the distribution of dystonia to date have focused on primary dystonia. Even within this category, clinical features range from generalized disease to focal disorders involving only a few muscles, such as spasmodic dysphonia or writer’s cramp. The secondary dystonias include many rare neurologic disorders, but also include more common conditions, such as dystonia due to drugs (neuroleptics and therapies for parkinsonism) and dystonia as part of more extensive neurologic injuries, such as cerebral palsy, stroke, and traumatic brain injury. A few clinical series suggest that these forms may be common, but the full impact remains an unknown, though likely significant, source of disability.

A further difficulty in studying dystonia is that the clinical features of the syndrome may be unfamiliar to many practitioners. Because primary dystonia frequently manifests clinical signs only when specific motor tasks are repetitively performed, mild cases or early cases of dystonia are commonly misdiagnosed. In the secondary dystonias, the unique dystonic phenomenology may not be recognized or may not be recorded in a format that can be easily retrieved. The threshold for recognition of dystonia as a problem appropriate for medical attention may vary as well. While those with severe, generalized disease are likely to seek medical attention, many persons with mild or moderate features of disease may not do so, or may not persist in seeking attention if the dystonia is not recognized by the first practitioner. To determine the extent to which dystonia is missed, the ‘gold-standard’ approach would be direct evaluation of
a population by expert diagnosticians, including the appropriate provocative tests to identify task-specific syndromes. The costs and practical difficulties of such an effort have, so far, rendered this approach impossible. More efficient approaches, beginning with a questionnaire screening for symptoms of dystonia, followed by expert exam in those endorsing symptoms, have been successful in identifying undiagnosed cases. For example, a postal survey in northern England found 10% of respondents to advertisements describing dystonic syndromes were previously undiagnosed. Similarly, in an Italian survey of adults aged ≥50 years, 4/6 cases of dystonia had not previously been diagnosed.

EPIDEMIOLOGY OF PRIMARY DYSTONIAS

Incidence and prevalence have been estimated for primary dystonia in small studies – other measures of disease in populations, such as mortality, are not available. For primary dystonia, precision of both incidence and prevalence estimates is problematic because of the small number of cases identified in published, community-based studies.

Incidence

Incidence estimates are theoretically a better representation of disease distribution, as those with shortened survival are more likely to be included. Only two studies7,8 have estimated overall annual incidence of primary dystonia, and the results differ considerably. Korczyn et al7 estimated incidence in Israeli Jews based on 1969–1975 hospital discharge data verified by examination. The crude annual incidence in Jews of European descent was estimated at 0.42/10^6 based on seven cases, and of Afro-Asian descent at 0.11/10^6, based on a single case. Whether this figure represents all PTD or only generalized dystonia is not clearly stated. Nutt et al8 estimated PTD incidence in Rochester, Minnesota, based on records linkage with review of medical records for the period 1950–1982. Crude annual incidence of generalized PTD was 2/10^6 person-years (p-y) (based on three cases), of torticollis was 11/10^6 p-y (based on 11 cases), of blepharospasm was 4.6/10^6 p-y (based on seven cases), of oromandibular dystonia was 3.3/10^6 p-y (based on five cases), of both writer's cramp and spasmodic dysphonia was 2.7/10^6 p-y (based on four cases each). Thus, the total knowledge of the incidence of PTD is based only on a total of 41 cases from two populations observed between 1950 and 1982. There is, at a minimum, a five-fold difference in the estimates of generalized dystonia between these two studies. Neither study presented age- or gender-specific incidence, and only one of the total cases was non-white. In a separate report, the incidence of torticollis in Finland was 1/10^6, but no methodologic information was provided in this abstract.9

Prevalence

The prevalence of primary dystonia is reported in a number of different studies,5–8,10–26 at 30–7320 cases per million for late-onset and 2–50 cases per million for early-onset dystonia. Estimates of prevalence for generalized dystonia ranged from 0.3/10^6 in a German service-based study14 (based on four cases) to 50/10^6 in a Chinese community-based, door-to-door study10 (based on three cases) and are further described in Table 2.1. For focal and segmental dystonia, estimated prevalence ranged from 30/10^6 based on three cases identified in a door-to-door study in China10 to 2250/10^6 based on six cases identified in a population sample of older adults in Italy.6

The variation in reported prevalence seen from study to study can be at least partially explained by differences in case ascertainment methods and the fact that all the reported rates are crude rates. Adjusted rates for primary dystonia are not available, and crude rates always result in larger variance because adjustment for influencing factors such as differences in mean age, gender distribution, or risk-factor profile in the study population is not possible.

Only five studies estimating the prevalence of PTD have been conducted in enumerated populations.8,10,12,15,24 Precision in these studies is poor, as only 74 cases were identified over all four studies. Service-based studies that included patients from tertiary care or treatment centers (botulinum toxin clinics)11,13,14,16–20,22 reported overall prevalences of 61–117/million for focal dystonia11,13,14,16,20 and 3–50/million for generalized dystonia.14,19 Service-based approaches do not account for differences in access to care or treatment response for dystonia subtypes. This is important, as some subtypes are harder to recognize than others, mild cases may not seek medical attention, and misdiagnosed cases may not be referred to the center. Error in estimating prevalence and bias in subgroup comparisons is likely using a service-based approach.

Age, gender, and ethnicity

The number of cases observed in enumerated populations is too small to be able to describe distribution. Therefore, we must rely on clinical series, recognizing that many differences in access to care associated with these factors could influence these observations.

Age

The age at onset of primary dystonia appears to be bimodal based on clinical series, with modes at 9 years
Table 2.1 Prevalence of generalized PTD

<table>
<thead>
<tr>
<th>Location of study</th>
<th>Number of cases</th>
<th>Estimated prevalence/million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Germany (Castelon-Konkiewitz, 2002)</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>UK (Duffey et al, 1998)</td>
<td>37</td>
<td>1.4</td>
</tr>
<tr>
<td>Iceland (Asgeirsson et al, 2006)</td>
<td>1</td>
<td>3.0</td>
</tr>
<tr>
<td>Japan (Sugawara et al, 2006)</td>
<td>8</td>
<td>6.8</td>
</tr>
<tr>
<td>Israel (Korczyn et al, 1980)</td>
<td>35</td>
<td>9.6</td>
</tr>
<tr>
<td>USA (Nutt et al, 1988)</td>
<td>3</td>
<td>34</td>
</tr>
<tr>
<td>China (Li et al, 1985)</td>
<td>3</td>
<td>50</td>
</tr>
</tbody>
</table>

*Results not adjusted for differences in underlying populations.

PTD = primary torsion dystonia.

While PTD has been reported in all races, the relative distribution of PTD across racial groups is not known. The methods, geographic area, ethnicity, age distribution, and case definition criteria differ considerably among the available studies. One study investigated distribution and characteristics by race and ethnicity, but obtaining prevalence and incidence data was not a primary aim. In addition, the study used a preselected population and does not provide information about the distribution in an unselected population. Data from family studies indicate the prevalence of early-onset generalized dystonia is highest in Ashkenazi Jews; about 90% of these cases are due to DYT1 mutations and an underlying founder mutation has been shown in this population. Ashkenazi Jews had an earlier age at onset and greater frequency of limb onset than did non-Jewish Caucasians. In the same study, African-Americans tended to have cranial and laryngeal involvement; however, only 29 cases were observed. The numbers of Hispanics and Asians in this study were too small to allow analysis. Recently, the frequency of DYT1 mutations among primary dystonia patients in Singapore has been published, indicating such mutations are rare in this population (1%) and not significantly different than the rate reported in Western populations. In a study of the Icelandic population, a haplotype of torsinA was associated with sporadic dystonia, but no such correlation was evident in a group of German patients with sporadic dystonia, suggesting that the former finding may be unique to the Icelandic population.

Risk factors for primary dystonia

Some of the primary dystonias are clearly familial and, for a few, a gene has been identified. However, there is
significant phenotypic heterogeneity even within the forms with a known genetic cause. Probably, environmental factors account for at least some of this heterogeneity. The limited work to identify environmental risk factors for primary dystonia is reviewed in this section. The low penetrance and variable expressivity of DYT1 suggest that such research is critically important to understanding the disorder. Clues to environmental causes or modifiers may be obtained from studying the function of DYT1 or other dystonia-associated genes. Possible risk factors may also be derived from investigations of the natural history of individuals with dystonia, in an attempt to identify ‘triggers’ of disease. In addition, investigation of the population distribution of dystonia may provide clues to environmental determinants. These proposed risk factors must then be tested systematically in other populations, and biologic plausibility assessed in cooperation with laboratory scientists. To date, very little work has been done. However, if specific risk factors can be identified, this could improve our understanding of the pathogenesis of dystonia, and possibly provide strategies for prevention or treatment.

**Antecedent illness**

Because the DYT1 gene encodes a protein in the heat-shock family, the expression of torsinA might be modulated by infection or fever. Preliminary work suggests infection with fever may cause earlier onset of generalized dystonia. Comparisons of antecedent severe febrile illness and trauma in manifesting and non-manifesting DYT1 carriers indicate that early-onset childhood illness was associated with manifesting dystonia. This suggests that factors modifying metabolic pathways including torsinA may be important in DYT1 and possibly other forms of dystonia. However, more work will be needed in the laboratory and in populations.

**Trauma**

For more than a century, whether focal or generalized trauma can cause PTD has been controversial. Nevertheless, trauma is the most frequently proposed risk factor and is typically described as an injury to the dystonic body part, preceding dystonia onset by months or longer. Commonly reported injuries in various clinical series include ‘whiplash’ from a motor vehicle accident, reported in up to 20% of spasmodic torticollis patients; hand trauma, in up to 10% of those with focal hand dystonia; and ocular lesions, such as keratitis, in 10–20% of patients with blepharospasm. Sensory symptoms such as pain, discomfort, and distortion of sensory modalities have been reported as the earliest manifestations of dystonia; patients with postural tremor may be more likely to develop dystonia in response to trauma. The proposed pathologic mechanism for this association is injury-induced alteration of sensory input that causes central nervous system reorganization and results in a movement disorder, and data from experimental animals provide indirect support for this proposed mechanism. Alternatively, torsinA expression may be modulated by trauma. Since head injury has also been associated with primary dystonia, altered torsinA function might explain both focal and non-focal trauma as precipitants of dystonia. However, a recent multicenter case–control study in 177 cases with primary adult-onset cranial dystonia and 217 age- and gender-matched controls with primary hemifacial spasm did not find trauma to be associated with an increased risk of
dystonia when compared with the disease control group. Whether there would be a similarly negative finding if a non-affected control group were chosen must be determined by future investigations.

**Occupation**

Repetitive motion has been proposed as a risk factor for dystonia, but there are no epidemiologic data confirming this. Focal hand dystonias (writer’s cramp, occupational dystonia) are commonly associated with tasks involving repetitive movements, such as typing or playing a musical instrument. Although musician’s dystonia and other focal task-specific dystonias are generally considered sporadic conditions, study of three multiplex families suggests that an autosomally dominant genetic contribution with phenotypic variability may play a role in the development of these disorders in some cases. Occupational dystonia can be devastating, often causing a career change. A study of musicians showed that anxiety disorders occurred more often in dystonic musicians and in musicians with chronic pain than in controls. The authors hypothesized, however, that these psychological conditions were already present before the onset of playing-related disorders. Focal dystonia has been associated with a degradation of hand representations in the somatosensory cortex, and a parallel finding of cortical reorganization has also been reported in the somatosensory areas of patients with chronic pain. Similarly, childhood-onset DYT1 generalized dystonia frequently presents with focal signs, often manifesting only after prolonged task-specific activity (e.g., writing, running). In animal models, prolonged repetitive motions can alter central nervous system function and ultimately produce a movement disorder. In humans, aberrant plasticity from excessive repetitive use has been thought to cause dystonia, although a causal association of repetitive motion and dystonia has never been shown. If specific occupations, hobbies, or characteristic physical activities are shown to be associated with dystonia, avoidance of these could be important in those at risk (i.e., in non-manifesting DYT1 carriers). Indirect support for this proposition is provided by a recent clinical study of aberrant plasticity in patients with writer’s cramp.

**Cigarette smoking**

One case–control study of adults found an inverse association of cigarette smoking with primary dystonia. The magnitude of the association was similar to that observed in Parkinson’s disease (PD). Dystonia can occur in PD and is presumed to be mediated by the same general brain circuitry (basal ganglia and nigrostriatal pathways). Alterations of central dopaminergic systems may cause both PD and dystonia, and it is plausible these disorders may have common risk factors.

**Thyroid disorders**

Large clinical series reports indicate dystonia may be associated with autoimmune disease and thyroid disorders. Antecedent thyroid disease was observed in adults with primary torsion dystonia in Olmsted County, although only six cases were seen. The high frequency of thyroid disorders among the torticollis patients in this study may only reflect the risk of thyroid disease in that community – indeed, thyroid conditions may be too prevalent in a given patient population to warrant consideration. Nevertheless, controls with peripheral sensory neuropathy had a much lower frequency of thyroid disease, and it was suggested a possible increased frequency in those with torticollis might represent an effect of an autoimmune mechanism.

**Hypertension**

In a case–control study, primary torsion dystonia was inversely associated with hypertension in adults; however, the effect was largely due to over-representation of hypertension in a control group with hemifacial spasm.

**Vestibular changes**

Neuro-otological tests in patients with idiopathic spasmodic torticollis often identify a breakdown of the mechanisms responsible for signaling head posture. However, there is some evidence that lesions of the VIIIth nerve may aggravate spasmodic torticollis by further disrupting processing of sensory information about head position. Thus, interventions on the vestibular system are not likely to improve the clinical condition of patients with spasmodic torticollis.

**EPIDEMIOLOGY OF SECONDARY DYSTONIAS**

No published studies have estimated the distribution of all forms of secondary dystonia in populations. This work would be important to determine the burden of disease due to secondary dystonia, and may also provide new understandings of the pathogenesis of primary dystonia. Work has been limited for several reasons. First, describing the distribution of secondary dystonia requires a clear definition of the conditions. This is difficult to achieve given the large collection of symptoms and
dystonic syndromes that the term is used to encompass. Secondly, when dystonia is part of a more extensive syndrome, examination may be required in order to determine whether an individual is affected.

We have concentrated on:

- drug-induced dystonia due to neuroleptic exposure, acute dystonic reactions, and tardive dystonia
- dystonia associated with PD.

In each case, information is available only within the context of clinical series (Table 2.3), and is not truly population based. Although these forms of the disease are the most commonly recognized, even clinical descriptions of disease frequency are few.

### Table 2.3 Age, gender, ethnicity, and other factors with neuroleptic-associated secondary dystonia syndromes

<table>
<thead>
<tr>
<th>Factor</th>
<th>Acute dystonia</th>
<th>Tardive dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Younger</td>
<td>Younger</td>
</tr>
<tr>
<td>Gender</td>
<td>Uncertain</td>
<td>Men</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td>Low prevalence in Hong Kong Chinese</td>
</tr>
<tr>
<td>Antipsychotic</td>
<td></td>
<td>Higher dosage</td>
</tr>
<tr>
<td>Birth injury</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Electroconvulsive therapy</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Affective disorder</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Mental retardation</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Temporal relationship with neuroleptic treatment</td>
<td>Early, first 48–72 hours</td>
<td>Late</td>
</tr>
</tbody>
</table>

### Acute dystonic reactions associated with neuroleptic agents

It is difficult to clearly distinguish the incidence and prevalence of acute dystonic reactions as their duration rarely exceeds several hours, which often makes expert consultation impossible. Incidence rates vary widely from 2 to 70% \(^{53-57}\) and appear to depend on the drug administered and the dose. Haloperidol therapy is generally associated with the highest incidence of acute dystonia. \(^{56,57}\) Anticholinergic prophylaxis is known to reduce the likelihood of neuroleptic-induced acute dystonia \(^{58-60}\) but may cause unwanted side effects and is not recommended in patients at low risk of acute dystonia.

In almost all studies, a young age of exposure appears to be an important risk factor for the development of acute dystonic reactions. \(^{56,61,62}\) One small study \((n = 39)\) showed a significantly higher incidence in patients <30 years old (72.2%) as compared to those >30 years old (33.3%) \([p <0.05]\). \(^{61}\) In this same study, acute dystonic reactions were more frequent in men than in women, \(^{61}\) although male preponderance is not consistent across all studies. \(^{56,62}\) Men may be more likely to receive higher dosages of neuroleptics, and Kondo et al reported a 91.7% frequency of acute dystonic reactions in young men (11 out of 12). \(^{61}\) Information about the incidence and prevalence of acute dystonic reactions among different ethnic groups is extremely scarce, with only one study including data comparing patients of different ethnic backgrounds. \(^{62}\) In this study, the frequency of acute dystonic reactions was 13 out of 32 (41%) in blacks and 13 out of 41 (32%) in whites, and the difference was not statistically significant.

### Tardive or persistent dystonia associated with neuroleptic agents

Tardive dystonia is a dystonic syndrome resulting from chronic neuroleptic exposure. \(^{63}\) It is distinguished from acute dystonia chiefly by the duration of exposure. Tardive dystonia is differentiated from other tardive movement disorders on clinical grounds, but there is some overlap of syndromes. Although described in clinical series reports, tardive dystonia has not been studied epidemiologically. In clinical series, tardive dystonia is often a severe and disabling disorder, poorly responsive to therapy. Finding ways to prevent this iatrogenic disorder is important. Like PTD, tardive dystonia is a rare disease with considerable variation in its symptoms and presentation and requires a diagnosis by a specialist. Drawing conclusions about the relationships of age, ethnicity, or gender is difficult given the small number and highly selected ascertainment of patients studied to date.
Incidence/prevalence

There are no incidence data for tardive dystonia. The overall annual incidence for all tardive movement disorders has been reported to be 3.7–12%, and tardive dystonia would probably be a small proportion of the cases in any of these series. \(^{64,65}\) Prevalence rates between 0.4 and 4% have been reported in other studies. \(^{66–69}\) Table 2.4 shows prevalence data, but results should be interpreted with care, as the studies are not prospective or longitudinal, differ considerably in underlying populations, and lack information about the types and dosages of medications given.

Age and gender  Several studies indicate an association between younger age and higher risk for tardive dystonia, \(^{63,67}\) male preponderance, \(^{63,69}\) and a younger age of onset in men, \(^{63}\) but these studies did not incorporate possible confounders, so the results may be questionable. Unlike in tardive dyskinesia, neither female gender nor advanced age appears to be risk factors. \(^{70}\) For example, Burke et al. \(^{63}\) reported an age of onset of 29.0 years old for men (\(n = 26\)) and 41.5 years old for women (\(n = 16\)), but without age at first exposure. The reported male:female ratios for tardive dystonia range from 1:1 to 1.7:1 [Chiu et al (1:1)\(^{68}\); Gimenez-Roldan et al (1.2:1)\(^{71}\); Burke et al (1.6:1)\(^{63}\); Raja (1.7:1)\(^{69}\)]. Possible confounders include the age at onset of schizophrenia in men\(^{70}\) and that men may develop tardive dystonia with a shorter length of exposure to neuroleptics than women. \(^{72}\) The daily dosage of neuroleptics is reported to be lower in women, and the distribution of underlying psychiatric disorders may influence the likelihood of developing tardive dystonia. \(^{69}\) Many of the studies cited included only referred patients; further study in unselected populations exposed to neuroleptics or in larger case–control studies are needed to confirm these observations.

Ethnicity  Among the studies described above, the lowest reported prevalence of tardive dystonia was 0.4% in Chinese psychiatric inpatients. \(^{68}\)

Dystonia in parkinsonism

Although dystonia in PD was first described by Charcot in 1877, \(^{73}\) there is no published epidemiologic study of the incidence or prevalence of dystonic features in PD or parkinsonism; the information reviewed here has been extracted from case series and clinical descriptions. These have been derived primarily from specialty clinics. Patients in these clinics may differ from those not seeking specialty care in many ways. It would, therefore, not be appropriate to extrapolate these findings to other populations.

Dystonia in PD is most frequently described in the course of levodopa (L-dopa) treatment, although it can occur prior to the initiation of dopaminergic therapy. Dystonia is the second most common L-dopa-associated movement disorder. Dystonia associated with L-dopa treatment in PD can be maximal at the peak beneficial effect of the drug ('on') or can manifest as drug efficacy wanes (wearing 'off'). In one study, dystonic symptoms

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of population</th>
<th>No. of cases</th>
<th>Prevalence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yassa et al, 1986(^{66})</td>
<td>351</td>
<td>7</td>
<td>2.0%</td>
<td>Inpatient population, includes psychogeriatric units, meet criteria of Burke et al 1982(^{63})</td>
</tr>
<tr>
<td>Friedman et al, 1987(^{67})</td>
<td>331</td>
<td>5</td>
<td>1.5%</td>
<td>Inpatient population, complete histories not available for all patients; all were ‘believed’ to have had exposure to neuroleptics</td>
</tr>
<tr>
<td>Chiu et al, 1992(^{68})</td>
<td>917</td>
<td>4</td>
<td>0.4%</td>
<td>Inpatient population, meet criteria of Burke et al 1982(^{63})</td>
</tr>
<tr>
<td>Raja, 1995(^{69})</td>
<td>200</td>
<td>8</td>
<td>4.0%</td>
<td>Inpatient population, meet criteria of Burke et al 1982(^{63})</td>
</tr>
</tbody>
</table>

\(^*\)Results not adjusted for differences in underlying populations.
occurred in 30% of PD patients and most often presented as early-morning foot dystonia (33 of 207 patients, 16%). Biphasic ‘on’ dystonia was relatively rare in this study (15 of 207 patients, 7%). In another study, 46 of 56 patients also showed ‘off’ dystonia that tended to occur in the early morning before their first doses of L-dopa had taken effect.

The frequency of dystonic symptoms in PD is linked with young age at onset. Frequency was about 50% in patients whose onset occurred before 35, 40, or 45 years of age. In our series, only 10% of patients with old-onset PD had dystonia, and in another series, none of the old-onset patients had dystonia. In a separate series, dystonia accompanied or preceded the onset of parkinsonism in 14% of young-onset PD patients, and early-morning dystonia occurred during treatment in 59%. No information is available to judge the influences of gender or ethnicity on the development of dystonia in PD.

Risk factors for secondary dystonia

Drugs

Neuroleptic exposure causes acute and tardive dystonia. Both ‘atypical’ and ‘typical’ neuroleptics, as well as antiemetics blocking central dopamine receptors can cause tardive dystonia. Even very short periods of exposure may cause a persistent movement disorder. Longer duration of exposure to neuroleptics does not necessarily correlate with severity of tardive dystonia.

Other medications associated with tardive dystonia include some antidepressants (e.g. amoxapine, amitriptyline, and doxepin), and the benzamide derivative ventalipride.

Genetics

For some forms of secondary dystonia, the genetic background has been extensively studied and the involved genes are known (e.g. Huntington’s disease and other heredodegenerative diseases). There is less information about tardive dystonia, but it has been proposed to be associated with certain CYP2D6 genotypes that are associated with decreased drug metabolism. The results of three studies of genotyping and tardive dystonia or acute dystonic reaction were inconsistent, however, as the case numbers were small and few ‘poor metabolizers’ were included. Another study in 663 schizophrenic patients analyzing dopamine (D2) receptor subtypes did not show a significant association between any subtype and any adverse effect of neuroleptic treatment. In a separate study, however, a family history of primary movement disorders was a significant predictor for development of a secondary movement disorder following neuroleptic treatment, and a positive family history of dystonia was associated with higher prevalence of acute dystonic reaction. There are no data regarding family history and tardive dystonia, as family history is an exclusion in the criteria for tardive dystonia defined by Burke.

Other factors

Brain injury may influence the onset of dystonia in neuroleptic-treated patients. In one study, a high frequency of lenticular or thalamic lesions was seen in patients who developed dystonia after head trauma – such associations highlight the potential importance of damage to the putaminopallidalthalamic neuronal circuit in the development of dystonias. Birth injury may also predispose to the development of tardive dystonia and mental retardation and convulsive therapy are risk factors as well.

CONCLUSIONS

Few studies have estimated the incidence of PTD and only one of these studies included all clinical subtypes – neither reported age- or gender-specific incidence. Among the studies that estimated prevalence, none has done so in age-, gender-, and race/ethnicity-specific strata, including all clinical subtypes. Despite the reduced penetrance and variable expressivity of genetic PTD, there have been few investigations of environmental risk factors, even though identifying specific risk factors is important in understanding the pathogenesis of the disease. Thus, neither the distribution nor the determinants of PTD are known. Even fewer studies have explored the epidemiology of secondary dystonia, and none has examined the combined frequency of all dystonia in a population. The overall burden of dystonia remains unknown. As has been true for many other disorders, such as cancer, observation of patterns in populations can provide important clues to potential differences in susceptibility factors – either genetic or environmental. This information may provide important clues to differential susceptibility by race or gender, leading in turn to laboratory investigations that determine underlying biologic mechanisms of these patterns. A better understanding of the incidence and prevalence of dystonia and the identification of risk factors for the disorder and its subtypes will be beneficial in healthcare planning, and may lead directly to preventive recommendations or may provide new directions for development of treatments.
ACKNOWLEDGMENTS

Michael J Fox Foundation Fellowships (Drs Chade and Kasten); NIH (NINDS) R01 NS046340 (Dr Tanner); Jennifer Wright for editorial support.

REFERENCES


24 CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA


INTRODUCTION

Genetic etiologies have long been suspected for many subtypes of dystonia. Recent molecular advances have led to the identification of an increasing number of genes for primary and secondary dystonia subtypes (Table 3.1). This information has opened the way for studies aimed at characterizing basic pathogenic mechanisms, including cellular and animal models. It has also allowed for a broader analysis of phenotype and endophenotype to further characterize the spectrum of gene expression. Defining genetic etiologies has altered the way neurologists diagnose and counsel patients, including the important need to provide genetic counseling to patients and their families. Ultimately, understanding the genetic causes of dystonia, and the effects of these alterations, holds the promise of rational, targeted therapies.

There are many classification schemes to organize the causes of dystonia. Most create at least two broad categories: primary torsion dystonia (previously named idiopathic torsion dystonia) and secondary (or non-primary) dystonia (see Table 3.1 and Chapter 1). Primary torsion dystonia (PTD) is defined as a syndrome in which dystonia is the only clinical sign (except for tremor) and there is no evidence of neuronal degeneration or an acquired cause. Secondary (non-primary) dystonias include all other dystonia subtypes and can further divided into inherited, complex, and acquired etiologies.

To date 15 different (DYT) genetic loci have been mapped or cloned. A number of these have led to crucial advances in our understanding of molecular mechanisms underlying dystonic movements and therefore have warranted separate chapters within this book (DYT1 and non-DYT1 dystonia, dystonia-plus syndromes, paroxysmal dyskinesias). In addition, even for the common focal forms of primary torsion dystonia, such as cervical dystonia (spasmodic torticollis), blepharospasm, writer’s cramp, and other limb dystonias which do not appear to have a clear genetic basis, population and family studies have found evidence for a genetic contribution to their etiology.

The dystonia genetic loci and genes are summarized in Tables 3.2–3.4. The molecular classification is somewhat complex and confusing and contains mapped loci, cloned genes including primary dystonia, dystonia-plus syndromes (dopa-responsive dystonia, myoclonus-dystonia syndrome, and rapid-onset dystonia-parkinsonism) and one heredodegenerative condition (X-linked dystonia-parkinsonism). Within this classification, two loci (DYT2 and DYT4) have been assigned on the basis of clinical descriptions alone. It is clear that there are other dystonia genes yet to be discovered.

PRIMARY TORSION DYSTONIA

Early-onset autosomal dominant primary torsion dystonia (DYT1)

Early-onset PTD is 3–5 times more common in Ashkenazi Jews compared to other populations and is transmitted in an autosomal dominant fashion with reduced penetrance of 30–40% in both Ashkenazi Jews and non-Ashkenazim. The difference in disease frequency is thought to be the result of a founder mutation in DYT1 that was introduced into the Ashkenazi population at the time of a ‘bottleneck’ in the 1600s, followed by a period of tremendous population growth.

The gene at locus DYT1 was initially mapped to chromosome 9q34 and subsequently identified in 1997 and is responsible for a large proportion of early limb-onset PTD (also known as dystonia musculorum deformans or Oppenheim’s disease) across many different populations. Only one recurring mutation in DYT1, an in-frame GAG deletion, has been associated unequivocally with PTD. The DYT1 gene encodes a
A novel protein, torsinA, that is 332 amino acids long (∼38 kD), with potential sites for glycosylation and phosphorylation, as well as an amino terminal hydrophobic leader sequence consistent with membrane translocation/targeting. The GAG deletion results in the loss of one of a pair of glutamic acid residues near the carboxy terminus of the protein.

Typical DYT1 dystonia develops before the age of 28 years old, often beginning in a limb (leg > arm), often with subsequent spread to other body parts. The clinical phenotype and molecular pathology of DYT1 and torsinA are described in Chapter 6.

### Autosomal recessive primary torsion dystonia (DYT2)

There is limited evidence for autosomal recessive primary torsion dystonia and much of it comes from three consanguineous families of Spanish gypsies. In two of the three families the phenotype resembled DYT1 dystonia and in the third family oromandibular dystonia and torticollis were the most prominent manifestations. The genetic locus is designated on the basis of the clinical description and no linkage to a chromosomal region has ever been identified. More recently, a further family of Sephardic Jewish origin has been described and purported to represent a case of DYT2 dystonia. The difficulty with the description is that in the dominant form there is often reduced penetrance and it is possible that that is what these families represent.

### Non-DYT1 primary torsion dystonia

There remains a large group of early-onset PTD, especially among non-Jewish populations, that is not due to DYT1. Two loci, DYT6 and DYT13, have been mapped in kindreds having an average age onset in adolescence. However, neither locus has been confirmed in other families and they are suspected to account for only a minority of non-DYT1 early-onset cases. Furthermore, overall clinical features in these two families differ from DYT1 (although features in any single family member may overlap with DYT1). The family phenotypes for DYT6 and DYT13 are marked by prominent involvement of cranial and cervical muscles with variable spread; also, compared to DYT1, a greater proportion of family members have later adolescent and adult onset. To distinguish this phenotype from the typical early-onset phenotype associated with DYT1 and typical late-onset focal phenotypes, the term 'mixed' has been applied. These forms of PTD are described further in Chapter 7.

### Late-onset PTD

Like early-onset PTD, late-onset PTD also appears to have autosomal dominant inheritance. However, unlike early-onset dystonia, most studies show that penetrance is even more reduced (about 12–15% compared with 30% for early-onset dystonia); alternatively, penetrance...
may be higher in a subset, with the remainder sporadic. Consistent with the notion of increased penetrance in a subset of late-onset PTD, are descriptions of large families with more highly penetrant autosomal dominant disease. One such family with adult-onset torticollis was studied and resulted in the mapping of $\text{DYT7}$.$^{16}$

**Table 3.2 Genetic forms of primary torsion dystonia**

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical features</th>
<th>Frequency</th>
<th>Age of onset</th>
<th>Inheritance and penetrance</th>
<th>Inheritance/locus/gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT1</td>
<td>Limb onset; generalized; can present as focal</td>
<td>50% cases; early onset in non-Jews, 90% in Ashkenazi Jews</td>
<td>Childhood; most present by 26 years old</td>
<td>Autosomal dominant with reduced penetrance (30%)</td>
<td>$\text{TOR1A}$ gene on chromosome 9q34; Mutation: GAG deletion leading to loss of glutamate residue in protein torsinA</td>
</tr>
<tr>
<td>DYT2</td>
<td>Focal and generalized</td>
<td>Spanish gypsy families and single Iranian family</td>
<td>Childhood to adult</td>
<td>Autosomal recessive</td>
<td>Locus unknown</td>
</tr>
<tr>
<td>DYT4</td>
<td>Laryngeal and cervical, some generalize</td>
<td>Single Australian family</td>
<td>13–37 years old</td>
<td>Autosomal dominant</td>
<td>Locus unknown</td>
</tr>
<tr>
<td>DYT6</td>
<td>Focal or generalized; cranial, cervical, or limb</td>
<td>Two Mennonite Amish families</td>
<td>Mean age of onset 19 years old</td>
<td>Autosomal dominant</td>
<td>$\text{DYT6}$ locus on chromosome 8p21-q22</td>
</tr>
<tr>
<td>DYT7</td>
<td>Focal dystonia; cervical and laryngeal</td>
<td>Single German family</td>
<td>28–70 years old</td>
<td>Autosomal dominant</td>
<td>$\text{DYT7}$ locus on chromosome 18p</td>
</tr>
<tr>
<td>DYT13</td>
<td>Cranial or cervical; some generalize</td>
<td>Single Italian family</td>
<td>Childhood to adult</td>
<td>Autosomal dominant</td>
<td>$\text{DYT13}$ locus on chromosome 1p36</td>
</tr>
</tbody>
</table>

**Adult-onset focal primary torsion dystonia (DYT7)**

This locus was originally mapped in a family from northwest Germany in which seven members were affected with late-onset torticollis, although other members had mild facial and arm involvement and spasmodic dysphonia was noted in some of the family. The gene was mapped to a 30 cM region on chromosome 18p.$^{16}$ In support of a dystonia locus on chromosome 18p is the finding that patients with the deletion of the short arm of chromosome 18 can also show dystonic symptoms.$^{17}$ Other clinically similar families have been excluded from DYT7, suggesting yet other loci for adult-onset focal PTD.$^{18}$

**The role of primary torsion dystonia genes and susceptibility loci in late-onset primary torsion dystonia**

The extent to which the genes $\text{DYT1}, \text{DYT6}, \text{DYT7}$, and $\text{DYT13}$ account for adult-onset, seemingly sporadic, focal dystonias is unclear. It is almost certain that there
Table 3.3 Dystonia-plus syndromes

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical features</th>
<th>Age of onset</th>
<th>Inheritance, penetrance, and locus</th>
<th>Gene, protein, and mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT5: Dopa-responsive dystonia (Segawa’s disease)</td>
<td>Dystonia, often limbs; parkinsonism; diurnal variation; dramatic response to levodopa</td>
<td>Usually childhood</td>
<td>Autosomal dominant for DYT5 on chromosome 14q22.1-q22.2; penetrance 30%</td>
<td>DYT5: GTP-cyclohydrolase 1; biotin synthesis – mutations</td>
</tr>
<tr>
<td>DYT11: Myoclonus-dystonia syndrome</td>
<td>Myoclonus of limbs and upper torso; dystonia of upper limbs and neck; alcohol responsive</td>
<td>Variable but usually childhood/adolescent</td>
<td>Autosomal dominant; incomplete penetrance, higher when inherited paternally (imprinting); DYT11 locus 7q21-q31</td>
<td>DYT11: α-sarcoglycan; various heterozygous mutations</td>
</tr>
<tr>
<td>DYT12: Rapid-onset dystonia-parkinsonism</td>
<td>Acute or subacute onset of generalized dystonia-plus parkinsonism</td>
<td>Childhood to adulthood</td>
<td>Autosomal dominant with incomplete penetrance; locus 19q13</td>
<td>Na⁺/K⁺-ATPase ( \alpha ) subunit (ATP1A3).</td>
</tr>
</tbody>
</table>

SECONDARY DYSTONIA AND DYSTONIA-PLUS SYNDROMES (SEE TABLES 3.3 AND 3.4)

Etiological subgroups for secondary dystonias include (1) inherited causes; (2) a group of primarily parkinsonian disorders, such as Parkinson’s disease, that are thought to have complex etiologies; and (3) environmental or acquired causes. In addition, most classifications also include other movement disorders that may display dystonic phenomenology such as tics and the paroxysmal dyskinesias and the pseudodystonias. The latter are not considered true dystonia but muscle contractions mimicking dystonia, such as seen in Sandifer’s syndrome, orthopedic conditions, and psychogenic dystonia (see Chapter 1).

Among the inherited forms of secondary dystonia is a relatively newly defined category of dystonia-plus syndromes, consisting of three clinically defined entities:

- dopa-responsive dystonia (DRD)\(^{29–32}\)
- myoclonus-dystonia (M-D)\(^{33,34}\)
- rapid-onset dystonia-parkinsonism (RDP)\(^{35–37}\)

are other as yet unmapped genes.\(^{19–21}\) The role of susceptibility loci has also been studied in cohorts of primary focal dystonia. An association has been found between a polymorphism in the dopamine D\(_5\) receptor and patients with cervical dystonia and blepharospasm.\(^{22,23}\) Although the polymorphism is not functional and therefore does not affect the receptor function, it could be linked to a nearby pathogenic mutation.

In view of the fact that the DYT7 locus causes focal dystonia, research has looked at allelic association for several markers in the region of chromosome 18p in cases of sporadic cervical dystonia (torticollis) from northwest Germany and reported an association.\(^{24,25}\) This however, was not replicated and the finding is of uncertain significance.\(^{18,26}\)

More recently, an association of the single nucleotide polymorphisms within the 3-UTR of the DYT1 gene has been found in sporadic idiopathic predominantly focal dystonia in Finland, Germany, and Austria.\(^{27,28}\) However, in the Icelandic population, the rarer of the two major haplotypes was associated with dystonia risk, whereas in the German/Austrian study a strong protective effect was observed for the same haplotype.
These are further described in Chapter 12. The dystonia-plus category was distinguished from both primary dystonia and other inherited secondary dystonias because it shares some but not all features of both groups; i.e. like primary dystonia, these three syndromes do not appear to be degenerative. Although pathology is limited, evidence to date supports genetic defects that result in functional brain changes not associated with progressive neuronal death. Furthermore, unlike primary dystonia, but similar to the other degenerative secondary dystonias, the dystonia-plus group has (as characteristic clinical features) signs other than dystonia.

### Table 3.4 Other genetic forms of dystonia

<table>
<thead>
<tr>
<th>Type</th>
<th>Clinical features</th>
<th>Age of onset</th>
<th>Inheritance, penetrance, and locus</th>
<th>Gene, protein, and mutations</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT3: X-linked dystonia-parkinsonism (Lubag)</td>
<td>Philippino males with focal dystonia which becomes generalized; parkinsonism develops in 50%</td>
<td>Childhood to early adulthood</td>
<td>X-linked; Xq13.1; penetrance 100% by 5th decade</td>
<td>TAF1 gene; encodes transcription factor, may regulate dopamine D2 receptors</td>
</tr>
<tr>
<td>DYT8: Paroxysmal dystonic choreoathetosis (non-kinesigenic dyskinesia)</td>
<td>Episodic dystonia and chorea lasting hours</td>
<td>Childhood to early adulthood</td>
<td>Autosomal dominant; incomplete penetrance, 2q33-q36</td>
<td>MR-1 gene; encodes myofibrillogenesis regulator 1 protein</td>
</tr>
<tr>
<td>DYT9: Paroxysmal choreoathetosis with episodic ataxia and spasticity</td>
<td>Chronic spastic paraplegia plus episodes of dystonia, choreoathetosis</td>
<td>Childhood</td>
<td>Autosomal dominant, 1p13.3-p21</td>
<td>Unknown</td>
</tr>
<tr>
<td>DYT10: Paroxysmal kinesigenic choreoathetosis</td>
<td>Episodes of dystonia and chorea triggered by sudden movements</td>
<td>Childhood</td>
<td>Autosomal dominant, 16p11.2-q12.1</td>
<td>Unknown</td>
</tr>
<tr>
<td>Deafness-dystonia syndrome; Mohr–Tranebjaerg syndrome</td>
<td>Dystonia, sensorineural deafness, spasticity, mental retardation, female carriers may have adult-onset focal dystonia alone</td>
<td>Childhood</td>
<td>X-linked with incomplete penetrance, Xq22</td>
<td>Mutations in dystonia-deafness peptide, mitochondrial protein import</td>
</tr>
<tr>
<td>Leber's hereditary optic neuropathy plus dystonia</td>
<td>Dystonia, optic atrophy, or both</td>
<td>Variable</td>
<td>Maternal inheritance, mitochondrial DNA</td>
<td>NADH dehydrogenase subunit 6, complex 1</td>
</tr>
</tbody>
</table>
including parkinsonism for DRD and RDP and myoclonus for M-D.

As our understanding of these syndromes is expanding, the complexity of their genetic and clinical heterogeneity is being detailed. For example, for DRD there are currently several known genetic biochemical etiologies, each with protean clinical manifestations, and for myoclonus-dystonia, there appear to be at least two genetic etiologies (see Table 3.3).38

PAROXYSMAL DYSTONIAS

This rare group of conditions manifests with abnormal involuntary movements that occur episodically and are of brief duration. The abnormal movements are mixed, but include dystonia, chorea, and ballism. They can be acquired or genetic in origin and the key feature is that the patient is normal between attacks. The genetic subtypes are shown in Table 3.4 and these disorders are described in more detail in Chapter 15.

CONCLUSIONS

Over the last 20 years our understanding of PTD, ‘dystonia-plus’, and secondary dystonia syndromes has been transformed due to the advances made in unraveling their genetic causes. The identification of genes for dystonia has already impacted dramatically both in clinical practice and research realms. It has altered the way clinicians diagnose and counsel families and their approach to therapeutics. For example, with the availability of genetic testing for DYT1, a direct diagnosis of this genetic subtype is easily made. Patients with DYT1 PTD are no longer routinely subjected to more costly and invasive investigations. In addition, because they appear to respond particularly favorably to pallidal deep brain stimulation (DBS), this form of therapy is now considered earlier in the course of disease.39 The identification of disease genes has also opened the way for the gene-specific application of imaging, neurophysiologic, and other measures for determining phenotypic and endophenotypic expression. It has allowed for the development of disease gene-specific cellular and animal models and is revising our notions about pathogenesis. PTD due to DYT1, once considered idiopathic and due to functional brain changes, appears to be associated with anatomic brain changes, such as inclusion bodies in brainstem structures not previously considered significant in the pathogenic process. Whereas previous studies, such as therapeutics focused on dopamine transmission in PTD, it is becoming evident that motor dysfunction may also relate to other mechanisms that influence the physical foundation for corticocortical and subcortico-cortical connectivity.40 The finding of PTD genes also holds the promise of novel therapeutic strategies, such as the use of small interfering RNA to silence expression of mutant torsinA.41

REFERENCES

INTRODUCTION

Dystonia is a disorder characterized by excessive movements, including sustained involuntary movements, distorted voluntary movements, and abnormal postures. Some patients may also have quick movements, called myoclonic dystonia, or tremor, but ordinarily there will have to be some sustained movements for dystonia to be recognized as such. While dystonia can be present at rest, it is brought out more by attempted voluntary movements. Dystonia movements are slow, clumsy, and characterized by overflow (excessive activity in muscles not needed for the task).

In understanding dystonia, it seems appropriate to start by examining the involuntary movements themselves. Several observations over many years have shown that dystonic movements are characterized by an abnormal pattern of electromyographic (EMG) activity with excessive co-contraction of antagonist muscles and overflow into extraneous muscles. Cohen and Hallett reported detailed observations on 19 patients with focal dystonia of the hand, including writer’s cramp and cramps in piano, guitar, clarinet, and organ players. Five features, identified by physiologic investigation, were indicative of impaired motor control. The first was co-contraction, which could be a brief burst or continuous. Normally, in repetitive alternating movements at a single joint, antagonist muscles alternate their firing. The dystonia patients might co-contract even with such quick movements. The second feature was prolongation of EMG bursts. EMG bursts of even a briefest movement usually last no longer than about 100 ms. Dystonia patients had bursts of 200 or 300 ms as well as very prolonged spasms. A third feature was tremor. A fourth feature was lack of selectivity in attempts to perform independent finger movements, and a fifth feature was occasional failure of willed activity to occur. All five features emphasize excessiveness of movements and lack of fine control.

The problem of excessive co-contraction could be due to deficient reciprocal inhibition. Reciprocal inhibition is represented at multiple levels in the central nervous system and can be evaluated in humans by the stimulation of the radial nerve at various times prior to producing an H-reflex with median nerve stimulation. The radial nerve afferents come from muscles that are antagonists to median nerve muscles. Via various pathways, the radial afferent traffic can inhibit motor neuron pools of median nerve muscles. Reciprocal inhibition is impaired in generalized dystonia, writer’s cramp, spasmodic torticollis, and blepharospasm. Valls-Solé and Hallett have evaluated the effects of radial nerve stimulation on the EMG activity of the wrist flexor muscles during a sustained contraction and showed that the first inhibitory period was reduced in patients with writer’s cramp consistent with reduced reciprocal inhibition during movement. This deficit is not limited to the symptomatic body part. For example, the soleus H-reflex of the lower limb is also abnormal in patients with cervical dystonia. Additionally, the H-reflex recovery curve showed greater disinhibition in generalized dystonia compared to cervical dystonia and normal subjects during the early inhibition phase. The late facilitation phase of the recovery curve showed higher facilitation in both generalized and cervical dystonia compared with normal controls.

Other spinal and brainstem reflexes have been studied, and a common result is that inhibitory processes are reduced in dystonia. Another example that has been extensively studied is the blink reflex recovery curve, evaluation of inhibition of a second blink reflex at short intervals from the first. The blink reflex is generated by stimulation of the supraorbital nerve and the response measured from the orbicularis oculi muscles. Its afferent limb is mediated by the ophthalmic division of the trigeminal nerve (V₁) and the efferent limb is the facial nerve. Abnormalities of blink reflex recovery were identified for blepharospasm, generalized dystonia,
spasmodic torticollis, and spasmodic dysphonia. In the last two conditions, abnormal blink reflex recovery can be seen even without clinical involvement of the eyelids. Similarly, abnormalities are seen with perioral reflexes and exteroceptive silent periods, again showing a process of disinhibition common among these various types of dystonia.

A DISORDER OF SENSORY DYSFUNCTION

On first appearance, dystonia is solely a movement disorder. Its disabling characteristics of abnormal postures and movements appear entirely motor in nature. Sensation seems normal. There are clues, however, that sensory function may not be completely normal and that sensory features play an important role. In fact, it has been shown that patients with dystonia have subtle abnormalities of graphesthesia, stereognosis, and kinesthesia.

Abnormal sensory discrimination

Psychophysical studies have revealed evidence of abnormal somatosensory spatial discrimination and temporal discrimination in dystonia patients. Temporal discrimination is the shortest time interval for which two successive stimuli are perceived as separate. This is essential for somatosensory functions such as kinesthesia, graphesthesia, vibratory sense, and stereognosis. Temporal discrimination is impaired in patients with dystonia, and the deficit is more pronounced in focal dystonia compared with the generalized form. Fiorio et al demonstrated temporal discrimination deficits not only for tactile but also for visuotactile stimuli in writer’s cramp patients. The authors suggested that their finding implies dysfunction of a neural network involving the basal ganglia, which is implicated in temporal processing and integration of visuotactile stimuli. The degree of temporal discrimination impairment is positively correlated with the degree of severity of dystonia. This discrimination deficit was identified in both the affected and unaffected hand, implying that the deficit is a result of a central process of dystonia itself, rather than a by-product of the abnormal muscle contractions.

Spatial discrimination differentiates two spatially separated stimuli and is measured as the shortest distance between the stimuli that are perceived as separate. Impaired spatial discrimination might be a clinical correlate of the abnormal finger representation in the primary somatosensory cortex (S1) seen in dystonia patients. Molloy and colleagues studied spatial sensory discrimination in a wide range of focal and generalized dystonia patients. Spatial discrimination was impaired in patients with writer’s cramp, as well as in the clinically normal hands of patients with spasmodic torticollis and blepharospasm, but unaffected in generalized DYT1 dystonia. The authors suggest that this latter finding implies a possibility of partially separate pathophysiological processes in the focal and generalized subtypes of dystonia. It is also possible that the initially impaired sensorimotor integration in generalized dystonia may have been normalized by early adaptive changes or compensatory mechanisms.

Since the sensory system is an important influence on the motor system, abnormalities of the sensory system could be relevant in causing motor dysfunction. If abnormal sensory system leads to motor symptoms of dystonia, restored sensory input may at least partially reverse these motor symptoms. Indeed, when spatial acuity improved after sensory training by Braille reading, motor improvement also followed. This strong influence of the sensory system to motor system functions and mechanism of dystonia is also nicely illustrated by the unique phenomenon of sensory tricks.

Sensory ‘tricks’

One characteristic feature of idiopathic focal dystonia is the role of sensory feedback that manifests as the little understood phenomenon of geste antagoniste or ‘tricks’, which refers to various maneuvers used by patients with focal dystonia to temporarily relieve their dystonic spasms. The most commonly noted is the geste in spasmodic torticollis, where, for example, a finger placed lightly on the face will eliminate the spasm. Such tricks are seen in all forms of dystonia. Pressure on the eyelids might improve blepharospasm, a toothpick in the mouth might relieve tongue dystonia, and sensation applied to parts of the arm might improve a writer’s cramp. It has been shown that the application of sensory tricks resulted in the reduction of EMG activity in the sternocleidomastoid, trapezius, and splenius capitis in patients with cervical dystonia. Effects of sensory tricks on cortical activation have also been demonstrated by H15O positron emission tomography (PET), showing change in activation in the parietal cortex in cervical dystonia during the application of tricks. Murase et al suggested that in patients with writer’s cramp there is a flaw in the interpretation of sensory input that occurs prior to, and perhaps during the movements, and that tricks supply this missing sensory input. The phenomenon of ‘tricks’ offers strong evidence that dystonia is also a sensory disorder.

A role of sensory input

On the other hand, sensory stimulation might trigger dystonia. This might be called a reverse geste.
Examples include a tart taste producing tongue dystonia or a loud noise producing spasmodic torticollis. Sensory symptoms may well precede the appearance of dystonia. Common examples would be a gritty sensation in the eye preceding blepharospasm and irritation of the throat preceding spasmodic dysphonia. Photophobia is an example of distorted sensation. In some situations, patients may say that they made voluntary repetitive movements in order to relieve the sensory symptom, but the movements eventually got out of voluntary control. Abnormal sensory input might well be a trigger for dystonia. Trauma to a body part is often a precedent to dystonia of that part. A blow to the head might precede torticollis, irritations of the eye are common in blepharospasm, and a deep cut of the hand might occur just before writer’s cramp develops.

There may be an important problem with processing muscle spindle input. In patients with hand cramps, vibration can induce the patient’s dystonia. Cutaneous input similar to that which produces the sensory trick can reverse the vibration-induced dystonia. Conversely, when muscular afferent inputs are blocked by lidocaine injections which leave the cutaneous afferents relatively unaffected, both action-induced and vibration-induced dystonia improve.

The brain response to somatosensory input is abnormal in dystonia. This can be demonstrated with PET studies and evoked potential studies using electroencephalography (EEG). In addition, studies of sensory receptive fields of thalamic neurons in humans with dystonia show expanded regions where all cells respond to the same passive movement. Mapping of cortical sensory areas of the different fingers is abnormal in dystonia; this is potentially consistent with the idea that there is abnormal cortical plasticity.

**A DISORDER OF DISINHIBITION**

Several studies have shown hyperexcitability of the motor cortex in dystonia. The likely explanation of the hyperexcitability is loss of inhibition. Ridding et al studied intracortical inhibition with transcranial magnetic stimulation (TMS) using the ‘double-pulse paradigm’. Motor evoked potentials (MEPs) are inhibited when conditioned by a subthreshold TMS stimulus given at intervals of 1–5 ms prior to the test stimulus. Inhibition was impaired in patients with focal hand dystonia in both affected and unaffected hemispheres. Decreased inhibition in writer’s cramp patients can also be seen with longer interstimulus intervals (ISIs), where the most prominent decrease was identified at ISIs of 60–80 ms. This deficiency was found only in the symptomatic hand and only with background contraction. This abnormality is particularly interesting since it is restricted to the symptomatic setting, as opposed to many other physiologic abnormalities in dystonia that are more generalized. Using a modified TMS double-pulse paradigm which utilized two magnetic coils and allowed for an evaluation of areas surrounding the hand motor representation and distribution of inhibition, Sommer et al demonstrated deficient intracortical inhibition in the cortical hand muscle representation not only in patients with hand dystonia but also in patients with blepharospasm whose hand muscles are clinically normal. Inhibition is also found to be defective during the preparation of movement. Gilio and colleagues studied motor cortex excitability before the execution of voluntary wrist extension in a mixed group of eight hand dystonia and two generalized dystonia patients. The decreased inhibition usually seen just before the EMG onset in normal subjects is absent in dystonia patients (Figures 4.1 and 4.2).

Another TMS measure that relates to intracortical inhibition is the silent period (SP), which refers to the duration of interruption of voluntary motor activity after TMS. Chen et al found that the SP following an MEP was slightly shorter for the symptomatic hemisphere in patients with focal hand dystonia. Moreover, the SP is shorter during dystonic contractions than during voluntary movements with the same intensity.

![Figure 4.1 Paired-pulse TMS study of both hands of patients with hand dystonia and the dominant hand of normal controls. The percent amplitude change of the conditioned MEPs is plotted against the paired-pulse interval. Normal controls show inhibition for intervals up to 6 ms (and facilitation for intervals of 10 and 15 ms). Note the loss of inhibition in both the dystonic hand and clinically normal hand of the patients compared with normal. (Reproduced from Ridding et al, with permission.)](attachment://image.png)
These findings indicate a deficiency of inhibition specifically during the dystonic contraction while normal movements occur when cortical inhibition is less impaired. The implication is that the dystonic contraction is ‘dystonic’ because of deficient inhibition, while movements performed by the same dystonia patients when cortical inhibition was unimpaired are more normal. There is also loss of inhibition produced by cutaneous stimulation. Stimulation of the median nerve or index finger typically leads to inhibition of MEPs in hand and forearm muscles at various intervals, becoming maximal at 200 ms. This inhibition is lacking in patients with focal hand dystonia who show facilitation instead. Generalized DYT1 dystonia patients have, in common with focal dystonia patients, reduced intracortical inhibition, shorter SP, and abnormal spinal reciprocal inhibition. Interestingly, carriers of the DYT1 gene who are clinically normal were found to have abnormal intracortical inhibition and SPs, but normal reciprocal inhibition of the median H-reflex. The finding of abnormal electrophysiology in non-manifesting carriers is evidence of the significant role of other modifying factors such as environmental input.

The concept of surround inhibition

Given that the central nervous system operates as a balance between excitation and inhibition, excessive movement could arise from increased excitability or reduced inhibition. Evidence has been emerging that dystonia is generated by a loss of inhibition, or, in particular, a loss of ‘surround inhibition’.

Surround inhibition is a concept well accepted in sensory physiology. For example, receptive fields in the visual cortex are organized such that light in the center of the field will activate a cell, whereas light in the periphery will inhibit it. Such a pattern helps to sharpen borders and is an important step in the formation of patterns and objects. Surround inhibition is not yet well known in the motor system, but the concept is a logical one. When making a movement, the brain must activate the motor system. The brain may simply activate the specific movement, but it is more likely that when one specific movement is generated, other possible movements are suppressed simultaneously. The suppression of unwanted movements is surround inhibition. Surround inhibition should be essential for the production of precise, functional movement, just as surround inhibition in the visual system leads to more precise perceptions. If such a surround inhibition in the motor system is lacking, it is not surprising that a disorder like dystonia should emerge.

Leocani et al evaluated corticospinal excitability of both hemispheres during the auditory reaction time (RT) tasks with movement of either the right or left hand using TMS. There is facilitation of MEP amplitudes on the side of movement in the 80–120 ms period before EMG onset, while the resting side showed inhibition. During the movement of the dominant hand, MEPs of contralateral hand muscles were suppressed for 60–100 ms after EMG onset, while the non-dominant hand movement failed to suppress MEPs of the dominant hand. This suppression of MEPs of the non-dominant hand by voluntary movements of a single digit in the dominant hand is not limited to the hand but also covers the...
proximal arm muscles that are not in any way involved in the movement, demonstrating widespread surround inhibition in normal subjects (Figure 4.3). Corticospinal inhibition on the side not to be moved suggests that suppression of movement is an active process and additional proof of this comes from studies of no-go trials.

A lack of surround inhibition

Liepert et al. used paired pulse TMS to study task-dependent modulation of cortical inhibition using muscles that act as agonist (abductor pollicis brevis, APB)-synergist (fourth dorsal interosseous muscles, 4DIO) pair in selective and non-selective tasks. Selective tasks required activation of the APB only with complete relaxation of 4DIO. In normal subjects, during selective tasks, surround inhibition could be seen as the conditioned MEP amplitudes of the agonist (APB) increased, while the conditioned MEPs of synergist were suppressed. In the non-selective task, the conditioned MEP of both muscles increased in normal and dystonia subjects. Using similar experimental design, Bütefisch et al. studied task-dependent modulation of inhibition in dystonia and showed that the during selective task, conditioned MEPs of both synergistic and agonist muscles increased in dystonia patients, demonstrating a disturbed surround inhibition in dystonia. Sohn and Hallett were able to show an inhibition of the adductor digiti minimi (an uninvolved muscle in the 'surround') when the flexor digitorum superficialis (FDS) of the second digit is activated. This effect is less in patients with focal hand dystonia.

There are also data from sensory function that are compatible with loss of inhibition. Using TMS, Tamburin et al. found increased intracortical inhibition 20–50 ms after cutaneous electrical stimulation to the fingers. In normal subjects, the inhibition is stronger in the finger receiving the stimulation itself, compared to an uninvolved surrounding finger. This difference in inhibition is lost in dystonia, consistent with a tendency towards fusion of finger representations as seen in earlier work. Tinazzi et al. studied median and ulnar nerve somatosensory evoked potentials (SEPs) in patients who had dystonia involving at least one upper limb. They compared the amplitude of spinal N13, brainstem P14, parietal N20 and P27, and frontal N30 SEPs obtained by stimulating the median and ulnar nerves simultaneously (MU), the amplitude value being obtained from the arithmetic sum of the SEPs elicited by stimulating the same nerves separately (M + U). The MU:(M + U) ratio

Figure 4.3 Time course changes in left sided MEPs triggered by right first dorsal interosseus (FDI) activation at stimulation intensity of 140% resting motor threshold (RMT). There is significant inhibition at intervals of 35 and 50 ms in FDI and extensor indicis proprius (EIP). There is a prominent, although not statistically significant inhibition in MEP amplitude of biceps brachii (BB) of 75% of control MEP at 35 and 50 ms, suggesting the spread of inhibition to muscles of the proximal arm not involved in the movement. (Reproduced from Sohn et al., with permission.)
indicates the interaction between afferent inputs from the two peripheral nerves. No significant difference was found between SEP amplitudes and latencies for individually stimulated median and ulnar nerves in dystonic patients and normal subjects, but recordings in patients yielded a significantly higher percentage ratio for spinal N13, brainstem P14, and cortical N20, P27, and N30 components. The authors state that:

these findings suggest that the inhibitory integration of afferent inputs, mainly proprioceptive inputs, coming from adjacent body parts is abnormal in dystonia. This inefficient integration, which is probably due to altered surrounding inhibition, could give rise to an abnormal motor output and might therefore contribute to the motor impairment present in dystonia.

A DISORDER OF CORTICAL MOTOR DYSFUNCTION

There are several abnormalities of the cortical motor system that suggest deficient function. The movement-related cortical potentials (MRCPs) begin with the Bereitschaftspotential, the slow negative shift of the EEG that start 1–2 seconds prior to self-initiated voluntary movements and is thought to reflect movement preparation. The Bereitschaftspotential consists of two components, the early part, which probably comes mainly from premotor cortex, and the later part, which adds a generator in the motor cortex. MRCPs associated with self-paced finger movement in patients with hand dystonia show a diminished late component. A focal abnormality of the contralateral central region was confirmed with an analysis of event-related desynchronization of the EEG prior to movement, which showed a localized deficiency in desynchronization of β-frequency activity. These results are consistent with reduced activation of the primary sensorimotor region. Feve et al studied MRCPs in patients with symptomatic dystonia, including those with lesions in the striatum, pallidum, and thalamus. Patients with bilateral lesions showed deficient gradients for the Bereitschaftspotential. With unilateral lesions, the problem was worse for the symptomatic hand. Abnormal Bereitschaftspotential amplitude was also found preceding voluntary jaw opening in patients with oromandibular dystonia. These findings confirm reduced activation of the primary sensorimotor cortex.

The contingent negative variation (CNV) is the EEG potential that appears between a warning stimulus and a go stimulus in a reaction time task. The CNV shows deficient late negativity with head turning in patients with torticollis and for hand movement in patients with writer’s cramp. This late negativity represents motor function similar to the movement-related cortical potential. Such defective negativity in the MRCP and CNV are consistent with loss of inhibition in cortical processing.

Hyperexcitability of the motor cortex has been shown in a number of studies. Using TMS, increased excitability can be demonstrated by an abnormal increase in MEP size with increasing stimulus intensity; however, there is no change in the motor threshold, nor is there any abnormality of MEP size with increase in the level of background contraction. As mentioned earlier, abnormal intracortical inhibition in dystonia patients was seen in TMS studies using the double-pulse paradigm, as well as enlarged motor maps of dystonic muscles.

All these results fit together with the hypothesis that deficient inhibition leads to motor cortex hyperexcitability. This is a likely explanation for the excessive movement seen in patients with dystonia. Strong evidence for lack of cortical inhibition leading to a disturbance of motor function similar to dystonia was obtained by Matsumura et al in several primate studies. In the first study, local application of bicuculline, a γ-aminobutyric acid (GABA) antagonist, onto the motor cortex led to disordered movement and changed the movement pattern from reciprocal inhibition of antagonist muscles to co-contraction, the movement pattern of dystonia. In the second study, the authors showed that bicuculline caused cells to lose their crisp directionality, converted unidirectional cells to bidirectional cells, and increased firing rates of most cells, including making silent cells into active ones.

Origin of the abnormality in the basal ganglia

Most of the clinical evidence points to the basal ganglia as the site of pathology in dystonia. There is some evidence that the basal ganglia do affect cortical inhibition. In conditions where the basal ganglia are affected, cortical inhibition is also altered. The first line of evidence is the effect of basal ganglia disorders on the silent period following TMS. The silent period is shortened in Parkinson’s disease and can be partially restored with dopaminergic treatment. In Huntington’s disease, the silent period is longer than normal, and this length is correlated with the degree of chorea. The second line of evidence is the dopaminergic control of short-interval, intracortical inhibition. Bromocriptine given to normal subjects will increase the amount of inhibition.

The third line of evidence is that thalamocortical influences on the cortex can be both excitatory and inhibitory, and, in some circumstances, the inhibitory influence is more profound. It is not unreasonable to think, therefore, that if cortical inhibition is diminished in dystonia the basal ganglia could be responsible.

The basal ganglia are anatomically organized to work in a center-surround mechanism. This idea of center-
surround organization was one of the possible functions of the basal ganglia circuitry suggested by Alexander and Crutcher.50 This was followed up by Mink, who detailed the possible anatomy.51 The direct pathway has a focused inhibition in the globus pallidus while the subthalamic nucleus has divergent excitation. The direct pathway (with two inhibitory synapses) is a net excitatory pathway and the indirect pathway (with three inhibitory synapses) is a net inhibitory pathway (Figure 4.4). Hence the direct pathway can be the center and the indirect pathway the surround of a center-surround mechanism.

Tremblay and Filion52 studied the reactions of single cells in the globus pallidus to stimulation in the striatum. The early inhibition was always displayed by neurons located in the center of the pallidal zone of influence of each striatal stimulation site, and was ended and often curtailed by excitation. At the periphery of the zone, excitation occurred alone or as the initial component of responses. The authors state that:

this topological arrangement suggests that excitation is used, temporally, to control the magnitude of the
central striatopallidal inhibitory signal and, spatially, to focus and contrast it onto a restricted number of pallidal neurons.

In interpreting these data, it is important to remember that the output of the globus pallidus is inhibitory, so that inhibition would be the ‘center’ signal and excitation the ‘surround’ signal.

The cortex also has anatomic and functional connections that allow for surround inhibition. Activation of a region gives rise to activity in short inhibitory interneurons that inhibit nearby neurons. This pattern has been well characterized in models of focal epilepsy where neurons surrounding a focus are inhibited.

**GENESIS OF DYSTONIA FROM REPETITIVE ACTIVITY**

Studies of focal dystonia provide a variety of lines of evidence that this form of the disorder could arise from aberrant motor learning, possibly on a substrate of an abnormal motor system produced by a genetic or other abnormality. The basic idea is that repetitive activity leads to enlargement of the regions of the brain involved with that activity. If the enlargement gets out of control, perhaps dystonia develops. Loss of inhibition might be a substrate that would permit excessive plastic changes. In an animal model, a facial palsy coupled with dopamine deficiency can produce blepharospasm.53 The facial palsy will lead to an increased gain of eye closure, and with the appropriate background abnormality produced by the dopamine deficiency, the dystonia can develop. Facial palsy can be a precedent to blepharospasm in humans and can increase blink reflex excitability.54 Hence, a situation similar to the animal model might exist in humans.

In another animal model, repetitive activity of the hand can induce a motor disorder akin to dystonia that is associated with enlargement of somatosensory receptive fields of neurons in primary sensory cortex.55 As noted earlier, enlarged somatosensory fields are seen in thalamic neurons in patients with dystonia, and SEP studies are compatible with enlargement and overlap of sensory receptive fields. Thus, there can be similar pathology of sensory as well as motor function in dystonia.

**PLASTICITY**

The idea that repetitive activity can lead to dystonia is made more attractive by the finding that plasticity itself is abnormal. This was first found as an abnormal plasticity of the motor cortex in patients with focal hand

---

**Figure 4.4** Model diagram of the basal ganglia showing possible pathways for surround inhibition. The center is the direct pathway and produces the desired movement. The periphery is the indirect pathway and functions to suppress unwanted movements. GPi is the internal division of the globus pallidus; STN is the subthalamic nucleus; VLo/MEA is the oralis portion of the ventrolateral nucleus of the thalamus and the midbrain extrapyramidal area. (Reproduced from Mink,51 with permission.)
dystonia\textsuperscript{56} demonstrated using the technique of paired associative stimulation. In paired associative stimulation, a median nerve shock is paired with a TMS pulse to the sensorimotor cortex timed to be immediately after the arrival of the sensory volley. This intervention increases the amplitude of the MEP produced by TMS to the motor cortex. Paired associative stimulation produces motor learning similar to long-term potentiation. In patients with dystonia, paired associative stimulation produces a larger increase in the MEP than what is seen in normal subjects. These results have been confirmed.\textsuperscript{57}

Another technique that shows increased plasticity is the pairing of high-frequency stimulation of the supraorbital nerve during the R2 of the blink reflex. This leads to an increase in the R2, and this increase is exaggerated in patients with blepharospasm.\textsuperscript{58} There is also an abnormality in homeostatic plasticity.\textsuperscript{59} Homeostatic plasticity is the phenomenon whereby plasticity remains within limits; this can be exceeded in dystonia.

It is probably relevant that increased plasticity may arise from decreased inhibition, so the inhibitory problem may well be more fundamental.

CONCLUSION

Evidence has accumulated showing that dystonia is a disorder of central nervous system inhibition that affects sensory as well as motor function. A model of dystonia as a disease with abnormal ‘surround inhibition’ may explain the generation of uncontrolled excessive movements. Dystonia could result from dysfunction of the basal ganglia which fails to focus movement. Focal hand dystonia appears to be caused by repetitive use of the dystonic body parts, and this suggests an important role for plasticity. Clearly, dystonia also has some hereditary component. There appears to be a requirement for a combination of a background central nervous system abnormality, perhaps genetically based, and a genetic modifier, such as an environmental influence.

ACKNOWLEDGMENT


REFERENCES

22. Ridding MC, Sheean G, Rothwell JC, Inzelberg R, Kujirai T. Changes in the balance between motor cortical excitation and
INTRODUCTION

Primary torsion dystonia (PTD) has been generally conceptualized as a functional disorder of the basal ganglia and its output. Electrophysiologic studies have revealed abnormal input from the thalamus to the premotor cortex (PMC) attributable to alterations in the activity of pallidal projections to the ventral tier and intralaminar thalamic nuclei, as well as to overexcitability of PMC regions. By contrast, postmortem studies have failed to reveal substantial structural or neurochemical changes in the brains of PTD patients. In this context, functional imaging can provide a unique in-vivo tool to expand the current understanding of the pathophysiology of PTD and related disorders.

In this chapter we review imaging studies on resting state metabolism in PTD as well as in dopamine-responsive dystonia (DRD). We further discuss the impact of these changes on regional activation responses during motor, sensory, and cognitive tasks. Additionally, we present data on dopamine metabolism and discuss the potential relevance of these findings to the pathophysiology of the dystonias.

PRIMARY TORSION DYSTONIA

Abnormal resting state metabolism

Despite the promising nature of in-vivo functional imaging, investigations of resting regional metabolism in dystonia have yielded conflicting results, particularly in the highly relevant corpus striatum and globus pallidus. Positron emission tomography (PET) with $^{18}F$-fluorodeoxyglucose (FDG) in the resting state is an indicator of local synaptic activity in the brain tissue. This versatile imaging method does not require a simultaneous behavioral challenge, and has the advantages of high-signal, technical simplicity, and increasingly widespread availability. While some studies using radiolabeled FDG have reported increased striatal glucose utilization in PTD, other studies have demonstrated decreased striatal metabolism. Because the heterogeneity of dystonia cohorts could potentially confound imaging results, we have focused our studies on genotypically and phenotypically homogeneous groups. Using a novel regional network analytical approach in PTD patients, we identified a reproducible pattern of abnormal regional glucose utilization in two independent cohorts of clinically non-manifesting DYT1 carriers. We found that these subjects express a specific metabolic topography characterized by increases in the posterior putamen/globus pallidus, cerebellum, and supplementary motor area (SMA). In an ancillary study, we demonstrated that this abnormal torsion dystonia-related pattern (TDRP) was also present in clinically affected patients, persisting even following the suppression of involuntary dystonic movements by sleep induction. Moreover, abnormal TDRP expression proved not to be specific for the DYT1 genotype: it was also detected in a cohort of manifesting and non-manifesting carriers of the DYT6 dystonia mutation (North American Mennonites), but not in DRD patients. In summary, these findings suggest that TDRP expression is a feature of certain primary dystonia genotypes and is not only linked to the presence of clinical manifestations.

Despite the presence of a distinct metabolic network as a shared trait feature in manifesting and non-manifesting DYT1 and DYT6 mutation carriers, functional activity within TDRP nodes may differ across genotypes (DYT1 and DYT6) and phenotypes (manifesting and non-manifesting). Manifesting carriers of both genotypes exhibited hypermetabolism in the
pre-supplementary motor area (Pre-SMA, BA 6) and parietal association cortices (BA 40/7) compared to their non-manifesting counterparts. These regional changes were also present when compared to age-matched gene-negative controls (Figure 5.1). The Pre-SMA is thought to be in a key function in higher-order motor planning, while the superior parietal cortices function as visuomotor integrators. Therefore, these observations support the notion of dystonia as a syndrome of abnormal movement preparation caused by defective sensorimotor integration.19 In addition, regardless of clinical penetrance, genotype-specific metabolic increases in DYT1 carriers were present in the putamen and cerebellar hemispheres bilaterally. By contrast, DYT6 carriers have relative hypometabolism of the putamen, associated with hypermetabolism in the middle temporal gyrus (BA 21). Thus, the neocortical changes in Pre-SMA and parietal cortex may be a constant feature of the phenomenology of dystonia; the subcortical metabolic changes may relate to the underlying pathologic mechanisms associated with different PTD mutations. The genotype-specific differences in local metabolic activity suggest that primary dystonia may be mediated by a variety of biologic mechanisms depending on the nature of the underlying mutation.

Abnormal motor activation patterns

The presence of an abnormal resting metabolic topography may affect the functional activity of key nodes of the motor cortico-striato-pallido-thalamo-cortical (CSPTC) loops and related cerebellar pathways.14,20,21 Activation studies are usually performed with $^{15}$O-water ($H_2^{15}O$) and PET to describe changes in regional cerebral blood flow (rCBF). Alternatively, functional magnetic resonance imaging (fMRI) measures the blood oxygenation level dependent (BOLD) response. The meaning of this signal is not yet clearly understood, but it is believed to reflect changes in local hemodynamics.22 Overall, activation studies in dystonia have demonstrated differences in brain activation responses mainly in the prefrontal cortex and the sensorimotor cortex (SMC). However, these results have largely differed regarding the amount and the direction of these differences. In idiopathic generalized dystonia, simple motor execution was related to relative activation increases in the prefrontal cortex, PMC,23–25 and putamen23,24 concomitant with relatively decreased activation of the SMC.23,24 Studies into writers’ cramp have been more conflicting. Some studies showed SMC overactivation during symptom-provoking writing tasks26–28 or during simple motor execution.29 Yet others demonstrated relatively decreased activity in the SMC during writing25 or during sustained contraction30,31 as well as during relaxation.31 Additionally, increased activity was found in PMC26,27,32 and the cerebellum26,27,32 as well as in the thalamus26,27 and parietal association cortices.32 Contrasting with the results in writers’ cramp as one form of task-induced hand dystonia, musicians’ dystonia studied in fMRI33 was characterized by the reverse pattern, i.e. an overactivity of the primary motor cortex concomitant to an under-activation of PMC. Importantly, recent studies have demonstrated somatotopic disorganization of motor activation in writers’ cramp with impaired segregation of cortical24 and putamenal55 activation. Similarly, Blood and colleagues29 recently reported putaminal dysfunction in focal hand dystonia. They found abnormally persistent activation of the putamen during rest periods after tapping and suggested that these elevations reflected impaired inhibitory control within the basal ganglia.

Similar to the results in focal hand dystonia, studies into orofacial dystonia have yielded heterogeneous results. Blepharospasm was related to dysfunction of the putamen during eyelid spasm periods.36 Symptom-provoking vocal tasks demonstrated marked activation deficits of the SMC37 and PMC37,38 in orofacial dystonia. In addition, relatively increased activation of the SMC and somatosensory cortex was found independent of the affected body part during whistling.37 Activation studies in affected dystonia subjects may be confounded by the epiphenomena of abnormal movement, such as smaller ranges of motion, or by harder button presses. In our studies, we therefore
chose to use kinematically controlled tasks\(^\text{39}\) and to focus our investigations on non-manifesting \(DYT\) gene carriers. We used a simple motor task that required subjects to reach for radially arrayed targets in a predictable order with their right hand. Compared to controls, \(DYTI\) carriers had increased activation in the right SMA, the left lateral PMC, and inferior parietal cortex (BA 40).\(^\text{40}\) By contrast, a relative reduction in motor activation was present in \(DYTI\) carriers in the left posterior medial cerebellum, possibly reflecting the functional consequences of increased deposition of torsin A in this region.\(^\text{41,42}\) Notably, these abnormalities in regional activation were present in carriers, despite normal movement trajectories.\(^\text{40}\)

As the basal ganglia have been shown to mediate specific aspects of motor learning, especially the process of combining individual movements into sequences,\(^\text{43}\) we selected motor sequence learning as a behavioral paradigm to study brain-performance relationships in \(DYTI\) carriers.\(^\text{44}\) Interestingly, non-manifesting \(DYTI\) gene carriers, despite being otherwise highly functional, exhibited a striking deficit in motor sequence learning performance: the mean learning index across cycles\(^\text{39,45}\) was only 17.5 in \(DYTI\) gene carriers as compared to 42 in controls \((p < 0.008)\). As mentioned above, movements to predictable targets were unimpaired in the \(DYTI\) carriers as well as movements to random, unpredictable targets. In ancillary studies, we found that the deficit in sequence learning was not specific for motor functioning, but was also evident in a purely observational sequence learning paradigm.

To assess brain activation responses during task performance, we scanned seven \(DYTI\) gene carriers and seven age-matched controls with \(\text{H}_2\text{O}\) and PET while they performed two kinematically controlled sequence-learning tasks. Similar to the simple motor execution task, which served as the control, subjects had to reach for eight radially arrayed targets. However, in the motor sequence learning task (MSEQ), the eight targets appeared in an unknown, but repeating order over the 90s trial block. Additionally, in a trial-and-error guided sequence learning task (TE-SEQ), subjects had to detect the sequence order by reaching for the targets (video clips of all tasks are available at \(\text{http://feinsteinneuroscience.org}\)).\(^\text{46,47}\)

Activation patterns during MSEQ and TE-SEQ showed significant group differences. During MSEQ, non-manifesting \(DYTI\) carriers displayed significantly greater activation than controls in the right pre-SMA and posterior parietal cortex, the right anterior cerebellum, and the left prefrontal cortex.\(^\text{40}\) Nonetheless, this overactivation did not result in normal learning performance. For the analyses of TE-SEQ we used a parametric design\(^\text{48}\) and compared the two groups at equiperformance. \(DYTI\) carriers achieved an accuracy of 58.3% correct hit rate, with a group mean of 5.7 targets, and were accordingly matched to a group of healthy age-matched volunteers who performed TE-SEQ at the same level of accuracy. To achieve control performance levels, the \(DYTI\) carriers utilized more activation (right) in the cerebellar hemispheres, with comparatively less activation (left) in the premotor region \((p < 0.001, \text{uncorrected})\).

In order to expand these observations, we used network analysis to study the relationship between learning performance and patterns of brain activation in \(DYTI\) gene carriers. In previous \(\text{H}_2\text{O}\) studies of sequence learning,\(^\text{49}\) we identified a specific regional covariance pattern involving caudate, prefrontal, and posterior parietal activation that was highly correlated with the learning achieved during imaging in both healthy volunteers and in patients with Parkinson’s disease. While reproducible in three independent populations,\(^\text{45}\) this learning network failed to predict performance in the \(DYTI\) carrier group. To detect an
alternative network that mediates sequence learning in mutation carriers, we performed an exploratory analysis restricted only to gene-positive subjects. Indeed, a significant network with novel topography was identified in the \( \text{H}_2^{15}\text{O} \) PET data of these subjects scanned during motor sequence learning. This learning-related pattern was associated with activation in regions not generally employed by control subjects performing the same task. In particular, significant contributions to the network \((p < 0.01)\) were detected in the cerebellar cortex and dentate nucleus, as well as in the ventral prefrontal cortex. Interestingly, the caudate nucleus and the premotor regions contributed significantly to the learning network in normals, but not in \( \text{DYT1} \) carriers.

The presence of a different learning network in non-manifesting gene carriers raises the possibility of functional reorganization of frontostriatal pathways in these subjects, perhaps on a genetic and/or developmental basis. Indeed, using diffusion tensor MRI, we have recently detected impaired integrity of the subgyral white matter of the SMC in \( \text{DYT1} \) gene carriers. Abnormal anatomic connectivity of the SMC may contribute to the vulnerability of \( \text{DYT1} \) gene carriers for the development of torsion dystonia. Additionally, metabolic changes in the basal ganglia may lead to the shift from striatal to cerebellar processing as a feature of the \( \text{DYT1} \) carrier state. Notably, while activation changes during the simple execution task can be effective in compensating for resting metabolic pathology in non-manifesting carriers, such changes appear to be inadequate to achieve a normal degree of sequence learning performance. The presence of dystonic manifestations in select gene carriers may reflect an upper bound ('ceiling effect') for compensatory brain activation that is exceeded in a subset of individuals at risk.

**Abnormal sensory activation patterns**

Impaired sensory integration has also been discussed as a pathologic mechanism in dystonia. Experimental animal data have suggested that focal dystonias can result from dysfunctional remodeling of sensory cortical areas after peripheral distress. However, even in the absence of precipitating peripheral strain, abnormalities in sensorimotor integration have been illustrated by electrophysiologic means. To date, a line of neuroimaging research provides substantial evidence for impaired sensorimotor information processing in focal dystonias. Subjects with focal hand dystonia showed decreased responses to vibration in the hand region of the primary sensorimotor area and SMA of the affected or unaffected hand. Similarly, they also showed altered processing of simultaneous sensory stimuli. Expanding on these observations, impaired sensorimotor and somatosensory activation during sensory stimulation was also seen in subsequent cohorts. Feiwell and colleagues proposed a region-specific processing deficit in blepharospasm subjects, as the activation differences were most pronounced when the stimulus was localized to the face, while responses to vibrotactile stimulation of the hands only showed subthreshold differences. Taking advantage from the high resolution in MRI and stable source localization in magnetoencephalography, researchers were able to demonstrate differences in the cortical separation of digit representation in focal hand dystonia. Cortical representations of digits were clearly separated in controls but showed substantial overlap or reduced distances in affecteds. Whereas this line of research has established impaired somatosensory cortical processing, only one recent study (interestingly) identified altered basal ganglia activation in the context of sensory discrimination.

It has long been recognized that the so-called geste antagoniste, consisting of a sensory stimulation of the affected body part or an adjacent area, can effectively alleviate dystonic symptoms. Naumann et al demonstrated decreases in the ipsilateral SMA and sensorimotor cortex activation along with increases in the parietal cortex with the geste antagoniste. Although activation changes were not compared to controls in this study, the reported changes probably reflect a normalization of activation, as increased SMA metabolism is a characteristic of dystonic symptomatology in other rCBF studies.

**Treatment effects on brain activation**

To date, imaging studies have not played a major role in measuring treatment effects. Although botulinum toxin is the most effective therapy for focal dystonias, Ceballos-Baumann and colleagues demonstrated that the alleviating effect is symptomatic but does not reverse the cortical dysfunction associated with dystonia. Utilizing \( \text{H}_2^{15}\text{O} \) PET, they showed that brain activation responses increased during writing after botulinum toxin treatment in the parietal cortex and, importantly, in the SMA. Because these areas exhibit overactivation in writers’ cramp without treatment, it is conceivable that botulinum toxin treatment leads to compensatory brain activation rather than supporting adaptive changes by normalizing rCBF. Nonetheless, activation in the primary sensory cortex was facilitated by treatment, whereas it was inhibited relative to controls without therapy.

Deep brain stimulation (DBS) of the internal globus pallidus (Gpi) has recently been found to be safe and
effective in the treatment of PTD patients with medically intractable symptoms, especially DYT1 carriers.\(^{65}\) The mechanism by which this intervention alleviates dystonia is not known, although a reduction in the noise of pallidal output pathways with restoration of a more tonic pattern has been suggested.\(^{1}\) In a single case report,\(^{66}\) GPi DBS in dystonia was associated with comparatively reduced brain activation during joystick movements in the lateral and medial premotor cortices, SMC, anterior cingulate, and prefrontal cortices. By contrast, no motor activation increases with GPi DBS were found in a more recent study.\(^{25}\) In this study on six patients with primary generalized dystonia, unilateral GPi DBS induced relative decreases in motor activation in the prefrontal and temporal cortex as well as in the putamen and thalamus. Notably, the prefrontal cortex was the only region where abnormally increased motor activation at baseline was reversed by the treatment intervention. Thus, to date, imaging studies on the treatment effects in dystonia have failed to support the idea of a treatment-induced normalization of activation patterns.

**Dopamine metabolism**

PET also provides valuable measures on neurochemical changes in vivo. Early studies on the presynaptic dopaminergic function in PTD using \([^{18}F]\)-dopa PET found only slight uptake reductions in the putamen.\(^{67}\) Playford et al concluded that these mild reductions were unlikely to represent the major mechanism of pathology, although uptake in the three most severely affected subjects was outside the 2 SD ranges of normal controls.\(^{67}\) By contrast, Perlmutter et al,\(^{68}\) using \([^{18}F]\)-spiperone, showed a significantly decreased D\(_2\) receptor availability. We studied nine non-manifesting DYT1 gene carriers using \([^{11}C]\)-raclopride and PET to measure D\(_2\) receptor binding, and found a 14% reduction in both the putamen and caudate (\(p < 0.01\)).\(^{69}\) The magnitude of this estimated striatal reduction was less pronounced than the 29% reduction reported previously in focal dystonia.\(^{68}\) These data suggest that a threshold of D\(_2\) receptor availability may exist for the development of dystonic manifestations to appear. In other words, a subthreshold reduction of D\(_2\) receptor availability as seen in our cohort of non-manifesting DYT1 gene carriers may represent a genetically mediated ‘at risk’ state, while a more pronounced reduction may be needed for the development of actual clinical manifestations. However, to date, a marked reduction of dopamine content in the rostral putamen and caudate (54% and 50% of age-matched control values) has been reported in only one DYT1 autopsy case.\(^{70}\) An increase in dopamine turnover with trends toward D\(_1\) and D\(_2\) neuroreceptor binding loss was subsequently reported,\(^{51}\) without reduction in dopamine content. The role of dopaminergic transmission in DYT1 dystonia remains unclear. Indeed, the reported decrements in \([^{11}C]\)-raclopride binding in DYT1 dystonia may represent an effect of increased dopamine turnover alone, or in the company of D\(_2\) neuroreceptor loss.

**DOPAMINE-RESPONSIVE DYSTONIA**

Dopamine-responsive dystonia is an autosomal dominant inherited dystonia caused by mutation in the gene of the GTP cyclohydrolase 1 (GCH1).\(^{71}\) This mutation induces a dopaminergic deficit in the absence of histopathologic changes.\(^{72,73}\) A partial deficiency of tetrahydrobiopterin (BH\(_4\)) affects the function of tyrosine hydroxylase, the rate-limiting enzyme of dopamine synthesis. DRD is characterized by childhood onset and marked diurnal fluctuation.\(^{76}\) Although sharing the symptoms of dystonic impairment with primary torsion dystonia, DRD is distinguished from other early-onset dystonias by its profound and sustained response to low-dose \(l\)-dopa.

**Dopamine metabolism**

Although the rate of dopamine synthesis is impaired, presynaptic nigrostriatal dopamine function assessed by PET imaging appears to be only mildly impaired in DRD. Snow et al\(^{77}\) used \([^{18}F]\)-fluoro-\(l\)-dopa (F-DOPA) PET measures and reported normal striatal tracer uptake in DRD patients. By contrast, Sawle and colleagues\(^{80}\) found a mild but significant striatal F-DOPA uptake reduction. These finding suggest that \(l\)-dopa uptake, decarboxylation, and storage mechanisms are generally intact in DRD, as opposed to juvenile Parkinson’s disease (JPD). Other studies have demonstrated that dopamine transporter (DAT) density measured with \([^{123}I]\)-\(2\beta\)-carbomethoxy-3\(\beta\)-(4-iodophenyl)-N-(3-fluoropropyl)-nortropane (FP-CIT),\(^{82}\) was normal in DRD. Particular emphasis should be paid to the differentiation of JPD and clinical atypical DRD. Normal striatal DAT binding in a young parkinsonian patient points to a non-degenerative cause of parkinsonism and differentiates DRD from JPD. Similarly, postsynaptic dopaminergic function also appears to be minimally altered in DRD. Putamen and caudate D\(_2\) receptor binding was found to be mildly increased in \([^{11}C]\)-raclopride PET studies.\(^{83,84}\) The mild elevation of tracer uptake could possibly be due to compensatory up-regulation of dopamine D\(_2\) receptor density. Alternatively, the increased D\(_2\) binding could also reflect low synaptic dopamine concentration, which in turn...
Glucose metabolism in DRD

To examine the possibility that dopaminergic dysfunction in DRD is reflected by downstream changes in regional glucose utilization, we used FDG PET to assess metabolic network activity: specifically, we explored the possibility that the clinical distinction from other early-onset dystonias is linked to a parallel difference in resting glucose metabolism. Prospectively calculated network expression of the TDRP (see above) in a cohort of DRD subjects confirmed that the latter group does not express the abnormal increases seen in PTD mutation carriers.86 Similarly, the DRD group did not express the previously described metabolic network associated with Parkinson's disease.21,85 Network analysis of DRD patients and controls did, however, reveal a distinct disease-related pattern accurately discriminating the two groups (p < 0.005).86 This DRD-related pattern was characterized by bilateral metabolic increases in the supplemental motor areas and cerebellar hemispheres, associated with bilateral decrements in primary motor cortex and PMC, as well as ventral prefrontal cortex (BA 10/11). In a final analytical step, we found that DYTI carriers, even if affected, did not express this pattern, confirming both a unique clinical and metabolic phenotype.

In summary, functional imaging in dystonia can broaden our understanding of the pathologic mechanisms underlying clinically different subgroups within the dystonia spectrum. The identification of abnormal brain metabolism in dystonia has several practical implications. The presence of genotype-specific metabolic changes can possibly support linkage studies. Additionally, disease-related networks can prove useful for assessing mechanisms of therapeutic interventions, as has been demonstrated in Parkinson's disease.87,88 A combined network-performance approach may be especially relevant in characterizing the effects of treatment on higher-order motor functioning.21,45

ACKNOWLEDGMENTS

This work was supported by the National Institutes of Health (NIH RO1 NS 37564) and the Dystonia Medical Research Foundation. Dr Eidelberg was supported by NIH K24 NS 02101. In particular, the authors wish to thank Mr Nathaniel Brown and Mrs Toni Flanagan for valuable editorial assistance.

REFERENCES

22. Heeger DJ, Ress D. What does fMRI tell us about neuronal 
20. Wichmann T, DeLong MR. Functional and pathophysiological 
18. Carbon M, Su S, Dhawan V et al. Regional metabolism in 
CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA


DYT1 dystonia

Laurie J Ozelius and Susan B Bressman

INTRODUCTION

In 1908, Schwalbe described an Eastern European family of Ashkenazi Jewish descent in which three siblings were affected with childhood-onset dystonia. The term dystonia was not yet coined and Schwalbe called them chronic cramps; he also described the movements as hysterical. Three years later, Oppenheim reported the same disorder, invented the term dystonia, argued for an organic basis, and named the condition dystonia musculorum deformans. Because of his contribution characterizing this form of dystonia, DYT1 dystonia has also been named ‘Oppenheim’s dystonia’. But Oppenheim didn’t recognize that the disorder was inherited; that was considered in yet another report. Thus, within its very first descriptions, lay important clues to the etiology of DYT1 dystonia. But for over half a century progress was stymied. In part this was due to nosologic confusion and the lumping of what we now categorize as primary and secondary dystonias. Racist political doctrine also contributed. In 1944 Herz resurrected primary dystonia as a distinct condition, but he chose to ignore its predilection to affect Jews. He wrote:

I have not elaborated on the possible prevalence of dystonia in any one group . . . recent experiences with Rassebiologie have been so depressing and grotesque that they do not encourage speculations.

The changing political and scientific environments over the last 30 years have, thankfully, led to a flourishing in our knowledge. Astute clinical observation and disease classification, led by David Marsden and Stanley Fahn, along with the application of genetic epidemiologic tools and molecular advances, have been critical to progress in our understanding of both primary dystonia and secondary dystonias. This chapter provides an overview of dystonia caused by mutations in the DYT1 gene, describing clinical and genetic aspects as well as current knowledge of the encoded protein, torsinA.

EARLY-ONSET PRIMARY DYSTONIA AND IDENTIFYING DYT1

As alluded to above, early-onset primary dystonia was first described by Schwalbe and Oppenheim and its familial nature was noted. Over 50 years later, in a hallmark paper, Zeman and Dyken analyzed pedigrees of 253 primary dystonia cases and concluded that the disorder was inherited as an autosomal trait with reduced penetrance; they also estimated a fivefold increased gene frequency in Ashkenazi Jews compared to non-Jews. Subsequent systematic family studies confirmed autosomal dominant transmission with reduced penetrance of 30–40% in Ashkenazi Jews and non-Ashkenazim and confirmed a higher prevalence in Jews. Because of the reduced penetrance, large multiplex families with this phenotype are uncommon. Using one such large North American non-Jewish family with 13 affected members, a gene for early-onset primary dystonia (DYT1) was mapped to chromosome 9q32-34 in 1989. Clinically similar Ashkenazi and non-Jewish families were subsequently also found to be linked to the same 9q region. A common haplotype spanning about 2 cM indicative of linkage disequilibrium was then identified among Ashkenazi Jews. The finding of linkage disequilibrium supported the idea posited earlier by Risch et al. that a single mutational event is responsible for most early-onset primary dystonia in the Ashkenazi population. Using haplotype data across this 2 cM interval, Risch and colleagues calculated that the mutation was introduced into the Ashkenazi population about 350 years ago and probably originated in Lithuania or Byelorussia. They also argued that the current high prevalence of the disease in Ashkenazim (estimated to be about 1:3000–1:9000, with a gene
frequency of about 1:2000–1:6000) is due to the tremendous growth of that population in the 18th century from a small reproducing founder population. A founder mutation and genetic drift (changes in gene frequency due to chance events such as migrations, population expansions), rather than a heterozygote advantage (i.e. non-penetrant DYTI carriers have some advantage that leads to carriers being more prevalent), is probably responsible for the high frequency of DYTI dystonia in Ashkenazim.

Examining the haplotypes for the markers in linkage disequilibrium, evolutionary recombination events were identified among Ashkenazi families that defined the candidate gene to a 150 kb region containing four genes. An in-frame deletion of three base pairs (GAG) was identified in the coding sequence of one of these genes, DYTI; it was present in affected members from both Ashkenazi and non-Jewish primary dystonia families, but not controls. Subsequently, this same mutation was found in families of diverse ethnic backgrounds. Haplotype analysis indicated that deletions in the non-Ashkenazi population originated from multiple independent mutation events, including de-novo mutations. In contrast, among the great majority of Ashkenazi Jews, the GAG deletion derives from the same founder mutation. The reason for the GAG deletion’s singular disease-causing status is not known but it is hypothesized that genetic instability due to an imperfect tandem 24 bp repeat in the region of the deletion leads to an increased frequency of the mutation.

Despite extensive screening the GAG deletion is the only definitive DYTI disease-producing mutation identified to date. Three other variations in DYTI have been found that change the amino acid sequence, but none have been unequivocally associated with disease. First, an 18 bp deletion causes loss of residues 323–328 and was identified in a family that included affected individuals with both dystonia and myoclonus. This family was later found to have a mutation in the ε-sarcoglycan gene, thus casting doubt on whether the 18 bp deletion contributes to disease. A second deletion of 4 bp was identified which causes a frameshift and truncation starting at residue 312; however, this was found in a single control blood donor who was not examined neurologically. Finally, a polymorphism in the coding sequence for residue 216 encodes aspartic acid in 88% and histidine in 12% of alleles in control populations and its disease-modifying effects are discussed below.

**GENE AND PROTEIN PROPERTIES**

The DYTI (also known as TOR1A) cDNA is 998 bp long and encodes two ubiquitously expressed messages on Northern blot analysis of 1.8 kb and 2.2 kb. These two messages are a consequence of two poly-A addition sites in the 3’ untranslated region of the gene. Sequence analysis of the human genome reveals three other genes that are highly homologous to DYTI: TOR1B, TOR2A, and TOR3A. TOR1B is 70% identical to DYTI at both the DNA and protein level. The two genes each have five exons with their splice sites conserved. They are located in a tail-to-tail orientation adjacent to each other on chromosome 9q34 and presumably arose from a tandem duplication of an evolutionary precursor gene. TOR2A and TOR3A, share about 50% homology with DYTI at the amino acid level (References 27 and 32, unpublished results). TOR2A also has a similar structure, with five exons encoding a 321 amino acid protein. It is located about 10 cM centromeric to DYTI and TOR1B on chromosome 9q34. TOR3A is also known as ADIR1 (ATP-dependent interferon responsive gene), as it was independently cloned by virtue of transcriptional regulation in response to γ-interferon.

It is located on chromosome 1q24 and has alternative splicing of a sixth exon, resulting in two protein products of 397 amino acids or 336 amino acids (ADIR2). All three DYTI homologs, TOR1B, TOR2A, and TOR3A, are ubiquitously expressed by Northern blot analysis. Comparative sequence analyses have revealed torsin-like genes, in mouse, rat, nematode, fruit fly, pig, cow, zebrafish, chicken, hamster, and Xenopus.

The DYTI gene encodes a 332 amino acid (37 kDa) protein called torsinA. The protein has a signal sequence and membrane-spanning region in the N-terminus as well as a glycosylation site and putative phosphorylation sites. The 3 bp GAG deletion in the DYTI gene results in the loss of one of a pair of glutamic acid residues in the C-terminal region of the protein. Analysis of torsinA protein sequence reveals that it is a novel member of a superfamily of ATPases associated with a variety of cellular activities (AAA+). These proteins typically possess Mg2+-dependent ATPase activity, form six-membered homomeric ring structures, and share a secondary structure. This superfamily of chaperone proteins mediates conformational changes in target proteins and performs a variety of functions, including degradation of denatured proteins, membrane trafficking, vesicle fusion and organelle movement, cytoskeletal dynamics, and correct folding of nascent proteins. Studies carried out both in vivo and in vitro and documented below suggest several of these are plausible functions for torsinA.

TorsinA is widely expressed in most cells in the body. In normal adult brain, torsinA is widely distributed with intense expression in substantia nigra dopamine neurons, cerebellar Purkinje cells, thalamus, globus pallidus, hippocampal formation, and cerebral cortex.
Both the mRNA and protein are localized to neurons and not to glia, and protein studies also showed torsinA in neuronal processes. Labeling is predominantly present in cytoplasm with some perinuclear staining. A similar widespread pattern of expression is seen in mouse and rat brains. Ultrastructural studies in human adult and macaque striatum demonstrate torsinA immunostaining of small vesicles in the presynaptic terminals, consistent with a role in modulating striatal signaling. A second study of four DYT1-positive brains found ubiquitin-positive perinuclear inclusions in the midbrain reticular formation and the periaqueductal gray but not in the substantia nigra, striatum, hippocampus, or select regions of the cerebral cortex. Although this finding has not been replicated in human brains, similar inclusions have been reported in several DYT1 mouse models.

**CELLULAR AND ANIMAL MODELS OF DISEASE**

**In vitro**

Cellular studies indicate that the majority of torsinA is in the lumen of the endoplasmic reticulum (ER), consistent with its deduced signal sequence and the observed high mannose content. Several studies suggest torsinA is associated with the ER membrane through its hydrophobic N-terminal region. However, according to a recent report, torsinA appears to be associated peripherally with the ER membrane, possibly through an interaction with an integral membrane protein. In cellular models with GAG-deleted torsinA there is a striking redistribution of torsinA from the ER to the nuclear envelope (NE). This also occurs with the introduction of an E171Q mutation in torsinA from the ER to the nuclear envelope (NE). This enrichment is presumably due to prolonged interaction of torsinA with substrate(s) at the NE.

**OF DISEASE**

In a study of a single DYT1-positive (i.e. with the DYT1 GAG deletion) brain, nigral cellularity was normal as were striatal dopamine and homovanillic acid levels, except in the rostral portions of the putamen and caudate nucleus, where they were slightly decreased compared with controls. Although this suggests that the DYT1 GAG deletion mutation is not associated with significant damage to the nigrostriatal dopaminergic system, an increase in the ratio of dopamine metabolites to dopamine compared to controls was reported in a second study of four DYT1 brains, consistent with increased dopamine turnover. At the protein level, several studies have not found torsinA immunostaining pattern differences between DYT1-positive, DYT1-negative, and control brains. However, comparing DYT1-positive and DYT1-negative brains to controls, larger and more closely spaced nigral dopaminergic neurons were identified in DYT1-positive dystonia brains as compared to controls. However, no evidence was found for neuronal loss, suggesting a functional rather than degenerative etiology. A further study examining four DYT1-positive brains found ubiquitin-positive perinuclear inclusions in the midbrain reticular formation and the periaqueductal gray but not in the substantia nigra, striatum, hippocampus, or select regions of the cerebral cortex. Although this finding has not been replicated in human brains, similar inclusions have been reported in several DYT1 mouse models.
with a role for torsinA in intracellular trafficking and an association with the cytoskeleton.

The role of torsinA in cellular stress has been examined by several different groups. Overexpression of wild-type but not mutant torsinA suppresses α-synuclein aggregation in cells.\(^7\) In PC12 cells, levels of endogenous torsinA increase and the protein redistributes in response to oxidative stress.\(^7\) Furthermore, overexpression of torsinA in both COS-1 and PC12 cells protects against cell death when cells are exposed to a variety of toxic insults.\(^7,7\) Taken together with the in-vivo experiments described below\(^7\), these studies point to a chaperone function for torsinA.

**Non-mammalian models**

In addition to the mammalian torsin family members, there are several torsin orthologs, including a single torsin-like gene in *Drosophila* and zebrafish and three torsin-related genes in nematodes.\(^27\) One of the nematode genes, OOC-5, is critical for rotation of the nuclear-centrosome complex during embryogenesis and, when defective, leads to misorientation of the mitotic spindle and disruption of asymmetric cell division and cell fate determination.\(^7\) Taken together with the information that torsinA interacts with KLC1\(^7\) and VIM,\(^7\) this provides additional evidence that torsinA interacts with the cytoskeleton and has a role in membrane movement. The OOC-5 protein is also found in the ER, suggesting that some essential ER-related function has been conserved throughout evolution in the torsin proteins.

Studies involving a second *Caenorhabditis elegans* torsin-like gene, TOR-2, show that wild-type torsin but not mutant torsin, has the ability to suppress polyglutamine-induced protein aggregation\(^7\) as well as protect dopaminergic neurons from cellular stress after treatment with the neurotoxin 6-hydroxydopamine (6-OHDA).\(^7\) Similarly, treatment with another dopaminergic toxin, MPTP, resulted in a significant increase in torsinA expression in the brains of mice several hours post treatment.\(^8\) These results are reminiscent of cell culture studies described above\(^7,7\), and provide evidence that torsinA has a role in protein folding and degradation.

Two *Drosophila* models of torsin have been described. In the first, overexpression of mutant human torsinA but not wild-type protein elicited locomotor defects in the flies.\(^8\) In neurons they identified enlarged synaptic boutons of irregular shape with reduced vesicle content; they also found dense torsinA-immunoreactive bodies associated with synaptic densities and nuclear envelope changes consistent with the increased perinuclear staining seen in cultured cells overexpressing this protein (see above).\(^6\) Both the locomotor and cellular defects could be suppressed with overexpression of human or fly Smad2, a downstream effector of the transforming growth factor-β (TGF-β) signaling pathway, suggesting that TGF-β signaling might be involved in early-onset dystonia.\(^8\) The second *Drosophila* model used overexpression and RNA interference (RNAi) to analyze the function of torp4a, the endogenous fly torsin. Using the eye as a model, overexpression protected the retina from age-related neural degeneration, while down-regulation of torp4a caused degeneration of the retina.\(^8\) Consistent with both cellular and mouse studies, torp4a was largely expressed in the ER but also found at the NE. A genetic screen to identify enhancers of torp4a demonstrated an association with components of the AP-3 adaptor complex, a protein related to myosin II function, and the superoxide dismutase 1 (SOD1) gene.\(^8\)

**Mouse**

A number of genetic models are available for DYT1 dystonia in mice, including both engineered lines where the endogenous mouse locus (Tor1a) has been modified, as well as overexpressing transgenic models, where the human gene has been randomly inserted into the mouse genome (for review see Reference 83).

In one transgenic model, human mutant torsinA is overexpressed using the neuron-specific enolase (NSE) promoter; in this model about 40% of the mice show hyperactivity, circling, and abnormal movement.\(^5\) These mice also demonstrate abnormal levels of dopamine metabolites as well as aggregates in the brainstem similar to those reported in DYT1 human brains.\(^5\) A second transgenic model expressing human mutant torsinA under the control of the CMV promoter does not show an overt movement disorder; these animals do, however, exhibit impaired motor sequence learning on the rotorod\(^8\) reminiscent of the motor learning difficulties reported in human DYT1 non-manifesting mutation carriers discussed below.\(^8\) Recordings of the activity of striatal cholinergic interneurons in slice preparations from these animals in the presence of quinpirole, demonstrate an increase in firing rate that was mediated by a greater inhibition of N-type calcium currents.\(^8\) An imbalance between striatal dopaminergic and cholinergic signaling in DYT1 dystonia is suggested by this study.

Three different types of engineered mice have been published to date. Knock-in (KI) mice bearing the 3 bp deletion in the heterozygous state, analogous to the human DYT1 dystonia, manifest hyperactivity in the open field, difficulty in beam walking, and possess abnormal levels of dopamine metabolites, but no overt dystonic posturing.\(^7\) These mice also have brainstem...
neuronal aggregates consistent with human pathologic data. In contrast, mice that are either homozygous KI or knock-out (KO) for the deletion die at birth with apparently normal morphology, but with postmigratory neurons showing abnormalities of the nuclear membranes. The fact that both the homozygous KO and KI animals display the same lethal phenotype suggests that DYT1 dystonia results from a loss of function of the torsinA protein. The knock-down (KD) mouse model in which a reduced level of torsinA protein is expressed, displays a phenotype very similar to the heterozygous KI mice, showing both deficits in motor control as well as dopamine metabolite levels. This mouse also supports a loss of function model because no deleted torsinA is necessary to produce the phenotype; this loss of function could be due to a dominant negative effect whereby the mutant protein interferes with the wild-type protein.

Although the exact function of torsinA remains elusive, the evidence presented above suggests a role in protein folding and degradation and/or membrane movement within cells. It seems clear from both the cellular and animal models that DYT1 dystonia results from a loss of function. Although DYT1 dystonia is inherited as a dominant trait, this loss of function may occur through a dominant negative mechanism as a result of the fact that AAA+ proteins usually form oligomeric complexes. The carboxy terminus of AAA+ proteins is important for both the binding of interacting proteins and for oligomerization. If mutant torsinA interacts with wild-type torsinA, forming inactive multimers, then suboptimal levels of functional torsinA might result. Alternatively, mutant torsinA could block binding to interacting partners or bind to and sequester partner proteins—either way, interfering with their functions. RNAi has been used in cell culture systems overexpressing the mutant torsin protein to block aggregate formation and restore normal distribution of wild-type torsinA. These results support the dominant negative model for torsinA function and suggest RNAi could be used therapeutically.

**DYT1 ROLE IN FOCAL DYSTONIA**

Recent studies implicate involvement of other variations in the DYT1/TORB genomic region in late-onset, mainly focal dystonias. In dystonia patients from Iceland, a significant association was observed with a haplotype spanning the DYT1 gene. Two studies from Germany failed to replicate this association. However, a study involving Italian and North American cohorts revealed an association in the Italian group with the same risk allele as was seen in Iceland but no association in the American group. Finally, a group of Austrian and German patients with predominantly focal dystonia showed a strong association with two single nucleotide polymorphisms (SNPs) in the 3' untranslated region of the gene (Figure 6.1C). However, rather than being a risk haplotype, as shown in the previous populations, the SNPs showed a strong protective effect. Whether these opposing results reflect population difference or, instead, indicate that the tested SNPs are in strong linkage disequilibrium with a real causal variant(s), is unknown. Nevertheless, the combined results support a role for genetic variability in the DYT1 genomic region as a contributing factor in the risk of developing late-onset, focal dystonia.

**OTHER DYT1 VARIANTS AND THEIR ROLE IN DISEASE**

As discussed above, when mutant torsinA is overexpressed in cells, it forms membrane inclusions that are thought to derive from the ER/NE. The only identified non-synonymous coding variant in the DYT1 gene is located in exon 4 and replaces an aspartic acid (D) at position 216 with a histidine (H) in about 12% of normal alleles. It has recently been shown that when the H allele is overexpressed in cells, similar membrane inclusions result. However, when the H allele is co-overexpressed with a construct carrying the GAG-deleted torsinA, fewer inclusions are formed (Figure 6.1). This suggests that the two alleles jointly have a canceling effect. This finding raises the possibility that this variant may play a role in the reduced penetrance associated with DYT1 dystonia or in causing other forms of dystonia. Regarding the latter, there have been two studies examining the role of the D216H SNP in focal dystonia, and in both no associations were identified. Regarding the role of the D216H allele in modifying penetrance of DYT1, a recent study assessed 119 GAG deletion carriers with signs of dystonia (‘manifesting’), 113 considered to be ‘non-manifesting’ carriers and 197 controls. There was a significantly increased frequency of the 216H allele in non-manifesting deletion carriers and a decreased frequency in manifesting carriers compared to the controls. Analysis of haplotypes demonstrated a highly protective effect of the H allele in trans with the GAG deletion; there was also suggestive evidence that the D216 allele in cis is required for disease to be penetrant. Although these results support this variant as a potent intragenic modifier, it has a relatively small role in explaining reduced penetrance because the H allele is not common (at most, occurring in 20% of the population).
CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA

DYT1 PHENOTYPE AND ENDOPHENOTYPE

With the identification of the DYT1 gene, it has become possible to return to the clinical domain to determine the phenotypic spectrum and role of DYT1 in the dystonia population. Clinical expression is extraordinarily broad, even within families; 70% of gene carriers have no definite signs of dystonia and among the remaining 30% dystonia ranges from focal to severe generalized. There are, however, common DYT1 clinical characteristics that have been described across ethnic groups. The vast majority of people with dystonia due to the DYT1 mutation have a 'window' of early onset (starting after age 3 years and before 26 years), with dystonia first affecting an arm or leg. About 65% progress over 5–10 years to a generalized or multifocal distribution, the rest having segmental (10%) or only focal (25%) involvement. When viewed in terms of body regions ultimately involved, one or more limbs are almost always affected (over 95% have an affected arm) and the dystonia can be jerky or tremulous, mimicking myoclonus-dystonia. The trunk and neck may also be affected (about 25–35%) and they may be the regions producing the greatest disability. The cranial muscles are less likely to be involved (<15–20%), and in one study of early-onset primary dystonia cranial involvement was the best clinical predictor of non-DYT1 status. Rarely, affected family members have been identified with late-onset (up to 64 years) dystonia. These individuals are generally identified in the course of family studies and often do not seek medical attention. Also, although the arm is the body region most commonly affected in those with focal disease, the neck or cranial muscles have been reported as isolated affected sites; however this is quite rare. Indeed, one study of patients with early-onset cervical dystonia failed to find any patients with the DYT1 GAG deletion and DYT1 very rarely causes adult focal dystonia, which constitutes the great majority of primary dystonia.

The DYT1 GAG deletion is more important in the Ashkenazi population, because of the founder effect, where it accounts for about 80% of early-onset (<26 years) dystonia.
cases;\textsuperscript{18,104} this compares with 16–53\% in early-onset non-Jewish populations (Figure 6.2).\textsuperscript{22–24,104,114,115} The frequency of DYT1 dystonia among Ashkenazi Jews was estimated in one study,\textsuperscript{13} using the founder haplotype. The mutation frequency was 1/6000–1/2000 (giving a carrier frequency of 1/3000–1/1000), which translates into a disease frequency of 1/3000–1/9000 (based on a penetrance of 30\%). A recent study from south-eastern France, using direct genotyping of 12 000 newborn dried blood samples, identified one disease allele.\textsuperscript{116} This carrier incidence of 1 in 12 000 is consistent with the approximately fivefold increased frequency of early-onset dystonia in Ashkenazim compared to non-Jews advanced in older studies, prior to gene identification.\textsuperscript{8} These studies also imply that a significant proportion of early-onset cases, especially among non-Ashkenazim, are not due to DYT1, and other causes, including autosomal dominant and recessive genes, have been implicated.\textsuperscript{105,117}

Another avenue opened by DYT1 identification is a further exploration of its range of expression, and also an exploration of DYT1 endophenotypes that use imaging, electrophysiologic, and other techniques to measure subclinical traits. Non-manifesting family members (i.e. those without overt dystonia), a group constituting 70\% of mutation carriers, can be studied; they can be compared to their non-carrier family members as well as those manifesting dystonia. Psychiatric expression of DYT1 was investigated using this strategy. Both manifesting and non-manifesting gene carriers had the same increased risk for early-onset recurrent major depression when compared to their non-carrier-related family members;\textsuperscript{118} differences in OCD (obsessive-compulsive disorder) frequency, a psychiatric feature associated with other movement disorders such as tics and myoclonus-dystonia, were not observed.\textsuperscript{119} Other subtle clinical abnormalities noted in non-manifesting carriers are deficiencies in sequence learning\textsuperscript{85} and probable dystonia. The latter, although increased in carriers compared to non-carriers, is not 100\% specific, raising concerns about using family members with only probable dystonia in genetic linkage studies.\textsuperscript{120}

DYT1 endophenotypes have been investigated using various imaging and neurophysiologic approaches. Eidelberg and colleagues demonstrated a characteristic pattern of glucose utilization with [\textsuperscript{18}F]-fluorodeoxyglucose (FDG) positron emission tomography (PET) and network analysis. There are covarying metabolic increases in the basal ganglia, cerebellum, and supplementary motor area (SMA) in both ‘manifesting’ and ‘non-manifesting’ gene carriers.\textsuperscript{121,122} Other imaging studies of DYT1 gene carriers, including

![Figure 6.2](image_url)
non-manifesting carriers, have found decreased striatal D₂ receptor binding,²¹ and microstructural changes involving the subgyral white matter of the sensorimotor cortex.¹²² Electrophysiologic analyses have also identified genotype-associated abnormalities – namely, reduced intracortical inhibition and a shortened cortical silent period¹²⁴ – as well as higher tactile and visuotactile temporal discrimination thresholds and temporal order judgments.¹²⁵ These studies strongly support the presence of wider clinical gene expression, abnormal brain processing, and associated structural brain changes in gene carriers regardless of overt motor signs of dystonia, expanding the notion of penetrance and phenotype.

GENETIC COUNSELING AND TESTING

As described above, many studies have assessed the frequency of the DYT1 GAG deletion in different clinical and ethnic populations. All studies confirm a very low rate of positive cases in adult-onset and focal primary dystonia populations and those suspected of having a secondary etiology. Two studies have formulated testing guidelines to help clinicians decide whom to screen. One study assessed 180 Ashkenazi and non-Jewish individuals with primary dystonia ascertained for diagnosis and treatment.¹⁰⁴ Features of dystonia in DYT1 GAG deletion carriers and non-carriers were compared to determine a classification scheme that optimized prediction of carriers. The optimal algorithm for classification was disease onset before age 24 years in a limb. Although application of this classification scheme provided good separation among Ashkenazim (sensitivity, 96%; specificity, 88%), as well as in the group overall, it was less specific in discriminating non-Jewish mutation carriers from non-carriers (sensitivity, 94%; specificity, 69%). Using age 26 years as the cut-off, any site at onset gave a sensitivity of 100%, although specificity decreased to 54%. Based on these findings, diagnostic DYT1 testing in conjunction with genetic counseling was recommended for primary dystonia patients (regardless of family history) with onset before age 26 years (Table 6.1). However, using this cut-off could miss the rare mutation carrier with later onset. Thus, a caveat was added advising that older-onset patients, especially those with writer’s cramp and an early-onset blood relative, should be considered for screening. In another summary report,¹²⁶ DYT1 testing in conjunction with genetic counseling was recommended for patients with primary dystonia with onset before age 30 years and in those with an affected relative with early onset. In both recommendations genetic counseling is an integral component. Counseling provides a format to explain the implications of both a positive and negative test. For instance, if a test is negative, a genetic etiology is not necessarily excluded and this needs to be explained. If the test is positive, a diagnosis is secured but this diagnosis impacts on other at-risk family members. These members, even if asymptomatic, may wish carrier testing, and genetic counseling for all asymptomatic family members is imperative before testing is performed. The psychological and social implications of autosomal dominant disorders with markedly reduced penetrance and very variable expression are complicated and require considerable time for patient and family education and counseling.

To obtain up-to-date information regarding genetic testing sites, a highly recommended on-line resource is www.geneclinics.org.

Table 6.1 DYT1 testing guidelines based on screening 180 medically diagnosed cases, including 89 DYT1 gene carriers

<table>
<thead>
<tr>
<th></th>
<th>AJ (n = 126)</th>
<th>NJ (n = 54)</th>
<th>All (n = 180)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age onset &lt; 26 years</td>
<td>Sensitivity = 100%</td>
<td>Sensitivity = 100%</td>
<td>Sensitivity = 100%</td>
</tr>
<tr>
<td></td>
<td>Specificity = 63%</td>
<td>Specificity = 43%</td>
<td>Specificity = 54%</td>
</tr>
<tr>
<td></td>
<td>PPV = 80%</td>
<td>PPV = 38%</td>
<td>PPV = 64%</td>
</tr>
<tr>
<td>Onset in a limb</td>
<td>Sensitivity = 96%</td>
<td>Sensitivity = 94%</td>
<td>Sensitivity = 95%</td>
</tr>
<tr>
<td>and age onset &lt; 24 years</td>
<td>Specificity = 88%</td>
<td>Specificity = 69%</td>
<td>Specificity = 80%</td>
</tr>
<tr>
<td>Two or more limbs</td>
<td>Sensitivity = 95%</td>
<td>Sensitivity = 93%</td>
<td>Sensitivity = 95%</td>
</tr>
<tr>
<td></td>
<td>Specificity = 98%</td>
<td>Specificity = 53%</td>
<td>Specificity = 79%</td>
</tr>
</tbody>
</table>

*AJ = Ashkenazi Jews; NJ = non-Jewish; PPV = positive predictive value. Modified from Bressman et al,¹⁰⁴ with permission.
SUMMARY AND FUTURE DIRECTIONS

There has been a veritable explosion in our understanding of the genetic underpinnings of that form of primary dystonia, termed dystonia musculorum deformans, first described by Oppenheim almost 100 years ago. This condition results from a single and recurring GAG deletion in the DYT1 gene which codes for a neuronal protein, torsinA, that appears to have many functions. Our understanding of normal and mutated torsinA is widening and no doubt will continue to progress along current paths, as cellular and animal models are further explored. Especially important will be investigations that not only focus on the striatum but also assess anatomic and functional changes elsewhere in the brain. Various lines of study suggest that the brainstem and cerebellum need closer scrutiny. Also, there are only a handful of human DYT1 neuropathologic studies, and confirmation and elaboration of the crucial findings of McNaught et al are needed. Other lines of investigation that hold great promise include additional search for DYT1 modifiers, genetic and environmental. Only 30% of GAG deletion carriers ever manifest dystonia, and clinical expression ranges from severe generalized dystonia to barely discernible action dystonias. The recent finding that a trans variation within DYT1 itself is highly protective against clinical expression is an important step in illuminating factors involved in disease expression. Understanding the naturally occurring modulators of disease expression will shed light on the mechanism of torsinA pathogenesis and the steps that take human motor control across a threshold into clinical dysfunction.

Finally, new avenues of research that hold the promise for targeted treatments of DYT1 dystonia are just being initiated. These derive from several different approaches, including the search for DYT1 modifiers, better understanding of the neurophysiologic correlates of DYT1, and cellular and animal models that not only shed light on disease mechanism but also allow for drug or other interventional screening. One such novel approach uses RNAi in cell culture systems overexpressing the mutant torsin protein to block aggregate formation and restore normal distribution of wild-type torsinA. These results support the dominant negative model for torsinA function but also suggest RNAi could be used therapeutically.

REFERENCES


62 CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA


Other primary generalized dystonias

Antonio E Elia, Anna Rita Bentivoglio, Enza Maria Valente, and Alberto Albanese

INTRODUCTION

Dystonia is the only clinical sign of primary torsion dystonias (PTDs) and there is no identifiable exogenous cause or other inherited or degenerative disease.\(^1\) The best-known PTD is DYT1 dystonia,\(^2\) but PTDs encompass several other genetically determined forms, none of which has been characterized. DYT1 dystonia was first identified among Ashkenazi Jews\(^3,4\) and was then recognized as a possible cause of early-onset generalized PTD in populations of any ethnic origin.\(^5-7\) Clinical observations have reported that DYT1 dystonia can have heterogeneous phenotypic expressions,\(^8-10\) making it difficult to differentiate DYT1 and non-DYT1 patients on clinical grounds.\(^11\)

This chapter revises the evidence collected during the last decade, in order to report the phenotype of non-DYT1 generalized PTD families either linked or unlinked to known loci, and to characterize the clinical features of non-DYT1 early-onset dystonia in sporadic and familial PTD patients.

EPIDEMIOLOGY

The available evidence suggests that non-DYT1 PTDs are by far more prevalent in the general population than DYT1 cases. In a large series of Italian PTD patients, it has been observed that DYT1 cases accounted for 41% of the patients with generalized dystonia and for only 5.4% of all PTD cases.\(^12\) A large Italian study on early-onset (<21 years) PTD showed that non-DYT1 cases account for 75% of all early-onset cases.\(^13\) This finding is consistent with previous data showing that DYT1 cases account for only 7.9% of total PTDs in Serbia,\(^13\) for 15% in Denmark,\(^14\) and for 16% in Italy.\(^15\)

There are no published data on the prevalence of generalized (or early-onset) non-DYT1 dystonia in the general population, because most epidemiologic studies were service-based rather than community-based and were performed before DYT1 testing became available.\(^16,17\) Early-onset cases account for about 15% of all PTDs, the majority of which are represented by non-DYT1 late-onset (focal or segmental) cases.\(^18\)

CLINICAL FEATURES

Familial dystonias have been listed with progressive numbering preceded by the DYT code (meaning ‘dystonia’; Table 3.2). This list was originally supposed to include only primary dystonias, but currently encompasses several heterogeneous conditions, such as unmapped PTD familial loci (e.g. DYT2 and DYT4), heredodegenerative dystonias (e.g. DYT3), dystonia-plus syndromes (DYT5 and DYT11, DYT12, DYT14), and paroxysmal dyskinesias or choreoathetosis (DYT8, DYT9, DYT10). Therefore, of the 15 DYT loci, only six refer to PTDs, namely those marked as DYT1, DYT2, DYT4, DYT6, DYT7, and DYT13. With the exception of DYT2, all PTDs are inherited as a dominant trait with reduced penetrance.

Monogenic primary torsion dystonias

Four PTD genotypes have been identified, three of which present with generalized phenotypes.

**DYT1 phenotype**

A common cause of generalized PTD is the GAG deletion in the DYT1 gene encoding the protein torsinA.\(^4\) The disease was originally described among Ashkenazi Jews with a relatively homogeneous phenotype characterized by early limb-onset generalized dystonia.\(^3,19\)
It was later reported that, particularly in Caucasian patients, the DYT1 phenotype is broader than originally thought. The ‘classical’ DYT1 phenotype is characterized by early onset in a limb, generalization without spread to the craniocervical region. In a series of patients with early-onset PTD it has been confirmed that dystonia never starts in the craniocervical region in DYT1 carriers, but it has been shown that craniocervical sites can be involved in later stages. It is remarkable that DYT1 patients who develop severe generalized involvement may carry out their daily activities with significant adaptation in many cases. Extreme cases have also been observed, ranging from asymptomatic status to craniocervical involvement or even to status dystonicus.

Atypical DYT1 phenotypes can be grouped in five main types.

1. Generalized dystonia with cranial–cervical involvement, more frequent in Europe than in North America, with a record prevalence of 80% in DYT1 patients of a French series.
2. The generalized myoclonus-dystonia phenotype which is more severe than that observed in DYT11 myoclonus-dystonia.
3. Focal dystonia with slow progression; in these cases spread may occasionally occur several years after onset.
4. Late-onset DYT1.
5. Non-limb (cervical, laryngeal, or trunk) onset dystonia.

Regardless of onset, positron emission tomography (PET) studies have shown that DYT1 dystonia is associated with abnormal movement preparation due to defective sensorimotor integration. These features are genotype-specific, as putaminal metabolism is increased in DYT1 patients, but decreased, for example, in DYT6 patients. Since clinical criteria can hardly distinguish DYT1 from non-DYT1 patients, the identification of endophenotypes associated with DYT1 carriers (either affected or non-affected) provides a new potential diagnostic tool. Striatal D2 receptor binding is reduced in manifesting as well as in non-manifesting DYT1 carriers. Another possible endophenotype of DYT1 carriers is the finding of higher tactile and visuoactile temporal discrimination thresholds or temporal order judgments.

**DYT6 phenotype**

The DYT6 locus has been mapped in two Mennonite families, where dystonia was inherited as an autosomal dominant trait with an estimated penetrance of 30%. The locus was mapped to 8p21-q22 and a founder effect was supported by the observation that haplotypes across the candidate region were identical in the affected members of the two families, suggesting a common underlying mutation. A total of 15 definitely affected individuals were identified among 220 family members.

The DYT6 phenotype has been described as ‘mixed type’, characterized by early or adult onset and prevalent segmental (craniocervical) distribution, with presentation at onset equally involving limb, cervical, and cranial muscles. Four patients presented generalized dystonia, and some had a classical DYT1 phenotype. DYT6 patients with generalized phenotype had (on average) an older age at disease onset than DYT1 patients (18.9 ± 11.9 years; range: 5–38 years); in addition, they commonly had craniocervical involvement either at onset or later during disease progression. Many DYT6 patients were remarkably disabled in their living activities by this craniocervical involvement. It has been shown that manifesting DYT6 gene carriers have bilateral hypermetabolism in the supplementary motor area and the temporoparietal cortex, and bilateral hypometabolism in the putamen.

**DYT7 phenotype**

The DYT7 locus mapping to the short arm of chromosome 18 was identified in a large German family with autosomal dominant focal dystonia. The mean age of disease onset was 40 years and no patient had generalized dystonia.

**DYT13 phenotype**

The DYT13 locus was mapped in a family with prominent upper body involvement (craniocervical and upper limb), the majority of whom had onset in infancy or adolescence. Disease progression was evaluated for 6 years in this family. There were 11 definitely affected individuals, two of whom had generalized dystonia with early onset in the upper limb or in the cervical region. The peculiar features of the DYT13 phenotype are prominent cervical or upper limb involvement; disability is mild, even in generalized cases.

The first patient with generalized PTD was a woman who presented postural tremor of the upper limbs at age 5. The tremor rapidly spread to involve the whole body and did not aggravate. Upon observation in her sixties, the patient had generalized dystonia with prominent action tremor affecting the larynx, limbs, and trunk. Despite this widespread involvement, her disability was mild. Being a housekeeper, she could run her daily duties without help. The second patient with generalized dystonia was a man, who had cervical onset at age 20. This did not progress for the following 30 years. In his fifties,
dystonia spread to the right hand, then to both upper limbs, and to the head. He was last examined at age 56, when he had a generalized dystonia involving the neck and all the limbs. Similar to the other patient, his disability was mild: he could still work on a farm and was engaged in full-time labor.

PTD pedigrees

Two familial PTD phenotypes with occasional generalization have been coded. In addition, several other pedigrees, many of which with generalization, have also been described.

**DYT2 phenotype**

This is a recessive dystonia locus originally described in three consanguineous pedigrees of Spanish Gypsies. The disease was named ‘autosomal recessive dystonia in Gypsies’ and listed as DYT2. In two of the families, the phenotype was similar to that of DYT1 dystonia, consisting of early limb onset and progression to generalization; in the third family, dystonia presented with prominent oromandibular and cervical dystonia.

A Sephardic Jewish Iranian family with a similar phenotype and autosomal recessive inheritance has been described more recently. Three siblings in this family had PTD with limb onset in childhood, and slow progression to generalized dystonia with predominant craniocervical involvement. Two patients first developed in-turning of the foot with gait abnormalities, and all had cervical involvement, facial grimacing, blepharospasm, and involvement of the upper and lower limbs. Two patients also had dystonic dysphagia. It was hypothesized that this Sephardic family originating from Spain could be related to the DYT2 Gypsy family, but this possibility appears unlikely, also because most Iranian Jews do not originate from Spain or Portugal.

A third family with childhood-onset, generalized dystonia, and autosomal recessive inheritance was also classified as DYT2.

Overall, the DYT2 phenotype is consistent in the three families described and is characterized by early onset, generalization, and autosomal recessive transmission. DYT2 dystonia should be considered in every family with such features, particularly if there is prominent craniocervical involvement. Unfortunately, DYT2 dystonia has not been mapped to a genetic locus yet.

**DYT4 phenotype**

A large Australian pedigree had 20 members affected by dystonia in at least five consecutive generations and autosomal dominant inheritance. This PTD pedigree was classified as DYT4. Penetrance was complete in all the examined obligate gene carriers; age at onset varied from 13 to 37 years. Many of the patients presented with ‘whispering dysphonia’, others had cervical dystonia; most eventually developed generalized dystonia. Wilson’s disease coexisted in the same pedigree, but was excluded as a cause of dystonia in the affected individuals. The DYT4 phenotype has not been observed in other families or individual cases.

**Non-coded pedigrees**

In some PTD families not carrying the DYT1 mutation, the phenotype has been described in the affected individuals. Linkage studies have not been performed in these small pedigrees, which have remained unclassified.

A non-Jewish American family presented with adult-onset DYT1-negative PTD. The disease started in the neck in six cases and in a leg in one. All patients developed cervical dystonia, and language impairment (dysarthria or dysphonia) occurred in five patients. Four patients developed generalization of symptoms. In another Swedish family, transmission was autosomal dominant with variable phenotype. There was involvement of the face and larynx, and generalization occurred in three of the 10 patients. A family from South Tyrol had six affected individuals, four of whom developed generalization approximately 5 years after onset. Limbs were involved at onset in all but one patient, who started with cervical dystonia. Upper body involvement was observed in three of the four generalized cases. An Italian family had six affected individuals, one of whom had severe segmental dystonia. The prevalent phenotype was with adult-onset craniocervical dystonia with occasional axial involvement but no generalization.

Table 7.1 provides a synopsis of unclassified PTD pedigrees with a generalized phenotype.

**Non-DYT1 early-onset PTD cases**

The observation that early-onset dystonia cases progress to severe forms has been reported since the first descriptions of dystonia. In their seminal description of the natural history of PTD, Marsden et al. identified age at onset as one of the most important features in determining outcome. A consensus meeting later identified three age groups for PTD onset: childhood (0–12 years), adolescent (13–20 years), and adult (>20 years). Based on this consensus, cases with early onset (encompassing onset in childhood or in adolescence) were distinguished from those with adult onset by the threshold age of 21 years. Later retrospective series have confirmed that patients with early onset are more likely to have
Table 7.1 Clinical features of unclassified PTD pedigrees with generalized dystonia; cases without generalization are not listed

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Mean age at onset (years, range)</th>
<th>Site of onset: number</th>
<th>Progression: number</th>
<th>Cranial involvement: number</th>
<th>Additional features</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Leg: 1</td>
<td>Segmental: 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>27.3 (17–50)</td>
<td>Face: 4</td>
<td>Generalized: 3</td>
<td>Yes: 4</td>
<td>Prominent cranial involvement. Family with AD inheritance</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm: 2</td>
<td>Multifocal: 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unknown: 1</td>
<td>Focal: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>23.3 (4–50)</td>
<td>Cervical: 1</td>
<td>Generalized: 4</td>
<td>Yes: 2</td>
<td>Prominent cervical involvement. Family with AD inheritance</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm: 3</td>
<td>Segmental: 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leg: 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>16 probands</td>
<td>The proband with generalized dystonia was early onset</td>
<td>NA</td>
<td>Generalized: 1</td>
<td>NA</td>
<td>At least one early-onset patient in each family</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Segmental: 7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Focal: 8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>25 patients</td>
<td>7.7 (1.5–15)</td>
<td>Crani: 1</td>
<td>Generalized: 22</td>
<td>Yes: 16</td>
<td>Series of both sporadic and familial patients</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Neck: 1</td>
<td>Segmental: 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm: 12</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trunk: 2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leg: 9</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>Leg: 1</td>
<td>Generalized: 1</td>
<td>No</td>
<td>Myoclonus dystonia-like phenotype with familial occurrence. AD inheritance</td>
<td>54</td>
</tr>
<tr>
<td>7 probands</td>
<td>13.9 (1–17)</td>
<td>Cervical: 3</td>
<td>Generalized: 3</td>
<td>Yes: 2</td>
<td>The proband of DYT13 family is included</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Arm: 2</td>
<td>Multifocal: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Leg: 2</td>
<td>Segmental: 2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Focal: 1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AD = autosomal dominant; NA = not available.
a generalized form than those with older age at onset and that there is a bimodal curve representing the frequency distribution of age at disease onset, with a nadir separating two clusters of patients.50,51

Later series described the frequency distribution of ages at onset and attempted to identify the predictive value of early vs adult age at disease onset for the probability of developing a generalized form of dystonia.3,51 In a North American series (characterized by a predominance of Ashkenazi Jewish patients), a threshold age at disease onset of more than 26 years indicated a low probability of being carrier of a DYT1 mutation,26 but this was not confirmed in other series based on different populations.52 Thus, while all retrospective series confirm a bimodal distribution of age at onset for PTD, with a higher likelihood of generalization for the early age group, the measured predictive value of the age thresholds vary based on the populations considered.

In a large Italian series, encompassing a majority of non-DYT1 patients, the frequency distribution of the ages at onset was a bimodal curve with modes at 9 and 57 years and a nadir at 21 years.12 The sensitivity and specificity of age at onset to predict generalization were calculated for all patients with a follow-up observation of at least 5 years. Receiver operating characteristic (ROC) curves were plotted and the best trade-off threshold predicting generalization was found at 32 years, yielding sensitivity and specificity of 83% (Figure 7.1). The negative predictive value was 99%, indicating a negligible probability that patients with age at onset higher than 32 years would progress to generalization.

The phenotype of non-DYT1 early-onset PTD cases is not completely characterized, but several series remarked differences from the DYT1 phenotype that may be unapparent in individual cases. In a French study of 100 patients with sporadic PTD,7 10 were affected by generalized dystonia, and five of them carried the DYT1 mutation. The phenotype of generalized dystonia in non-carriers was not described in detail, but it was reported that age at onset was higher in non-carriers. In a series of 30 Italian patients with early-onset sporadic PTD, 25 were not DYT1 carriers: 22 of them had generalized dystonia, and 16 presented oromandibular or laryngeal involvement.15

A series of 57 consecutive genetically characterized patients with early-onset PTD was recently reported.11 The majority of these patients (43 (75%), 27 men, 16 women; ratio, 1.7: 1) did not carry the DYT1 mutation. Twenty-nine non-DYT1 patients eventually developed generalized dystonia, with notable oromandibular involvement in 17 and laryngeal involvement in four. The remaining 14 non-DYT1 patients developed segmental (eight), multifocal (one), or focal (five) forms. Non-DYT1 patients with generalized dystonia had earlier onset than those without generalization.

The same series showed that sporadic non-DYT1 patients had cranial involvement and earlier generalization more often than DYT1 patients. By contrast, familial non-DYT1 cases had older age at onset and older age at generalization, more frequent cervical involvement, and less common limb onset. Progression was more rapid in sporadic non-DYT1 patients than in familial non-DYT1 patients, suggesting that the latter may belong to a different phenotype (Figure 7.2). In keeping with this, familial non-DYT1 cases of this Italian series had a relatively homogeneous phenotype, similar to the so-called 'mixed phenotype',30,34 with cervical involvement, frequent non-limb onset, relatively benign disease

![Figure 7.1 ROC curve plotting sensitivity and specificity for the prediction of dystonia generalization in 443 patients followed up for more than 5 years. Age at disease onset of 32 years predicts generalization with sensitivity and specificity of 83%.]
course, and uncommon generalization. This finding suggests that these non-DYT1 Italian families may share a common genetic defect.

CONCLUSIONS AND OUTLOOK

Generalized dystonias represent a heterogeneous group encompassing sporadic and familial cases with overlapping clinical features. A certain number of still unmapped genes are certainly responsible for these cases. Since large families suitable for linkage analysis are rare, it is useful to classify patients into homogeneous phenotypic groups and to look for endophenotypic markers before planning new linkage studies. The available data on familial PTD cases suggest that the traditional classification of ‘predominantly generalized’ and ‘predominantly focal’ forms53 may be reductive. Indeed, regardless of the predominant familial phenotype, generalized and focal PTDs often coexist in the same pedigree, making clinical heterogeneity a cardinal feature of inherited dystonias.

REFERENCES


26. Bressman SB, Sabatti C, Raymond D et al. The DYT1 phenotype
25. Edwards M, Wood N, Bhatia K. Unusual phenotypes in DYT1
23. Fasano A, Elia A, Albanese A. Early onset primary torsion dys-
DEFINITION AND CLINICAL FEATURES

Cervical dystonia (CD) is a focal dystonia of the cervical muscles that causes abnormal postures of the head, neck, and shoulders1 (Table 8.1). In the past, CD was considered a psychiatric disorder, and terms such as ‘torticollis mentalis’ were used to describe the condition.2 The reasons for this misconception arise from its unusual movements, worsening with certain actions or postures, enhancement by stress, improvement by touches or ‘tricks’ and the lack of anatomic, physiologic, and biochemical abnormalities.3 Patients were referred to psychiatrists, some receiving inpatient psychiatric treatment, counseling, and electroconvulsive therapy for ‘hysteria’.4 Subsequently, the neurologic basis of CD was recognized, it was redefined as a subtype of focal dystonia and is now referred to as cervical dystonia.3,5

CD is marked by deviation of the head around horizontal (torticollis), coronal (retrocollis, anterocollis), and vertical axis (laterocollis), often associated with reduced range of motion in the direction contralateral to the movement.6 CD has been categorized into three types associated with dystonic muscle activation: tonic, phasic, and tremulous.7 Horizontal rotation is the most common abnormal movement, present in approximately 80% of patients. Electromyography in superficial neck muscles showed that this posture typically arises from activity of the sternocleidomastoid muscle contralateral to the turn and splenius capitis muscle ipsilateral to the direction of turn. Deeper muscles, including the longissimus capitis, splenius cervicis, longus capitis, and obliquus capitis, can also be involved. Retrocollis is seen in 10–20% of patients, and is associated with electromyographic activity in ipsilateral splenius, sternocleidomastoid, and levator scapulae muscles. Retrocollis and anterocollis are less frequent, and involve bilateral posterior and anterior muscles, respectively. In most patients, these movements are not present in pure form, with combinations of torticollis and laterocollis.

<table>
<thead>
<tr>
<th>Table 8.1 Common clinical features of cervical dystonia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Movement of head, neck, and shoulders:</td>
</tr>
<tr>
<td>Horizontal (torticollis)</td>
</tr>
<tr>
<td>Sagittal</td>
</tr>
<tr>
<td>Coronal (retrocollis, anterocollis)</td>
</tr>
<tr>
<td>Lateral (laterocollis)</td>
</tr>
<tr>
<td>Shoulder elevation, anterior deviation</td>
</tr>
<tr>
<td>Neck pain, stiffness</td>
</tr>
<tr>
<td>Reduced range of motion</td>
</tr>
<tr>
<td>Overlying spasms</td>
</tr>
<tr>
<td>Sensory tricks (geste antagoniste)</td>
</tr>
</tbody>
</table>

Shoulder involvement is present in approximately half of the patients.

Approximately 70–75% of patients have pain associated with CD. Pain occurs mostly with more severe head turn and spasm, and contributes to a greater degree of disability.9 CD-related pain could be due to involuntary muscle contractions or to secondary phenomean such as cervical arthritis or nerve root compression with radicular symptoms.9 Premature arthritic changes have been observed in approximately 24% in small series and primarily affect the cervical spine ipsilateral to the direction of turn or tilt.10

One of the distinctive features of CD is the presence of a trick (geste antagoniste) that effectively alleviates symptoms. Although sometimes consisting of a forceful counterpressure that offsets the abnormal head posture,11 often the trick is related solely to sensory input that effectively reduces abnormal dystonic muscle activity.12 Common sensory tricks are touching the back of the head, cheek, or temple. Other tricks, such as chewing a toothpick, wrapping the head, or pulling the ear, can
also be present. Most patients will have more than one effective trick. The effect of the sensory trick may be in the movement of the arm or in the touch itself. In some CD patients, the mental imagery of a sensory trick may be as effective as the physical performance. The presence of a trick is more common in younger-onset CD patients and in most the effect of a trick is maintained throughout the course of disease.

The symptoms of focal CD usually begin in adulthood in the fifth decade. The initial symptoms of CD are diverse, with neck pain and head posturing being the most frequent. In some patients, there may be overlying muscle spasms causing quick, repetitive jerking movements that may resemble essential tremor, but can be differentiated by the directional preponderance of the movements. Head tremor in the horizontal axis (‘no-no’ tremor) may be an initial manifestation of CD.

Although variable, CD symptoms tend to worsen for the first 5 years and then stabilize. Focal dystonia may spread from the neck to contiguous body areas including the face and arm, but seldom generalizes. Spontaneous remission of symptoms can occur in up to 20% of CD patients, typically within 1–3 years of symptom onset. The remissions may last up to 20 years, but almost all patients relapse. The long-term complications of CD include cervical spine degeneration, spondylosis, disk herniation, vertebral subluxations and fractures, radiculopathies, and myelopathies. These complications are more frequent in generalized dystonia and cerebral palsy than focal dystonia and may affect from 20 to 40% of patients.

Although not life threatening, CD can be disabling, affecting employability and negatively affecting quality of life. In addition to the physical manifestations, CD patients have a variety of associated psychosocial issues, including a greater frequency of depression and an increased inability to maintain full-time employment. These issues are improved if CD symptoms are alleviated by effective treatment.

CD is the most common focal dystonia, with a crude incidence of 10.9 per million person-years, and a crude prevalence rate of 88.6 per million persons in Rochester, Minnesota and an incidence of 1.2 per 100 000 person-years. A cross-sectional study of dystonia conducted by the Epidemiologic Study of Dystonia in Europe found that CD constituted almost half of the cases of focal dystonia identified. CD is more common in women, with a ratio of women to men of 1.4–1.6 to 1.

Factors that predispose to the development of CD have not been identified. Scoliosis, defined as a lateral curvature of the spine exceeding 10° on radiography, is common in CD, affecting up to 39%. The increased frequency of scoliosis in CD has been suggested to be a manifestation of more widespread dystonic involvement of paraspinal muscles, extending from the neck into the back. Alternatively, it may be that spinal curvature arises secondary to the abnormal postures of the head and neck. A recent case-control study suggests that childhood scoliosis may increase the risk of developing CD in adulthood.

Although trauma has been hypothesized to be a risk factor for the development of CD, the role of trauma in the pathogenesis of CD has been controversial. In one study, CD patients with symptoms occurring within 4 weeks of a traumatic event had an increased frequency of lateralocollis, pain, and depression, and a minimal response to treatment with botulinum toxin. In contrast, another report of CD occurring within 1 year of neck trauma showed no distinctive clinical features. It has been suggested that CD related to acute trauma may arise secondary to peripheral muscle spasms and not to central mechanisms that underlie true dystonia. A third study demonstrated that patients with post-traumatic CD had an increase in psychological factors and associated non-neurologic features such as give-away weakness and distractibility. In all studies, post-traumatic CD patients were more likely to be involved in litigation or compensation issues. The association of trauma to dystonia remains an unsettled issue.

CD is a dynamic disorder that varies in severity depending on posture, activity, sensory input, presence of compensatory head postures, and the presence of dystonic spasms or tremor. These qualities make CD problematic to evaluate utilizing rating scales. The Tsui rating scale is a six-item scale that assesses amplitude and duration of involuntary neck movements, shoulder elevation, and head tremor. This scale was utilized in early studies of botulinum toxin and had excellent inter-rater reliability, but was limited by discrepancies between rating scores and patient assessments of severity. The Cervical Dystonia Severity Scale (CDSS) uses a protractor and wall chart to rate the severity of the head’s deviation from neutral in each of three planes of motion (rotation, lateralocollis, anterocollis/retrocollis). Although the CDSS has excellent inter-rater agreement, validity has not been assessed and the need to perform the measures in a fixed, seated position may not reflect the dynamic qualities of CD. The Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) consists of three subscales to assess motor severity, pain, and disability of CD. The motor subscale of the TWSTRS has good to excellent inter-rater reliability, and a published teaching tape. It has been utilized extensively in recent clinical trials of CD. The pain and disability subscales of the TWSTRS have not been adequately assessed for psychometric properties. Recently, a disease-specific quality of life rating scale for blepharospasm and cervical dystonia has been published.
Consisting of 24 items, the CDQ-24 was found to be a reliable and valid instrument that was sensitive to change following treatment.44 The CDQ-24 may be useful in future studies of CD. A description and comparison of these, and other rating scales, is described in Chapter 23.

In addition to clinical rating scales, numerous electrophysiologic techniques have been developed to quantify the positional aspects of CD utilizing three-dimensional motion detection and computer analysis.45,46 Although these may provide a more precise measurement of postural deviations, use in a clinical setting is currently limited due to the additional equipment and training needed for implementation.47,48

The pathophysiology of CD is not known. CD patients have abnormal orienting and postural responses to vibratory input and spatial perturbations that may increase with advancing disease.49 Abnormalities of spatial orientation,50,51 shifting of the perception of 'straight ahead' from the head to the trunk,52 and abnormal sway deviation53 have been described. Vestibular abnormalities have also been reported, although whether these are primary to the disorder or secondary to the chronic abnormal posture of the head have not been determined.

CD often occurs as a sporadic dystonia, without a major genetic contribution. However, twin pairs and families with non-progressive CD have been described.54 The familial occurrence of CD is probably underestimated. This may be due, in part, to inaccuracies in identifying affected relatives on the part of the probands,55 or failure to diagnose dystonia on the part of clinicians.56 A recent study found that 19% of probands with craniocervical dystonia had a family member with definite dystonia, and as many as 33% had definite or probable dystonia,57 suggesting that the genetic contribution in adult-onset CD may in fact be larger than anticipated from prior studies. Some investigators have suggested an autosomal dominant mode of inheritance with reduced penetrance.58 Others have found evidence for genetic anticipation in CD.59 The DYTI gene has largely been excluded in sporadic CD.60 The DYT7 locus linked to chromosome 18 has been reported to be associated with familial CD, and may be a common etiology in families in central Europe.61-63 This locus has been excluded as a cause of adult-onset focal dystonia in other families.64,65 As with other forms of dystonia, CD is likely to be a heterogeneous disorder.

Although in most adult patients, CD is a primary disorder without a defined etiology, secondary or symptomatic CD can occur and should be suspected, particularly if CD begins in infancy, or childhood, or is associated with other physical findings (Table 8.2). Symptomatic CD is distinguished from primary CD by the presence of additional neurologic, orthopedic, or medical disorders or a history of drug exposure or trauma prior to onset.

The differential diagnosis of secondary CD is extensive (Table 8.3). CD rarely occurs as a primary dystonia in children. Congenital muscular torticollis66 is the most frequent underlying etiology in infants and is the sequela of an intratruncal or perinatal compartment syndrome.67 Congenital torticollis, also called sternomastoid pseudotumor, typically presents with a shortened, tightened sternocleidomastoid muscle, an ipsilateral head tilt, and reduced range of motion. It is most frequently associated with a breech birth, hip dysplasia, and craniofacial asymmetry. If diagnosed and treated at an early age, congenital muscular torticollis has an excellent prognosis with manual stretching therapy or partial sectioning of the sternocleidomastoid muscle.68-70

Benign paroxysmal torticollis in infancy is a self-limiting condition that appears in early infancy before the age of 1 year and disappears spontaneously before the age of 5 years. The infant demonstrates recurrent episodes of sudden, stereotypic torticollis, that usually alternates from side to side and lasts from hours to days.71 The infant may also show pallor, vomiting, and ataxia during the episodes. Recently, two patients in a family with familial hemiplegic migraine linked to CACNA1A mutation were described with this syndrome, suggesting an association with the calcium channelopathies.72

Atlantoaxial subluxation occurs with excessive ligamentous laxity found in some children, and has also been observed in Marfan’s syndrome. Presenting symptoms include pain, abnormal posturing of the head (‘cock-robin’ position), and diminished range of motion of the neck. The onset is spontaneous and usually occurs following minor trauma.73 Another cause of atlantoaxial subluxation in children is Grisel’s syndrome, consisting of atlantoaxial subluxation associated with an inflammatory or infectious process, such as pharyngitis, mastoiditis, or a retropharyngeal abscess. These children may present with neck pain, fever, sore throat, a neck mass, and respiratory distress or stridor.74 Acute torticollis in children can also result from an inflammatory process that irritates the cervical muscles, nerves, or vertebrae, causing spasm of cervical muscles, in particular
the sternocleidomastoid muscle, in the absence of a subluxation.\textsuperscript{75}

A survey study of 288 pediatric patients with torticollis showed that 18% had a non-muscular etiology for their torticollis. Of these, Klippel–Feil anomalies and neurologic disorders were frequent. These neurologic conditions included ocular disorders in 23%, brachial plexus palsies in 17%, and lesions involving the central nervous system in 11% of the children.\textsuperscript{76}

The diagnostic evaluation of an infant or child with torticollis includes cervical radiographs, cervical tomography, dynamic computed tomography, and magnetic resonance imaging.\textsuperscript{77} If a subluxation is present, treatment approaches vary. In early cases (within 3 months of onset), analgesics, cervical traction, and immobilization are often effective.\textsuperscript{78} In chronic or severe cases, spinal fusion may be required.\textsuperscript{79} In cases secondary to infection or inflammation, treatment of the subluxation is combined with appropriate treatment of the inflammatory process.\textsuperscript{80}

Other disorders that can cause abnormal head postures in children that are mistaken for CD include intervertebral disc calcification\textsuperscript{81} and Chiari type 1 malformations.\textsuperscript{82} Abnormal head posturing can also arise from superior oblique muscle palsy,\textsuperscript{83} chordoma of the clivus,\textsuperscript{84} and Sandifer’s syndrome with gastric reflux into the esophagus.\textsuperscript{85}

Both children and adults may develop CD following treatment with dopamine receptor antagonist drugs, usually psychotropic or antiemetic medications. Dystonia may occur as an acute reaction or after months to years of chronic treatment. Acute dystonic symptoms may present as oculogyric crisis, which includes symptoms of retrocollis associated with ocular deviation (oculogyric reaction). CD can also be the only manifestation of an acute drug reaction. Acute dystonic reactions can develop following the first dose of drug after increasing the dose and respond well to anticholinergic administration or discontinuation of the offending drug.

Tardive CD occurs following chronic treatment (defined as 3 months) with dopamine receptor antagonists, and may be differentiated from primary dystonia by the presence of extracervical involvement, retrocollis, spasmodic head movements, and the absence of an effective sensory trick or family history.\textsuperscript{86} Although tardive dystonia typically begins as a focal dystonia, involving the cranio-cervical area in over 80% of cases, in most patients it progresses over months to years into generalized dystonia. The phenomenology of tardive dystonia may be indistinguishable from that of primary dystonia, although retrocollis and anterocollis are more common in tardive dystonia. Tardive CD is a persistent disorder, with less than 20% having a remission. Discontinuation of dopamine receptor antagonists increases the chance of remission but in many patients, tardive CD is irreversible and may not respond well to treatment.\textsuperscript{87}

In adults, secondary CD may arise as a part of a more extensive neurologic disorder. CD has been described in association with multiple system atrophy (MSA), Parkinson’s disease, and progressive supranuclear palsy.\textsuperscript{88} Structural lesions usually localized to the brainstem and cerebellum can be associated with cervical dystonia. Lesions of the cervical spinal cord and basal ganglia have also been reported. Typically, other neurologic abnormalities are also present in patients with CD secondary to a degenerative neurologic disease or to a structural lesion.\textsuperscript{89}

### Table 8.3 Causes of cervical dystonia associated with age of onset

<table>
<thead>
<tr>
<th>Infants and children</th>
<th>Adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral palsy</td>
<td>Primary dystonia</td>
</tr>
<tr>
<td>Congenital muscular torticollis</td>
<td>Drug-induced dystonic reactions:</td>
</tr>
<tr>
<td>Focal spasm</td>
<td>Acute</td>
</tr>
<tr>
<td>Trauma</td>
<td>Tardive</td>
</tr>
<tr>
<td>Benign paroxysmal torticollis in infancy</td>
<td>Associated with other neurologic disorders:</td>
</tr>
<tr>
<td>Oculogyric crisis</td>
<td>Parkinsonism</td>
</tr>
<tr>
<td>Atlantoaxial subluxation</td>
<td>Dystonia</td>
</tr>
<tr>
<td>Grisel's syndrome</td>
<td>Huntington’s disease</td>
</tr>
<tr>
<td>Ocular disorders:</td>
<td></td>
</tr>
<tr>
<td>Oculomotor palsies</td>
<td></td>
</tr>
<tr>
<td>Brachial plexus palsies</td>
<td></td>
</tr>
<tr>
<td>Anoxia</td>
<td></td>
</tr>
<tr>
<td>Central nervous system lesions</td>
<td></td>
</tr>
<tr>
<td>Intervertebral disc calcification</td>
<td></td>
</tr>
<tr>
<td>Chiari type 1 malformations</td>
<td></td>
</tr>
<tr>
<td>Chordoma of the clivus</td>
<td></td>
</tr>
<tr>
<td>Sandifer's syndrome</td>
<td></td>
</tr>
</tbody>
</table>

---

\textsuperscript{75} In chronic or severe cases, spinal fusion may be required.\textsuperscript{79} In cases secondary to infection or inflammation, treatment of the subluxation is combined with appropriate treatment of the inflammatory process.\textsuperscript{80}

Other disorders that can cause abnormal head postures in children that are mistaken for CD include intervertebral disc calcification\textsuperscript{81} and Chiari type 1 malformations.\textsuperscript{82} Abnormal head posturing can also arise from superior oblique muscle palsy,\textsuperscript{83} chordoma of the clivus,\textsuperscript{84} and Sandifer’s syndrome with gastric reflux into the esophagus.\textsuperscript{85}

Both children and adults may develop CD following treatment with dopamine receptor antagonist drugs, usually psychotropic or antiemetic medications. Dystonia may occur as an acute reaction or after months to years of chronic treatment. Acute dystonic symptoms may present as oculogyric crisis, which includes symptoms of retrocollis associated with ocular deviation (oculogyric reaction). CD can also be the only manifestation of an acute drug reaction. Acute dystonic reactions can develop following the first dose of drug after increasing the dose and respond well to anticholinergic administration or discontinuation of the offending drug.

Tardive CD occurs following chronic treatment (defined as 3 months) with dopamine receptor antagonists, and may be differentiated from primary dystonia by the presence of extracervical involvement, retrocollis, spasmodic head movements, and the absence of an effective sensory trick or family history.\textsuperscript{86} Although tardive dystonia typically begins as a focal dystonia, involving the cranio-cervical area in over 80% of cases, in most patients it progresses over months to years into generalized dystonia. The phenomenology of tardive dystonia may be indistinguishable from that of primary dystonia, although retrocollis and anterocollis are more common in tardive dystonia. Tardive CD is a persistent disorder, with less than 20% having a remission. Discontinuation of dopamine receptor antagonists increases the chance of remission but in many patients, tardive CD is irreversible and may not respond well to treatment.\textsuperscript{87}

In adults, secondary CD may arise as a part of a more extensive neurologic disorder. CD has been described in association with multiple system atrophy (MSA), Parkinson’s disease, and progressive supranuclear palsy.\textsuperscript{88} Structural lesions usually localized to the brainstem and cerebellum can be associated with cervical dystonia. Lesions of the cervical spinal cord and basal ganglia have also been reported. Typically, other neurologic abnormalities are also present in patients with CD secondary to a degenerative neurologic disease or to a structural lesion.\textsuperscript{89}
The extent of the diagnostic evaluation for CD depends on its presentation. In infants and children, the work-up can be extensive, as indicated above. In adults, if CD is typical and not associated with other abnormalities, no additional laboratory assessments are required. If CD is atypical at presentation, further evaluation for structural or metabolic abnormalities is indicated.

TREATMENT OF CERVICAL DYSTONIA

The treatment of CD has undergone important change in the past two decades. Oral pharmacologic agents used to date have not been adequately assessed and are of limited use for most patients with CD. A variety of agents have been tried, including drugs affecting cholinergic, dopaminergic, serotonergic, and γ-aminobutyric acid systems. Anticholinergic drugs, while useful for treatment of generalized dystonia, provide symptom relief for a limited number of patients with focal dystonia. A retrospective analysis of 71 CD patients reported 39% with a good response to anticholinergic agents, with women improving more than men. Peripheral side effects, such as dry mouth, blurred vision, and urinary retention, are frequent, but may be reversed using a peripheral cholinesterase inhibitor (glycopyrrolate). The central side effects of sedation and memory loss are dose limiting.

Other drugs that can be of benefit in some CD patients include carbidopa/levodopa, clonazepam, and baclofen. Although dopamine receptor antagonists can improve symptoms of CD, the potential adverse effects, including tardive dystonia, limit the usefulness of this class of drugs. Although also reported to be sometimes helpful, dopamine receptor blocking agents are discouraged. Tetrabenazine, a monoamine-depleting and a dopamine-receptor-blocking drug, is useful, but as many as 30% of patients will experience sedation, parkinsonism, depression, anxiety, or akathisia with treatment. Tetrabenazine is currently not generally available in the USA. Oral mexiletine was assessed in one open-label study of nine CD patients, and showed improvement in motor symptoms, with electrophysiologic dampening of dystonic activity in the sternocleidomastoid muscle. This effect persisted for the 6 months of the study, but these results have not been confirmed in a controlled study. Botulinum toxin injections have largely supplanted other treatment modalities for CD. Botulinum toxin type A is effective for the treatment of CD as has been demonstrated in both double-blind and open-label studies. Approximately 60–85% of patients improve, with reduced head movement and pain, and increased range of motion and quality of life. The adverse effects from botulinum toxin are frequent, affecting up to 30%. The most common adverse effects include dysphagia and neck weakness, which are related to the local effects of the toxin, and are usually mild and transient. A small percent of patients receiving repeated injections develop resistance to the effect of botulinum toxin type A. The development of new types of botulinum toxin provides an alternative for CD patients with resistance to type A. Controlled clinical trials using botulinum toxin type B show significant improvement in CD patients with and without resistance to type A.

Phenol is a neurolytic agent that has been used in a limited number of CD patients. Although initial results are promising, this agent requires specific training in its application and can cause serious adverse effects if used inappropriately.

Surgical treatments for CD are reserved for patients with disabling symptoms that fail to benefit from drug treatments and botulinum toxin. Chronic spinal cord stimulation, although initially promising in an open-label study, was not found to be an effective treatment for dystonia in a small, double-blind study. Rhizotomy and myectomy have, likewise, not been successful. Selective peripheral denervation, with specific lesion of the branch of the spinal accessory nerve to the sternocleidomastoid muscle and a selective ramisectomy of the branches serving the posterior neck muscles, is promising, but is often an extensive surgery with a prolonged recovery time requiring intensive rehabilitation. The success rate in carefully selected patients operated on by experienced surgeons is over 80% and the complication rate is low. The surgical technique has recently been modified to reduce the occurrence of postoperative numbness in the C2 distribution and lessen the frequency of postoperative occipital neuralgia.

Deep brain stimulation (DBS) is successful for the treatment of primary generalized dystonia. Preliminary results in a small number of CD patients show that pallidal DBS can be very effective. However, larger controlled clinical trials are needed.

REFERENCES

78 CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA


80 CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA


INTRODUCTION

Cranial muscles form a highly complex network that provides an amazing multitude of different functions, including some of the most sophisticated functions that muscles can perform. This complexity is reflected by the overproportional size of their motor cortical representation, as suggested by Penfield and Rasmussen’s homunculus. Cranial muscles are involved in psychomotor communication, in speech articulation, in exploration, intake, processing, transport and swallowing of food and liquids, in affective exploration, in eye movements, in vision control, in eye protection and in hearing.

With the exception of vision control and hearing, all of their functions can be impaired by dystonia. However, dystonia is just one of many disorders affecting cranial muscles, including other disorders of the basal ganglia, disorders of the limbic system, the frontal lobe, the pyramidal tract, the peripheral nervous system, and the cranial muscles themselves.

Cranial dystonia can be part of a complex movement disorder where dystonia occurs together with other abnormal movements, as in Huntington’s disease (see Chapter 2). Sometimes cranial dystonia can be the presenting feature of those complex movement disorders, as in neurodegeneration with brain accumulation of iron (NBAI) or in neuroacanthocytosis. Cranial dystonia can also be part of a widespread dystonic syndrome, as in Oppenheim’s dystonia. Sometimes, cranial dystonia is the predominant manifestation of those dystonic syndromes, as in tardive dystonia. Cranial dystonia can also occur in isolation, as in blepharospasm. There is reason to believe that the different context in which cranial dystonia occurs reflects different pathophysiologic and etiologic entities.

ANATOMY

As shown in Table 9.1, the cranial muscles comprise at least 58 paired muscles and 1 unpaired muscle and connect the skull and its associated structures, such as the mandible, the os hyoideum, the cranial and nuchal skin, the tongue, the pharynx, the eyes, and the ears. Muscles originating on those associated structures and inserting elsewhere are not considered cranial muscles.

Mimic muscles are cranial muscles originating from the skull and the jaw and inserting into the facial or nuchal skin or into aponeuroses. They form a highly complex functional network. Originating from the second visceral arch, they are all innervated by the facial nerve. Inserting into the skin, all mimic muscles lack a fascia, thus making them prone to transdermal infections. Figure 9.1 shows the mimic muscles. Mimic muscles model the skin and moving structures imbedded into the skin, such as the eyebrows, the mouth, and the eyelids. Activation of mimic muscles is performed with enormous precision and velocity. Mimic muscles are one of the main psychomotor output channels. Estimated by the amount of information transmitted, psychomotor communication is probably the most important output channel available to humans. Other mimic muscle functions include eye protection, exploratory lip movements, and food and liquid intake. Because of the functional complexity of the mimic muscle network, therapeutic interventions, such as botulinum toxin therapy or surgery, are complicated and often impair the fragile balance of agonistic and antagonistic muscle activity.

The orbicularis oculi muscle consists of the palpebral part covering the eyelids, the orbital part surrounding the palpebral part and connecting it to the surrounding mimic muscles, and the lacrimal part controlling
Cranial muscles connect the skull, the jaw, the os hyoideum, the cranial skin, the eyes, the tympanon, the tongue, and the pharynx. Muscles originating in those elements and inserting elsewhere are not considered cranial muscles.

Tear drainage. The fiber architecture of the orbicularis oculi muscle is shown in Figure 9.2. Figure 9.3 shows its complex movement sequence, producing eyelid closure, initiating tear drainage, and achieving foreign body removal. The orbicularis oris muscle is densely interconnected with the overlying skin. Because of its fiber architecture it is able to produce complex modeling of the lips. It is held in place entirely by its surrounding muscles. The depressor anguli oris muscle depresses the corner of the mouth and stabilizes the lower lip. The mentalis muscle forms the chin dimples. It also stabilizes the lower lip, however, to a lesser degree than the depressor anguli oris muscle. The risorius muscle abducts the corner of the mouth. The muscles above the dividing line between the lower lip and the upper lip – i.e. the levator anguli oris, levator labii superioris, zygomaticus major, zygomaticus minor, and levator labii superioris alaeque nasi muscles – fixate the orbicularis oris muscle.
protrusion, jaw retraction, and lateral jaw movements and, together with the muscles of the floor of the mouth and the infrahyal muscles, are involved in jaw opening. The jaw muscles stabilize the mandibular joint, which is otherwise a joint with an extreme degree of freedom. The masseter and the pterygoideus medialis muscles close the jaw, the pterygoideus lateralis muscle, the muscles of the floor of the mouth, and the infrahyal muscles open the jaw, the pterygoideus lateralis muscle supported by superficial fibers of the masseter and the medial pterygoideus muscles protrude the jaw, unilateral activation of the lateral pterygoideus muscle moves the jaw to one side, and the temporalis muscle retracts the jaw.

Tongue muscles form the shape of the tongue and move it around. The shape of the tongue is modeled by the internal tongue muscles. The tongue is shortened by the longitudinal tongue muscles, it is flattened by the vertical tongue muscles, and narrowed and rounded by the transversal tongue muscles. The external tongue muscles move the tongue. The styloglossus and the hyoglossus muscles retract the tongue and the genioglossus muscle moves the tongue forward.

Muscles of the floor of the mouth close the intermandibular space and are involved in jaw opening.

Pharynx muscles form the introitus to the esophagus and to the trachea, and are involved in food and liquid transport.

**DEFINITIONS**

Cranial dystonias are dystonias that affect the cranial muscles. Blepharospasm or periocular dystonia describes dystonia in the orbicularis oculi and – facultatively – its adjacent muscles, including the corrugator supercilii, procerus, nasalis, and levator labii superioris alaeque nasi muscles. When blepharospasm occurs in isolation, it is called essential blepharospasm or – slightly misleadingly – benign essential blepharospasm. Perioral dystonia refers to dystonia of the orbicularis oris and its adjacent muscles, orofacial dystonia to dystonia in the orbicularis oris and in other mimic muscles. Oromandibular dystonia describes dystonia in the orbicularis oris and its adjacent mimic muscles, in the jaw muscles, and in the floor of the mouth. Frequently, dystonia in the tongue and in the pharyngeal muscles is associated.

Orobuccolingual dystonia is dystonia in the orbicularis oris, its adjacent mimic muscles, and in the tongue. Meige syndrome, named after the French neurologist Henry Meige (1866–1940), describes the combination of facial and oromandibular dystonia. The term Brueghel’s syndrome was suggested by C David Marsdens for the combination of blepharospasm and oromandibular dystonia. It was named after the

**Figure 9.1** Mimic muscles. (Reproduced from Dressler, with permission.)
painting ‘De Gaper’ (‘The Yawner’) by Pieter Brueghel the Elder (1525–1569) (Figure 9.4), but was never widely accepted. We suggest describing cranial dystonia according to its localization as periocular (blepharospasm), perioral, facial (periocular and perioral), oromandibular and faciomandibular (Meige syndrome, Brueghel’s syndrome).

Sometimes the term dyskinesia is used to describe a mixture of choriform and dystonic cranial muscle hyperactivities usually as the result of chronic neuroleptic medication.

DIFFERENTIAL DIAGNOSES

Clinical conditions resembling cranial dystonia are numerous. In hemifacial spasm, involuntary muscle activity is virtually always unilateral, although bilateral cases have been reported.6–8 Hemifacial spasm produces a typical electromyographic pattern with brief high-frequency discharges occurring simultaneously in several mimic muscles. In advanced cases, perioral
facial weakness becomes frequent. Reinnervation synkinesias can occur after facial nerve lesions when aberrant nerve sprouting produces mismatched innervation of mimic muscles. Reinnervation synkinesias do not occur at rest. Usually, eyelid closure occurs when perioral activation is intended and vice versa. Tics consist of complex muscle activation patterns. Eye blinking is a common manifestation.\textsuperscript{9} Almost all idiopathic tics manifest before age 11 years.\textsuperscript{10} Frequently, vocal tics and obsessive-compulsive behavior are associated. Myasthenia gravis used to be a frequent misdiagnosis of blepharospasm before the concept of cranial dystonia received more widespread attention. Now, ocular myasthenia gravis, with all its diagnostic pitfalls, has to be considered in patients with lack of orbicularis oculi muscle hyperactivity and more pronounced diurnal fluctuations.\textsuperscript{11} Facial weakness in Lambert–Eaton myasthenic syndrome can be reminiscent of blepharospasm.\textsuperscript{12} Its diagnostic hallmarks include the typical increment of electromyographic responses to serial stimulation and antibodies against presynaptic calcium channels. Depression can produce a facial expression vaguely resembling blepharospasm. Again, no muscle hyperactivity in the orbicularis oculi muscle is detected to be caused by demyelinating lesions of the peripheral trigeminal motor fibers producing ephaptic neural activity, leading to painful forced jaw closures. It is believed to be caused by demyelinating lesions of the peripheral trigeminal motor fibers producing ephaptic neural activities similar to those seen in hemifacial spasm.\textsuperscript{13–17} Hemimasticatory spasms are a rare disorder presenting with frequent paroxysmal unilateral jaw muscle hyperactivity, leading to painful forced jaw closures. It is believed to be caused by demyelinating lesions of the peripheral trigeminal motor fibers producing ephaptic neural activities similar to those seen in hemifacial spasm.\textsuperscript{15–17} Hemifacial atrophy is frequently associated and possibly causes the trigeminal nerve lesion.\textsuperscript{17–19} Senile perioral dyskinesias or benign senile chorea, perioral choreiform movements, more often affect women than men. With a prevalence of 1.5% in individuals aged 67–87 years old,\textsuperscript{20} they are rarer than generally believed. They may include minor tardive syndromes, unusual cases of Huntington’s disease,\textsuperscript{21} or may be associated with Alzheimer’s disease.\textsuperscript{22} In non-dystonic blepharospasm, increased blinking and/or closure of the eyelids is caused by local eye irritation, as in conjunctival or corneal infection, foreign body entrapment, senile entropion, or use of personal defense sprays.\textsuperscript{23}

In some patients, eyelid opening is impaired not by hyperactivity of the orbicularis oculi muscle closing the eyelid but by the patient’s inability to activate the levator palpebrae muscle. This condition is called apraxia of eyelid opening or levator inhibition. It typically occurs in progressive supranuclear palsy,\textsuperscript{24} but also in idiopathic Parkinson’s disease.\textsuperscript{25} Electromyography demonstrates lack of orbicularis oculi muscle hyperactivity, delayed activation of the levator palpebrae muscle, and an impaired coordination between both muscles. It can occur in combination with blepharospasm.

Rare differential diagnoses of cranial dystonias include facial myokymia with clinically and electromyographically typical undulatory muscle activity due to demyelinating brainstem lesions or potassium channel abnormalities, Isaacs’ syndrome with its typical continuous muscle fiber activity, Schwartz–Jampel syndrome\textsuperscript{26} with continuous muscle fiber activity, and additional dysmorphic features.

**ETIOLOGY**

Cranial dystonias can occur isolated or as part of segmental, axial, or generalized dystonia. When they occur as part of a more widespread dystonia, they can be caused by the full spectrum of etiologies so far identified as producing dystonia; these are discussed in Chapter 1. Apart from a primary or idiopathic etiology with all its genetic options, cranial dystonias can be part of a dystonia-plus syndrome, i.e., dystonia with parkinsonism or dystonia with myoclonus, a secondary or symptomatic dystonia, and a dystonia in heredodegenerative or other degenerative disorders. When cranial dystonia is the prominent feature in a widespread dystonia, NBAI, neuroacanthocytosis, and tardive dystonia have to be considered.

**ESSENTIAL BLEPHAROSPASM**

**Prevalence**

Blepharospasm is the most common form of cranial dystonia. After cervical dystonia, it is the second most common form of focal dystonia. Its exact prevalence is not known. Service-based surveys indicate a prevalence of 3.1 in 100 000.\textsuperscript{27} Other data suggest a prevalence of 13.3 in 100 000.\textsuperscript{28} The sex ratio ranges from 1.8 females to 1 male\textsuperscript{29} to 2.5 females to 1 male.\textsuperscript{30}

**Clinical features**

Essential blepharospasm starts in adult life, most commonly in the sixth or seventh decade. Its onset is
insidious. Usually both eyes are affected equally, although unilateral onset has been described. Its first symptoms are often soreness of the eyes or the eyelids or dryness or excessive watering of the eyes. Later, excessive blinking occurs, especially on exposure to bright light or drafts, or when reading small texts, watching television, or when embarrassment, emotional tension, or fatigue occurs. Figure 9.5 gives an example of a patient with severe blepharospasm with additional perioral involvement. Frequently, patients wear dark glasses to protect their eyes from bright light and from drafts. Some patients avoid outdoor activities for these reasons. At this point, vision is impaired by losing text lines or focus during the blinking. Despite the relative mild vision impairment, patients are often severely disturbed, because of the constant additional effort to counteract blepharospasm. Socially, patients become stigmatized since the psychomotor communication with their environment becomes impaired and the increased blinking frequency is often misinterpreted as emotional instability or as a sign of substance abuse. Although increased blinking initially occurs only during certain periods, those periods later become prolonged and occur more frequently. The intensity of the blinking increases, so that eventually the eyelid closure is forced, and so prolonged that the patient is rendered functionally blind for long periods of the day. At this point, tension-type headache frequently occurs. During sleep, the condition disappears and in the morning the patient often feels relieved for the first few hours. Involvement of extraocular eye muscles does not occur. Some patients use tricks to open the eyes, such as forced jaw opening, yawning, neck extension, pressure with one finger against the temple bone, and preferentially using downward gaze. It is important to distinguish between primary dystonic muscle hyperactivity and secondary tricks to overcome it. Many patients experience corneal and conjunctival irritation due to impaired tear drainage. After prolonged courses, dehiscences of the eyelids can occur. In the upper eyelid, connective tissue may bulge over the pupil and may further impair vision. In the lower eyelid, entropion can develop with additional irritation of the cornea. One study suggested that Obsessive-compulsive symptoms are an associated feature of blepharospasm.31

Course

Essential blepharospasm usually begins insidiously. It slowly progresses to reach a plateau after some years. Once the condition has been stable for several years, further progress is rare. Spontaneous remissions are reported to occur in 10% of the patients within the first 5 years.32 According to our experience, this rate is lower. When essential blepharospasm progresses, it can expand into adjacent body areas, i.e. into other cranial muscles and into the neck muscles. Figure 9.6 shows a patient with Meige syndrome. Generalization is exceedingly rare.
Apraxia of eyelid opening

In some patients with essential blepharospasm, additional apraxia of eyelid opening can be detected by simultaneous electromyography of the orbicularis oculi and the levator palpebrae. Pure essential blepharospasm and pure apraxia of eyelid opening may be extremes of a spectrum, with some patients presenting with a mixture of both elements.

Etiology

Essential blepharospasm is considered a focal dystonia since the pivotal studies of C David Marsden. Its etiology is probably multifactorial, consisting of a genetic predisposition and additional factors. Occurrence of focal dystonia amongst first-degree relatives of patients with essential blepharospasm is reported to be about 6%. Special forms of inheritance have also been reported. Additional etiologic factors include basal ganglia or rostral brainstem lesions preceding eyelid or ocular surface irritation, including dry eye problems, and functional brainstem abnormalities.

Treatment

Treatment of cranial dystonia consists of botulinum toxin therapy, drugs, surgery, and additional measures. Sometimes it may be necessary to combine different therapeutic regimens.

Drugs

Drug treatment of essential blepharospasm is usually frustrating. As shown in Table 9.2, there are a large number of drugs with occasional positive effects reported in the literature. All drugs suggested to treat other focal or generalized dystonias can be used for essential blepharospasm as well. Chances of improvement after drug treatment, however, are poor. Times to gradually build up the dose of each of the potentially antidystonic drugs are long. Frequently, severe adverse reactions occur, including dryness of mouth, drowsiness, concentration difficulties, agitation, and accommodation difficulties. The best therapeutic effects are seen with trihexyphenidyl, probably followed by baclofen, clonazepam, and tetrabenazine.

Surgery

Traditional treatment of blepharospasm is the eyelid protractor myectomy procedure, including excision of the orbicularis oculi, the corrugator supercilii, and the procerus muscles. Reported results indicate subjective improvement with long-term benefit in most of the patients treated. Consecutive tissue defects can be compensated by muscle grafts. Additional application of botulinum toxin is possible. More recently, selective peripheral denervation procedures, so-called facial nerve avulsions, have been suggested. The main problem with this operation is to control the degree of denervation in the target muscles, partly because the facial nerve branches form a complex nerve plexus. Insufficient denervation produces suboptimal therapeutic effects and excessive denervation adverse effects, including ectropion and facial asymmetries. Reoperations to adjust the therapeutic effect, therefore, become frequently necessary. Reinnervation and facial pain are other frequent side effects. For the frontalis suspension operation, the upper eyelid is connected with subcutaneous strings to the frontalis muscle to facilitate eyelid opening. This operation is successful in apraxia of eyelid opening. In patients with apraxia of eyelid opening and blepharospasm, it should be combined with botulinum toxin therapy. In pure blepharospasm, it is not successful, since the eyelid closing forces may damage the string fixation. Pallidal stimulation has recently been tried for blepharospasm and Meige syndrome.

Botulinum toxin

Botulinum toxin is by far the most successful treatment of cranial dystonias. When injected into muscle tissue, i.e. the target muscle, botulinum toxin produces a well-controllable paresis by blocking the neuromuscular junction. Apart from some minor spread into muscles adjacent to the target muscle it does not participate in general metabolism and thus does not produce adverse effects otherwise frequently seen with antidystonic drugs.
The botulinum toxin effect usually starts after 3–5 days and lasts for up to 4 months. The therapeutic effect of botulinum toxin is caused by relaxation of the dystonic muscle, thus reducing functional impairment and pain. Early application of botulinum toxin can avoid secondary complications of dystonia. Additional effects of botulinum toxin on muscle spindles and on the central nervous system have been described; a contribution to the therapeutic effect, however, remains unclear. Direct analgesic effects of botulinum toxin have been hypothesized, but their relevance in clinical practice is unclear. In order to achieve optimal therapeutic effects, dystonic muscles need to be identified and their dystonic involvement needs to be established so that they can be injected with adequate doses and unaffected muscles can be spared. Botulinum toxin drugs include Botox (Allergen Inc., Irvine, CA, USA), Dysport (Ipsen Ltd, Slough, Berks, UK), NeuroBloc/Myobloc (Solstice, Malvern, PA, USA), and Xeomin (Merz Pharmaceuticals, Frankfurt, Germany). Whereas Botox and Xeomin doses can be converted on a 1:1 basis, the conversion ratio between Botox and Dysport has been a matter of debate. Currently a 1:2 to 1:3 conversion rate seems to be most appropriate. The conversion ratio between Botox and NeuroBloc/Myobloc seems to be in the order of 1:40.

Possible target muscles and botulinum toxin doses for the treatment of blepharospasm are shown in Table 9.3. The primary target muscle is the orbicularis oculi, which is usually injected in three or four sites between its orbital and its tarsal part. Sparing of the muscle part covering the levator palpebrae muscle helps to avoid ptosis. Botulinum toxin injections into the pretarsal parts of the orbicularis oculi can be used to intensify the therapeutic effect. They seem to be particularly helpful in patients with components of apraxia of eyelid opening.52,53 Mimic muscles adjacent to the orbicularis oculi, such as the procerus, the corrugator supercilii and the nasalis muscles, may also be used as target muscles. Injection of the frontalis muscle should be avoided because of its function as an auxiliary eyelid opening muscle. Botulinum toxin therapy of blepharospasm has a high success rate. Primary therapy failure is extremely rare and can be due to the presence of apraxia of eyelid opening and non-dystonic blepharospasm, excessive lid edema, eyelid dehiscences, doubled eyelids (shuang yan pi or dan yan pi) in Chinese patients,54 and to concomitant entropion. In some patients, blepharospasm is associated with intense sensory irritations that may persist despite botulinum toxin-induced reduction of dystonic muscle hyperactivity. Secondary therapy failure can be due to the formation of neutralizing antibodies against botulinum neurotoxin. It is, however, exceedingly rare.2 Side effects include hematoma, diplopia, ptosis, and ectropion. With the exception of hematoma, other side effects are rare and may be influenced by the botulinum toxin preparation used.55

### Additional measures

Dark glasses may reduce the facilitating effects of bright light and drafts. Wire springs attached to spectacle frames have been suggested to push up the upper eyelids. When blepharospasm is severe, this approach is not effective; in minor cases or when eyelid dehiscences are present, it may have some effect. The use of adhesive tapes may be temporarily effective in mild cases, but frequently causes skin lacerations. Sensory tricks, such as touching skin of the temporal bone, may be partially effective. When blepharospasm has existed for a prolonged period of time, sometimes eyelid dehiscences can occur. When botulinum toxin injections are applied, they may be mobilized and may impair vision. Eyelid lifting operations can correct them. They are not effective to treat the muscle hyperactivity of blepharospasm. Application of artificial tears may compensate impaired lacrimal drainage.

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Function</th>
<th>Botulinum toxin dose (100 MU Botox in 2.5 ml NaCl/H₂O) [MU Botox]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orbicularis oculi</td>
<td>Eyelid closing</td>
<td>18–36</td>
</tr>
<tr>
<td>Procerus</td>
<td>Formation of transversal nasal root fold</td>
<td>6–12</td>
</tr>
<tr>
<td>Corrugator supercilii</td>
<td>Eyebrow adduction</td>
<td>6–12</td>
</tr>
<tr>
<td>Nasalis</td>
<td>Formation of nasal dorsum fold</td>
<td>4–8</td>
</tr>
</tbody>
</table>

Modified from Dressler.2
OROMANDIBULAR DYSTONIA

Prevalence

Oromandibular dystonia is substantially less common than cervical dystonia and may have similar prevalence to blepharospasm. Valid data on the epidemiology, however, are lacking. There is a female preponderance of about 2:1.

Clinical features

Oromandibular dystonia presents as a jaw opening type, jaw closing type, and as a mixed type. Most of the patients suffer from the jaw closing type. Figure 9.7 shows a patient with oromandibular dystonia of the mixed type. Figure 9.8 shows two patients with oromandibular dystonia of the jaw opening type. Usually, oromandibular dystonia presents bilaterally, but side predominances may occur. Unilateral manifestations are very rare, but have been reported. Associated features can include tongue protrusion, tongue twisting, and involvement of facial, neck, and pharyngeal muscles. Frequently, dysarthria and relative hypersalivation develops. Dysphagia and dyspnea are less frequent. In advanced cases, the condition is extremely stigmatizing and patients try to hide the jaw opening, tongue protrusion, and hypersalivation with their hands or with

Figure 9.7
Orofaciomandibular dystonia with oromandibular dystonia of the mixed type and blepharospasm.
towels. After a prolonged duration, temporomandibular joint impairment and muscular pain frequently occur. Jaw and tongue movements may loosen natural and artificial teeth.

**Primary oromandibular dystonia**

As with other primary focal dystonias, the onset of oromandibular dystonia is insidious. It usually reaches a plateau after several years. Further exacerbations are then rare. Oromandibular dystonia can spread into adjacent body parts. Generalization, however, is exceedingly rare.

**Tardive oromandibular dystonia**

Tardive oromandibular dystonia seems to have a more acute onset than idiopathic oromandibular dystonia. In one study it developed around six years after onset of D2 blocking agent administration. In some patients this latency may be as short as 4 days or as long as 23 years. In 87% of patients with tardive muscle hyperactivity disorders, the first and predominant manifestation is in craniocervical muscles. Oromandibular involvement often presents with typical complex licking and smacking movements. Additionally, cervical involvement with a high rate of antecollis and retrocollis can be observed. Seven percent of patients present with respiratory problems, including shortness of breath, irregular breathing patterns, and involuntary grunting and gasping noises. Associated features include tremor, parkinsonian syndromes, akathisia, and limb stereotypes. Numerous medicolegal problems are associated with tardive oromandibular dystonia, including obtaining informed consent in psychotic patients and properly balancing risks and benefits of D2 receptor blocking agent therapy. Use of D2 receptor blocking agents for treatment of minor depression, anxiety, or psychosomatic disorders may constitute medical malpractice.

**Etiology**

Oromandibular dystonia can occur as part of a more severe dystonia phenotype. When it is the predominant manifestation, a tardive etiology has to be considered. Pathophysiology of tardive oromandibular dystonia is still not fully understood. Evidence for a causal role of D2 receptor blocking agents is compelling. A number of lines of evidence suggest a key role for dopamine receptor hypersensitivity in the pathogenesis. However, the effects of D2 receptor blocking agents on other transmitter systems may also play a role in the pathophysiology of tardive dystonia. In some patients, oromandibular-facial trauma, including dental procedures, may precipitate the onset of oromandibular dystonia.

**Treatment**

The decision to initiate treatment of oromandibular dystonia depends on the severity of the symptomatology. Especially in tardive oromandibular dystonia, some patients only have minor perioral muscle hyperactivities not requiring treatment.

**Drugs**

Drug treatment for primary oromandibular dystonia is similar to that for periocular or other dystonias. In tardive oromandibular dystonia, discontinuation of the causative agent provides a chance for spontaneous
remission. Debate is still open as to the percentage of patients improving. Whereas some authors report improvement in about half of their patients, others have seen improvement in only 14% of patients. On average, improvement occurs after 2.6 years, with some patients improving after 1 month, and others up to 9 years later. When discontinuation is contraindicated because of the psychiatric diagnosis, atypical neuroleptics should be used. Benzodiazepines, such as clonazepam, may be helpful in minor cases for reduction of dystonia and of associated anxiety. Tetrabenazine is also effective and does not bear the risk of further aggravating the dystonic symptomatology. However, it has a significant risk of causing parkinsonism. As a last resort, D2 blocking agents may be used successfully supporting the D2 hypersensitivity hypothesis. However, they are said to reinforce the underlying pathophysiology process and the dystonic symptomatology.

**Botulinum toxin**

Botulinum toxin therapy of oromandibular dystonia focuses on the jaw muscles. In the jaw closing type, botulinum toxin injections can be performed in the masseter bilaterally (Table 9.4). Rarely, additional botulinum toxin injections of the temporalis muscles are necessary. If there is remaining pain and jaw protrusion, botulinum toxin injections of the pterygoid muscles can also be performed. The therapeutic outcome of botulinum toxin therapy of jaw closing oromandibular dystonia is excellent. Apart from chewing fatigue, which can occur on prolonged chewing, adverse effects are rare. The jaw opening type is considerably more difficult to treat, since jaw opening is performed by numerous muscles in the front of the neck also involved in swallowing. The primary target muscles for jaw opening dystonia are the pterygoid muscles bilaterally.

Whereas the medial pterygoid is a jaw closing muscle, the lateral pterygoid is involved in all jaw movements, including jaw opening. For jaw opening dystonia, the lateral pterygoid should therefore be the primary target muscle. However, separation of both pterygoids would require electromyography and would, thus, complicate the elegant transcutaneous approach through the incisura mandibulae. Since isolated involvement of the lateral pterygoid has not been demonstrated anyway, transcutaneous injection of both pterygoids seems to be a practical approach. Often pain reduction and reduction of the jaw opening force is achieved. Additional injection of the mylohyoid muscles bilaterally and the infrahyoid muscles bilaterally can be tried. Swallowing difficulties, however, may be triggered. Botulinum toxin injections of the platysma can improve the cosmetic appearance, but have minor functional relevance. Botulinum toxin injections of perioral muscles are difficult because of a high risk of functional and cosmetically disturbing facial weakness. For this reason, botulinum toxin injections above the line between the upper and the lower lips should be avoided. Below this line, the depressor anguli oris muscle can be targeted.

**Table 9.4 Possible target muscles and dose ranges for botulinum toxin therapy of oromandibular dystonia**

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Function</th>
<th>Botulinum toxin dose (100 MU Botox in 2.5 ml NaCl/H₂O) [MU Botox]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Masseter</td>
<td>Jaw closing</td>
<td>40–60</td>
</tr>
<tr>
<td>Temporalis</td>
<td>Jaw closing</td>
<td>40–80</td>
</tr>
<tr>
<td>Pterygoidei</td>
<td>Jaw protrusion</td>
<td>20–60</td>
</tr>
<tr>
<td></td>
<td>Jaw closing</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jaw lateralization</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Jaw opening</td>
<td></td>
</tr>
<tr>
<td>Mylohyoideus</td>
<td>Jaw opening</td>
<td>20–40</td>
</tr>
<tr>
<td>Mentalis</td>
<td>Formation of chin dimple</td>
<td>6–12</td>
</tr>
<tr>
<td>Depressor anguli oris</td>
<td>Depresssion of the corner of the mouth</td>
<td>4–8</td>
</tr>
<tr>
<td>Risorius</td>
<td>Abduction of the corner of the mouth</td>
<td>4–8</td>
</tr>
<tr>
<td>Platysma</td>
<td>Jaw opening</td>
<td>16–32</td>
</tr>
<tr>
<td>Infrahyal muscles</td>
<td>Jaw opening</td>
<td>40–60</td>
</tr>
</tbody>
</table>

Modified from Dressler, with permission.
Occasionally, instability of the lower lip may result. Botulinum toxin injections of the mentalis muscle have minor functional relevance, but improve cosmetic appearance considerably. Rarely, they produce side effects. Genioglossal muscle injections may reduce tongue protrusion. Botulinum toxin injections into the parotid gland bilaterally are effective to reduce drooling and to alleviate stigmatization of the patient.

**Additional measures**

Splints have been used for many years to treat jaw closing oromandibular dystonia by diverting the jaw closing force to a larger area, and thus protecting the teeth. They may also reduce the generation of dystonic muscle hyperactivity by changing the jaw position and the jaw mechanics. In severe cases, application of a percutaneous endoscopic gastrostomy may become necessary.

**OTHER CRANIAL DYSTONIAS**

**Bruxism**

Bruxism is used to describe forceful jaw closures producing grinding or clenching of the teeth. Bruxism can be part of a more widespread oromandibular dystonia. It can also be an isolated occurrence. Isolated bruxism usually presents at night, justifying the term sleep bruxism. It is produced by a relatively typical electromyographic pattern. The prevalence of bruxism may be as high as 8% of the general population. In children and young adults, its prevalence may be considerably higher. Sex differences seem not to exist. The etiology of bruxism is not clear. Dopaminergic mechanisms may be involved, as suggested by the frequent association between isolated bruxism and periodic movements in sleep. Bruxism may also present exaggerated physiologic jaw movements. Facilitation of bruxism by emotional stress has been debated controversially. It becomes a pathologic condition in a minority of individuals affected, when tooth problems, jaw muscle pain, temporomandibular joint impairment, and non-restorative sleep occurs. Spouses may also be disturbed in their night sleep. Alcohol, amphetamine, cocaine, and tricyclic antidepressants can exacerbate isolated bruxism. Oral splinting has been used for decades and seems to help. It protects the teeth and may reduce bruxism’s intensity and frequency. Botulinum toxin therapy may also be tried in more severe cases.

**Acute dystonic reactions**

Acute dystonic reactions are tonic muscles hyperactivities induced by application of D₂ receptor blocking agents. They most often affect the external eye muscles, producing the clinical picture of oculogyric crisis with gaze deviation upward or sideward first described as sequelae of encephalitis lethargica. They also affect mimic muscles and jaw, tongue, and pharyngeal muscles, typically producing forced mouth opening and tongue protrusion. Extracranial manifestations include the neck and trunk muscles and less frequently the limb muscles, producing head tilt backward or sideways and trunk arching. Figure 9.9 shows a patient with an acute dystonic reaction with oculogyric crisis, retrocollis, right torticollis, jaw opening, and tongue protrusion. (Reproduced from Delay and Deniker, with permission.)
chlorpromazine bear a lower risk. Acute dystonic reactions can also be triggered by risperidone, clozapine, and serotonergics, probably by side effects or indirect effects on D2 receptors.

Figure 9.10 Neurodegeneration with brain accumulation of iron. The patient presents with severe oromandibular dystonia of the jaw opening type with temporomandibular joint subluxation. External pressure is used to keep the mouth shut. Additional features include blepharospasm and voluntary hyperextension of the finger joints. Later, the patient developed severe bilateral extensor type leg dystonia.

Figure 9.11 Wilson’s disease. The patient presents with oromandibular dystonia of the jaw closing type with typical abduction of the corners of the mouth (risus sardonicus).

D2 blocking agents are also used in antiemetics, such as metoclopramide and prochlorperazine, both of which can cause acute dystonic reactions. Applied to children, metoclopramide can trigger acute dystonic reactions in up to one-third of the patients. The pathophysiology of acute dystonic reactions is complex and not fully understood. A dysbalance between dopaminergic and cholinergic functions seems to be involved. Postacute D2 receptor sensitivity changes may also play a role. Application of anticholinergics, such as biperiden or benzotropine, or of antihistamines, such as diphenhydramine, almost invariably produces relief within 15–30 minutes. Occasionally, repeated application may become necessary. Without therapy, acute dystonic reactions resolve within 12–48 hours. Acute dystonic reactions should be prevented by using D2 receptor blocking agents in the lowest effective doses only. Contrary to antiquated belief, extrapyramidal side effects are not necessary to produce antipsychotic effects. Therefore, handwriting tests to monitor parkinsonism for optimal dose adjustment of neuroleptics are obsolete. In at-risk populations, prophylactic application of anticholinergics is justified.

Neurodegeneration with brain accumulation of iron (Hallervorden–Spatz syndrome)

NBAI is an autosomal recessive disorder characterized by dystonia, parkinsonism, and iron accumulation in the brain. Typically, it presents with predominant oromandibular dystonia. Figure 9.10 shows a patient with NBAI with severe oromandibular dystonia of the
jaw opening type. Classically, the syndrome starts in childhood and deteriorates rapidly. Atypical cases have a later onset and a slower progression.\(^{33}\) T2-weighted magnetic resonance imaging reveals a specific pattern of hyperintensity within the hypointense medial globus pallidus, the eye-of-the-tiger sign.\(^{34}\) A defect in the pan-

Familial nocturnal faciomandibular myoclonus is an extremely rare condition characterized by nocturnal tongue biting with bleeding. Muscle activities originate in the masseters and spread to the orbicularis oris and orbicularis oculi muscles. They only occur at sleep and seem to be familial.\(^{101}\) The term myoclonus may be misleading.

**REFERENCES**


INTRODUCTION
The dystonias have been classified by a variety of criteria, including age at onset, anatomic distribution, etiology, and, most recently, genetics. One of the most striking and puzzling features of certain types of dystonia has been the selective involvement of certain motor programs where dystonic muscle contractions are restricted to specific tasks or motor acts while the same muscles can be activated normally with most or all other activities. Writer’s cramp is the most common and prominent example of the task-specific dystonias, but selective hand dystonia can also affect a variety of other manual skills such as typing, sorting, and painting; playing string or keyboard instruments; or engaging in sports like tennis, golf, or snooker. The common theme to all task-specific dystonias is that they selectively affect highly overlearned and automated types of movement and that treatment often fails to restore the premorbid level of function for the tasks involved. This chapter reviews the clinical features, pathophysiology, prognosis, and treatment of the task-specific dystonias as well as other limb-selective dystonias.

WRITER’S CRAMP
Writer’s cramp is the most common type of task-specific dystonia. The reported frequency among the focal dystonias ranges from 5% to 19% in different epidemiologic studies and a European medical record-based study found a prevalence of 1.4 per 100 000. Recent epidemiologic studies suggest that the prevalence of primary focal dystonia, including writer’s cramp, in the general population may be much higher than assumed from hospital-based series.

Clinical features
Writer’s cramp, typically, is a disorder of mid-adulthood affecting patients between the third and fifth decade, with a mean age at onset in the mid thirties or mid forties. There is no specific precipitant in most cases, but occasional patients may report a history of trauma or strain to the affected limb, and, in historical series of patients with writer’s cramp, office clerks engaged in professional handwriting were over-represented. Initial symptoms may be feelings of tension in the fingers or forearms that interfere with the fluency of writing; a minority may also experience pain. The pen is held abnormally forcefully due to dystonic contraction of the hand and/or forearm muscles, causing different patterns of deviation from the normal or premorbid pen grip and hand posture (Figures 10.1 and 10.2). A common pattern involves excessive flexion of the thumb and index finger, with pronation of the hand and ulnar deviation of the wrist. Other patients may have abnormal activation of wrist flexors, with supination of the hand and flexion of the wrist. Individual patients may experience involuntary lifting off of the index or thumb from the pen or isolated extension of other fingers as well. When dystonic cramps affect up to three fingers only, Cohen and Hallett have suggested the term of ‘localized’ (vs non-localized) writer’s cramp. The forearm muscles most often involved in writer’s cramp are the flexor carpi ulnaris and radialis, flexor digitorum superficialis, flexor pollicis longus, and extensor digitorum communis muscles.

Up to 50% of patients with writer’s cramp may also show upper limb tremor. Like the dystonic movements themselves, tremor in writer’s cramp can be task specific, whereas in other instances it may resemble typical essential tremor. Several reports have emphasized the occurrence of task-specific tremor without...
associated dystonic features when writing and termed this condition primary writing tremor. Although possibly related to writer’s cramp, writing tremor is currently classified among tremor disorders rather than dystonias. 17

Although sensations of strain and aching in dystonic forearm muscles are common in writer’s cramp, pain – unlike in cervical dystonia – is rarely a prominent feature, presumably due to the task-specific and intermittent nature of the disorder where the build-up of pain would normally stop individuals from performing the task.

**Course and prognosis**

About a third of patients initially note intermittent problems and at the beginning of their illness may be able to write short stretches of text normally before dystonic cramping starts to interfere with their script. Such patients generally note progressive shortening of the time during which they can write without onset of dystonic finger or hand movements. A majority of patients with writer’s cramp, however, complain of difficulties with holding a pen and impaired script as soon as they start writing already at disease onset. 8–10

A minority of individuals with writer’s cramp also have dystonia when engaging their affected hand in other manual tasks, such as opening the lid of a jar or manipulating a variety of objects (shaving, brushing teeth, handling a knife and fork). Sheehy and Marsden8 have suggested the term ‘dystonic writer’s cramp’ to differentiate such patients from the majority where dystonia is selective for the act of writing (‘simple writer’s cramp’). These authors found that a proportion (8 of 21 in their series) of patients may progress from simple to dystonic writer’s cramp within months or years. 8

Whereas progression of writer’s cramp to involve other manual tasks is not uncommon, spontaneous remissions are rare and have only exceptionally been described. 18 Many patients with writer’s cramp develop strategies by which they try to overcome their writing problems. These include changes in the way they hold their pen, often supported by adaptations to the shape and size of the pen to support changes in finger and hand positions to the pen.

Some 50% of patients who are no longer able to write intelligibly attempt to learn to write with the contralateral unaffected hand and a proportion of these will develop similar difficulties in this hand over periods as short as a few months to many years. About 5% of patients who have relearned to write with their non-dominant hand will display dystonic mirror movements of their initially affected hand when writing. 19

**Investigations**

Writer’s cramp is a straightforward clinical diagnosis in cases with typical onset and presentation. Neurophysiologic studies reveal a number of abnormalities but are not strictly necessary in clinical routine. While routine electromyography (EMG) and nerve conduction studies of forearm muscles and nerves are usually normal, polymyographic recordings during writing show deficient reciprocal inhibition with co-contraction of antagonistic muscles, prolonged EMG bursts with or without tremor, and pathologic build up of co-contracting muscle activity (‘crescendo-phenomenon’; Figure 10.3). 7,20

Investigations of reciprocal inhibition of H-reflexes in forearm flexor muscles in patients with writer’s cramp and other task-specific dystonias show a normal disynaptic phase but a reduction in the amount of
presynaptic inhibition. Cutaneous silent periods and cortical inhibitory mechanisms are abnormal, as shown by several findings, including decreased silent periods following transcranial magnetic stimulation (TMS) in writer’s cramp and other task-specific dystonias. Siebner et al have shown reduced corticocortical inhibition in the primary motor cortex regions by using a repetitive TMS technique in patients with writer’s cramp, and TMS mapping procedures revealed displacement and distortion of cortical hand muscle representation in the primary motor cortex of patients with writer’s cramp. Crescendo phenomenon during build-up of tonic contraction is a characteristic sign of dystonic activity in writer’s cramp.

Functional imaging studies in patients with writer’s cramp using computed tomography (CT) or magnetic resonance imaging (MRI) are typically normal, but may serve to exclude rare symptomatic forms of writer’s cramp in patients with contra lateral basal ganglia pathology and in cases with atypical presentation or associated non-dystonic features like rigidity, akinesia, myoclonus, apraxia, or sensory loss (Table 10.1).

Figure 10.3 Surface EMG recordings from elbow and forearm muscles during a standardized writing task in a patient with writer’s cramp. Surface EMG recordings show increased tonic activation with disturbed reciprocal inhibition and co-contraction of forearm flexor and extensor muscles in a patient with simple writer’s cramp. Crescendo phenomenon during build-up of tonic contraction is a characteristic sign of dystonic activity in writer’s cramp.

luation of the hand, while writing a stereotyped word and during sustained contraction of the affected hand. In addition, Ceballos-Baumann et al reported a similar activation pattern during freely selected joystick movements in patients with focal and generalized dystonia. However, two more recent functional neuroimaging studies showed contradictory findings, with underactivity of prefrontal motor areas and overactivity of the primary sensorimotor cortex in patients with writer’s and musician’s cramp during full expression of their task-specific dystonia. Pujol et al suggested that these conflicting findings might result from different test conditions. Therefore, reduced activation of the primary sensorimotor cortex might result from a strategy used to circumvent dystonia, in which overactivity of premotor areas represents the attempt of the patient to suppress the unwanted dystonic movements.

Writer’s cramp can be a rare manifestation of DYT1 dystonia. The DYT1 GAG deletion was found to be responsible for juvenile onset writer’s cramp in a German family with five affected patients without further spread of symptoms. Additionally, in early-onset, DYT1 positive segmental and generalized cases, symptoms frequently start in an upper limb and DYT1 GAG deletion carriers with isolated writer’s cramp have been described in different families. However, the DYT1 GAG deletion was not found in a larger series of middle European patients with sporadic and familial writer’s cramp. Gasser et al did not find the DYT1 mutation in a series of Ashkenazi Jewish patients with isolated musician’s and writer’s cramp. These results indicate that task-specific limb dystonia is only in rare cases a phenotypic manifestation of the DYT1 mutation, and testing for DYT1 mutations is only recommended for patients with onset before age 26 years or in older patients having an affected relative with early-onset primary dystonia.

Occasional reports have described writer’s cramp as a presenting symptom in untreated Parkinson’s disease and this may be less rare in parkinson disease. When there is reasonable suspicion, dopamine transporter single-photon emission computed tomography (DAT-SPECT) imaging may aid in the differential diagnosis vs primary dystonia.

Treatment

Behavioral therapies

On the basis of the hypothesis that abnormal sensory processing could cause a motor disorder, Zeuner et al have studied the efficacy of learning to read Braille as a method of sensory training for patients with focal hand dystonia. After 8 weeks of daily practice, focal dystonia
improved in 50% of patients and spatial acuity also improved significantly in patients and controls. In addition, Byl and McKenzie have combined sensory discriminative training with traditional fitness exercises to improve sensory processing and motor control of the hand affected by dystonia and reported gains in motor control, sensory discrimination, and physical performance.

In conclusion, behavioral treatments to restore normal fine motor activities may be effective in some patients with writer’s cramp. However, the most effective form and necessary duration of these therapies as well as their long-term stability remain to be established.

**Systemic drug treatment**

Systemic drug treatment, including anticholinergics, benzodiazepines, baclofen, or atypical neuroleptics, may provide some benefit in patients with writer’s cramp but their usefulness is limited by low response rates and disproportionate side effects. Localized injections with botulinum toxin are generally far more effective.

**Botulinum toxin treatment**

Botulinum toxin (BTX) treatment is considered the treatment of choice for most patients with focal dystonia, including writer’s cramp. Double-blind and open trials have shown the efficacy of local BTX injections for writer’s cramp. However, the complex functional anatomy of finger and forearm muscles and their sensitivity to even very low doses of BTX indicate that task-specific dystonias should perhaps be treated only by neurologists with special experience in this field.

BTX has proven efficacy in improving function (Figure 10.4), relieving dystonic muscle overactivity, abnormal postures, and associated pain in patients with writer’s cramp and other task-specific dystonias as well as in secondary limb dystonia in atypical parkinsonian disorders.

---

**Table 10.1 Classification of writer’s cramp**

<table>
<thead>
<tr>
<th>Classification by clinical pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>● ‘Simple’ (dystonia is selective for the act of writing) vs ‘dystonic’ writer’s cramp (dystonia of the affected hand is induced by various manual tasks)</td>
</tr>
<tr>
<td>● ‘Localized’ (dystonic cramps affect up to three fingers) vs ‘non-localized’ writer’s cramp</td>
</tr>
<tr>
<td>● ‘Flexor’ vs ‘extensor’ type writer’s cramp</td>
</tr>
<tr>
<td>● Primary writing tremor (without dystonic posturing as form of essential tremor)</td>
</tr>
</tbody>
</table>

**Classification by etiology**

- Primary writer’s cramp with dystonia as sole manifestation:
  - Writer’s cramp without genetic association
  - Writer’s cramp associated with DYT1, DYT6, DYT7, and DYT13
- Symptomatic writer’s cramp:
  - Neurodegenerative:
    - Parkinson’s disease or atypical parkinsonian disorders
    - Wilson’s disease
    - Huntington’s disease
    - X-linked dystonia-parkinsonism (Lubag)
    - Pantethenate kinase-associated neurodegeneration (PKAN)
    - GM1 gangliosidosis
    - Leigh’s disease
  - CNS lesions (head injury, stroke, multiple sclerosis, tumor, encephalitis)
  - Peripheral lesions:
    - Focal nerve entrapment (carpal tunnel syndrome, ulnar neuropathy)
    - Cervical root entrapment
    - Soft-tissue disorders (tendinitis, epicondylitis)
  - Drug-induced
Except for pregnancy and lactation, there are no absolute contraindications to using BTX; relative contraindications include significant peripheral nerve or muscle disease, particularly disorders of the neuromuscular junction.

### Botulinum toxin trials

In open and double-blind studies, BTX injections have been shown to be effective in 50–85% of patients with writer’s and musician’s cramp10,13,14–16,42–49 (Table 10.2).

In many studies, muscle selection for BTX injections is based on clinical examinations. However, surface, wire, or needle EMG is also used for muscle selection (see Table 10.2). The majority of studies have utilized global response ratings and assessments of script quality to evaluate treatment results. Some trials have included response measures such as blinded video ratings of writing performance10,45,49 or measurements of either pen control15 or writing speed.10

### Muscle selection and injection technique

Selection of muscles for BTX injection requires examination of the act of writing or playing an instrument. During a standard writing or drawing task, dystonic postures of the fingers and wrist may be identified. Additional palpation of the muscles during activation of the dystonic posture may be helpful to detect overactive and painful muscles.

Common patterns in writer’s cramp include flexion of the wrist, often accompanied by ulnar deviation, involuntary flexion of one or more fingers, or of the thumb. Corresponding extensor patterns are also common.51 However, it is important to distinguish involuntary muscle activity from compensatory activity that patients have developed to prevent dystonic posturing. Patients may begin to perform these tasks using an altered writing technique: e.g. hyperflexion of the thumb and index finger in extensor writer’s cramp. Proximal abnormal postures may also occur, such as shoulder abduction. This may be attributed to a spread of dystonia to proximal limb muscles or represent a compensatory activity to counteract the dystonic posture.51

Based on clinical observation, the muscles considered overactive are injected with low initial doses to avoid excessive weakness. BTX doses may be increased gradually, with subsequent injection sessions, until optimal subjective benefit is obtained. BTX dose recommendations for selected upper limb muscles are given in Table 10.3.

The number of muscles and the anatomic complexity of the forearm require EMG guidance or electrical stimulation for accurate BTX injection into most distal upper limb muscles (see Table 10.3). The injection is given with a Teflon-coated hollow needle. EMG guidance may be limited by the inability of some patients with task-specific dystonia to voluntary contract one muscle or finger without co-activation of adjacent structures. In these cases, electrical stimulation may be used for accurate placement of BTX into the target muscle (Figure 10.5).

### Outcome measures

Outcome measures for clinical use may include handwriting examples (see Figure 10.4), a clinical measure of dystonic posturing and muscle strength (Medical Research Council 0–5 scale), as well as the patient’s overall confidence with BTX therapy. For objective evaluation, the writer’s cramp rating scale (WCRS) was developed to assess the degree of dystonic writing movement, posture, and impaired writing speed.10 The WCRS consists of two subscales: part A describes the writing movement and posture, while part B assesses writing speed. Part A allows the writing position of the elbow, wrist, and fingers I, II, and III each to be described separately, and includes an evaluation of the latency of dystonia onset and the degree of tremor present during writing.10 More comprehensive measures include EMG of stereotyped writing (Figure 10.6), computational analysis of handwriting,52 or spiral drawing53 on a digitizing tablet using specialized computer software.

### Surgery

Single reports in patients with writer’s cramp suggest that stereotactic nucleus ventrooralis thalamotomy may improve focal hand dystonia.54 Recently, a small series of eight patients with medically intractable writer’s cramp were reported to show immediate postoperative disappearance of dystonic symptoms which...
persisted in all except one patient during the follow-up period of 3–29 months. So far, there are no reports of deep brain stimulation (DBS) of the globus pallidus internus specifically in patients with writer’s cramp. However, the first sham-stimulation-controlled DBS study indicates that pallidal DBS may have differential effects on writer’s cramp in patients with generalized dystonia.

OTHER TASK-SPECIFIC DYSTONIAS

Although writer’s cramp is the most common form of focal task-specific dystonia, similar abnormalities with involuntary muscle contractions and loss of movement speed or fluency can also develop in the context of other highly learned motor skills. Such occupational cramps most commonly occur in professional musicians, craftsmen, or sportsmen whose work or hobby activity involves frequent, repetitive movements of particular muscle groups.

Clinical features

Task-specific dystonia may develop in about 0.5–1% of professional musicians and focal dystonia occurs more frequently in male musicians. The symptoms displayed depend mainly upon the type of instrument

<table>
<thead>
<tr>
<th>Author</th>
<th>Diagnosis (n)</th>
<th>Muscle selection</th>
<th>Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brin (1987)</td>
<td>Limb dystonia (3)</td>
<td>Clinical + EMG</td>
<td>Global rating scale</td>
</tr>
<tr>
<td>Cohen (1989)</td>
<td>Writer’s cramp (14) + others (5)</td>
<td>Clinical + EMG</td>
<td>Global rating scale</td>
</tr>
<tr>
<td>Jankovic (1990)</td>
<td>Writer’s cramp + others (28)</td>
<td>Clinical</td>
<td>Global rating scale</td>
</tr>
<tr>
<td>Yoshimura (1992)</td>
<td>Writer’s cramp (9) + others (8)</td>
<td>Clinical + EMG</td>
<td>Subjective response, video rating</td>
</tr>
<tr>
<td>Tsui (1993)</td>
<td>Writer’s cramp (20)</td>
<td>Clinical + EMG</td>
<td>Pen control, writing speed</td>
</tr>
<tr>
<td>Karp (1994)</td>
<td>Writer’s cramp (32) + others (21)</td>
<td>Clinical + EMG</td>
<td>Global rating scale</td>
</tr>
<tr>
<td>Pullman (1996)</td>
<td>Focal dystonia (91)</td>
<td>Clinical + EMG</td>
<td>Level of disability, pain rating</td>
</tr>
<tr>
<td>Wissel (1996)</td>
<td>Writer’s cramp (31)</td>
<td>Clinical + EMG</td>
<td>Writer’s cramp rating scale, writing speed, video rating</td>
</tr>
<tr>
<td>Turjanski (1996)</td>
<td>Writer’s cramp (44) + musician’s cramp</td>
<td>Clinical</td>
<td>Global rating scale, pain rating</td>
</tr>
<tr>
<td>Ross (1997)</td>
<td>Writer’s cramp (29) + musician’s cramp (11)</td>
<td>Clinical</td>
<td>Global rating scale</td>
</tr>
<tr>
<td>Chen (1999)</td>
<td>Writer’s cramp (9)</td>
<td>Clinical</td>
<td>Video rating, WCRS</td>
</tr>
</tbody>
</table>

EMG = electromyography; WCRS = writer’s cramp rating scale.
rather than hand dominance. Dystonia occurs more frequently in pianists and guitarists, particularly in the fourth and fifth fingers of the right hand in pianists, and in the third finger of the right hand of guitarists. For flutists, involuntary movements more often occur in the left hand, whereas for clarinetists and violinists, either hand is likely to be affected.

In wind instrument players, the hand supporting the instrument and doing the fingering at the same time is the most affected. Rarely, wind instrument players also develop orofacial dystonia with involuntary movements of the lower face like lip pursing or jaw opening.

Tremor accompanies task-specific dystonia in about 30–40% of the patients and hand dystonia can also affect a variety of other manual skills such as typing, sorting, and painting; playing string or keyboard instruments; or engaging in sports like tennis, golf, or snooker.

### Course and prognosis

In task-specific dystonia, the symptoms typically do not generalize. Only in rare cases, task-specific limb dystonia is a phenotypic manifestation of the DYT1 mutation.

Some patients report remissions after prolonged pauses in their professional or hobby musical activities, but these are rare and almost never sustained. The typical fate of musicians with task-specific dystonia is having to give up their performing career and to resort to other types of musical activities such as conducting or teaching.

Symptomatic treatment with botulinum toxin is less effective in musicians than in patients with writer’s cramp, which may be because of the musician’s

### Table 10.3 Botulinum toxin dose recommendations for selected upper limb muscles in dystonia

<table>
<thead>
<tr>
<th>Muscle</th>
<th>BOTOX (BTX-A), units</th>
<th>Dysport (BTX-A), units</th>
<th>EMG – control or stimulation recommended</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biceps brachii</td>
<td>50–80</td>
<td>150–300</td>
<td>–</td>
</tr>
<tr>
<td>Triceps brachii</td>
<td>50–80</td>
<td>150–300</td>
<td>–</td>
</tr>
<tr>
<td>Pronator teres</td>
<td>15–30</td>
<td>40–80</td>
<td>×</td>
</tr>
<tr>
<td>Flexor carpi radialis</td>
<td>15–30</td>
<td>40–80</td>
<td>×</td>
</tr>
<tr>
<td>Flexor carpi ulnaris</td>
<td>15–30</td>
<td>40–80</td>
<td>–</td>
</tr>
<tr>
<td>Extensor carpi radialis</td>
<td>7.5–20</td>
<td>20–60</td>
<td>×</td>
</tr>
<tr>
<td>Extensor carpi ulnaris</td>
<td>7.5–20</td>
<td>20–60</td>
<td>×</td>
</tr>
<tr>
<td>Flexor digitorum superficialis</td>
<td>10–30</td>
<td>30–80</td>
<td>×</td>
</tr>
<tr>
<td>Flexor digitorum profundus</td>
<td>10–30</td>
<td>30–80</td>
<td>×</td>
</tr>
<tr>
<td>Extensor digitorum communis</td>
<td>7.5–20</td>
<td>20–60</td>
<td>×</td>
</tr>
<tr>
<td>Flexor pollicis longus</td>
<td>7.5–15</td>
<td>20–40</td>
<td>×</td>
</tr>
<tr>
<td>Flexor pollicis brevis</td>
<td>5–10</td>
<td>15–30</td>
<td>×</td>
</tr>
<tr>
<td>Extensor pollicis longus</td>
<td>7.5–15</td>
<td>20–40</td>
<td>×</td>
</tr>
<tr>
<td>Abductor pollicis longus</td>
<td>5–10</td>
<td>15–30</td>
<td>×</td>
</tr>
<tr>
<td>Adductor pollicis</td>
<td>5–10</td>
<td>15–30</td>
<td>×</td>
</tr>
</tbody>
</table>

---

Figure 10.5 Botulinum toxin (BTX) injection given with a Teflon-coated hollow needle using electrical stimulation for accurate placement of BTX into the target muscle.
high demand for perfect performance so that anything less than a complete response is considered unsatisfactory.65

Investigations

In patients with task-specific dystonia, inflammation, damage, or strain of peripheral tissue such as tendinitis and tenosynovitis as potential sensory triggers should be excluded. Likewise, nerve conduction studies and ultrasound of the nerves and surrounding tissue may be applied to exclude peripheral nerve lesions. A possible relationship between ulnar neuropathy and focal dystonia was assumed by Ross and coworkers, who found EMG burst pattern abnormalities similar to those observed in focal dystonia in the majority of musicians with ulnar neuropathy.66 In addition, the same group reported ulnar neuropathy in 40% of their cases with musician’s cramp,67 while another more recently published study by Lederman did not find an association between focal nerve entrapment and dystonia in a large group of instrumental musicians with neuromuscular and musculoskeletal problems.68 Investigations of reciprocal inhibition in patients with different types of task-specific dystonia show a normal disynaptic phase but a reduction in the amount of presynaptic inhibition.21 Cutaneous silent periods and cortical inhibitory mechanisms are also abnormal in different types of task-specific dystonia.22,23 Magnetic source imaging in patients with musician’s cramp shows alterations in the representation of the digits of the affected hand in the primary somatosensory cortex of patients with musician’s cramp69 and focal hand dystonia.70 In addition, Byl and coworkers were able to demonstrate anatomic and function degradation in the hand representation area of a flutist with focal hand dystonia71 and a study by Meunier et al showed a bilateral disorganization of somatic hand representation in patients with unilateral task-specific dystonia using MEG.72 Routine neuroimaging studies in patients with task-specific dystonia are usually normal and cerebral MRI is only necessary in cases with additional neurologic symptoms to exclude a suspected structural brain pathology. Functional neuroimaging studies in task-specific dystonia have been mainly focused on writer’s cramp. However, Pujol and coworkers have studied cortical activation during guitar-induced hand dystonia by fMRI and found underactivity of prefrontal motor areas and overactivity of the primary sensorimotor cortex during full expression of the task-specific dystonia.31

Treatment

Behavioral therapies

Different types of behavioral treatment, with the goal of sensory motor retuning, have been applied to patients with task-specific dystonia. Priori et al have reported that simple limb immobilization of the forearm and hand with a plastic splint for 4–5 weeks may improve musician’s cramp for at least 6 months.73 Candia et al have shown the efficacy of constraint-induced movement therapy in patients with musician’s cramp. These authors have used splints to immobilize digits other than the fingers affected by dystonia while the dystonic finger performed systematic training with the respective musical instrument.74,75 All patients showed improvement in clinical rating scales and computer-based
measurements of fine finger movements. The clinical improvement was accompanied by functional reorganization of the somatosensory cortex as measured by whole-head magnetoencephalography.

**Botulinum toxin treatment**

Botulinum toxin is considered the treatment of choice for most patients with task-specific dystonia. BTX has proven efficacy in improving function, relieving muscle overactivity, abnormal postures, and associated pain in patients with different types of task-specific dystonia. (For further details, see Chapter 18 and Tables 10.2 and 10.3.)

However, BTX treatment is consistently less efficacious in patients with musician’s cramp than with writer’s cramp. The most likely explanation is that professional musicians require optimum fine motor control without any muscle weakness, which is hardly achievable with BTX treatment. The best results are obtained in patients with isolated task-induced flexion of single fingers. Treatment of complex postures or tremor with the need to inject several muscles is usually associated with a mild degree of muscle weakness, which interferes with high levels of musical performance. Finger extensor muscles are particularly sensitive to BTX and even the smallest amount of BTX required for control of dystonic movements may be associated with some degree of muscle weakness.

**LIMB DYSTONIA**

The reported relative frequency of focal limb dystonia (excluding writer’s cramp) is between 2.1% and 3.5% of all focal dystonias. In addition, limb-onset dystonia with non-task-specific dystonia is common in several of the childhood- or juvenile-onset primary dystonias, whereas limb-onset dystonia in adults should raise a suspicion of secondary causes (see Table 10.1).

**Clinical features**

**Limb dystonia in primary hereditary dystonia**

In 94% of DYT1 patients, dystonia primarily affects a limb (arm and leg equally), and over 70% of carriers progress to a generalized or multifocal distribution. Initially, upper limb dystonia may present as distal focal task-specific dystonia, with subsequent progression to a more sustained and fixed dystonic posture. Foot dystonia in DYT1 frequently starts insidiously as clumsiness in one leg while walking or running. With disease progression, limb dystonia with flexion and inversion of the affected foot and cranial involvement develops.

Adult-onset idiopathic torsion dystonia of mixed type (dystonia 6; gene locus DYT6) may show a phenotype indistinguishable from DYT1 with limb-onset dystonia. However, the site of onset was cranial or cervical in about half of the reported patients. Autosomal dominant adult-onset focal dystonia (dystonia 7; gene locus DYT7) has been linked to chromosome 18p in a large German family with a mean disease onset at age 43 years. One of the family members had writer’s cramp and several were affected by wrist tremor in addition to other types of focal dystonia. Valente and coworkers recently reported a large Italian family with predominant cranio-cervical or upper limb onset (dystonia 13; gene locus DYT13). About 25% of affected individuals had upper limb-onset dystonia, which either remained focal or showed occasional generalization.

Limb dystonia is also a key feature of dopa-responsive dystonia (DRD). Onset of dystonia in DRD occurs during childhood and nearly always involves the legs, progressing to other body parts in the majority of patients, with some features of parkinsonism such as bradykinesia and postural instability later in the course of the disease. Foot dystonia in DRD is characterized by equinovarus deformity and toe flexion plus extension of the great toe. Symptoms worsen significantly during the course of the day and improve after sleep.

**Limb dystonia in paroxysmal dyskinesias**

Paroxysmal dyskinesias are characterized by involuntary, intermittent limb movements consisting of dystonia alone or a combination of hyperkinetic movement disorders. Four categories of paroxysmal dyskinesias have been classified:

1. Paroxysmal kinesigenic dyskinesia (PKD), induced by sudden movement.
2. Paroxysmal non-kinesigenic dyskinesia (PNKD), occurring spontaneously.
3. Paroxysmal exertion-induced dyskinesia (PED), induced after prolonged exercise.
4. Paroxysmal hypnogenic dyskinesia (PHD).

PED consists mainly of attacks of dystonia, sometimes combined with chorea or athetosis. Attacks of PED are triggered by prolonged exertion and involve the lower limbs; the distribution is often bilateral, but can also be unilateral. The frequency of attacks in PED ranges from 1–2/day to 1–5/month, a single attack usually lasting 5–30 minutes.
Limb dystonia in neurodegenerative disorders

Limb dystonia may occur as a presenting feature of untreated Parkinson’s disease (PD) and as a late complication of levodopa treatment. Writer’s cramp and exercise-induced painful foot dystonia may be a rare presentation of PD that may precede the onset of parkinsonism by years. Dystonia as a presenting symptom has been found in 25% of patients with onset before age 45 years but was markedly more common (42%) in those early-onset PD patients carrying a parkin mutation. Dystonia in levodopa-treated PD develops during sustained levodopa treatment and can be classified as off-period, biphasic, or peak-dose dystonia. Off-period dystonia in PD primarily affects the feet and is characterized by equinovarus deformity and toe flexion plus extension of the great toe with calf stiffening and pain and occurs typically as early morning dystonia. Biphasic dystonia is characterized by dystonic symptoms both during the onset and end-of-dose phases of an individual dose. Biphasic dystonia is predominantly unilateral with involvement of the foot in an identical manner to that seen in off-period dystonia and frequent involvement of the ipsilateral arm and leg. Peak-dose involuntary movements may include both cranial dystonia and limb chorea.

Unilateral upper limb dystonia is common in the early course of corticobasal degeneration (CBD) and is observed in about 70% of patients in the late course of the disease. Non-task-specific upper limb dystonia in CBD is frequently accompanied by bradykinesia, rigidity, and alien limb syndrome, which may allow a clinical differentiation from other disorders associated with limb dystonia. Limb dystonia is also present in up to 30% of patients with progressive supranuclear palsy with hemidystonia as the most frequent distribution.

Limb dystonia associated with neurodegenerative disorders may also be observed in Wilson’s and Huntington’s disease as well as in multiple system atrophy and pantothenate kinase-associated neurodegeneration.

Symptomatic limb dystonia

Secondary dystonia due to contralateral structural basal ganglia pathology may rarely present as focal task-specific dystonia. This type of symptomatic dystonia typically occurs as non-task-specific dystonia and is frequently associated with additional neurologic symptoms. About 75% of patients with hemidystonia show contralateral basal ganglia lesions on CT or MRI. Infarction or hemorrhage involving the basal ganglia, particularly the putamen, is the most frequent cause of hemidystonia. Dystonia induced by drugs or toxins may also involve the limbs: acute dystonic reactions caused by neuroleptics, calcium channel blockers, tetrabenazine, or methamphetamine typically involve the craniocervical region but may also involve the trunk and limbs. Tardive dystonia induced by drugs interfering with dopaminergic transmission most commonly affects the craniocervical region; the upper and lower limbs are only rarely involved. Manganese intoxication may induce a characteristic type of foot dystonia with ‘cock gait’.

Psychogenic dystonia

Whereas lower limb onset is common in childhood dystonias and particularly in DYT1-positive patients, it is uncommon in primary adult-onset dystonia. In adult patients with isolated leg dystonia in whom secondary causes have been excluded, psychogenic dystonia may be considered.

Less than 5% of patients with dystonia are considered to have psychogenic dystonia. In a sample of 21 patients with psychogenic dystonia, 90% were women and 67% had limb onset. Clues to the diagnosis of psychogenic dystonia include abrupt onset, early fixed postures, foot/leg involvement in adults, paroxysmal symptoms, and complete remissions. By contrast, adult patients with organic dystonia usually report gradual onset, fixed postures develop late, foot or leg involvement as well as paroxysmal symptoms are rare, and complete remissions are uncommon. The clinical investigation of patients with psychogenic dystonia may show false weakness, false sensory symptoms, inconsistent movements, decreasing movements with distraction, increasing movements with attention, or responsiveness to placebo.

Course and prognosis

Dystonia in the childhood- or juvenile-onset primary dystonias tends to progress to a generalized or multifocal distribution in the majority of patients, whereas limb dystonia in adults usually remains focal or segmental. The course and prognosis of limb dystonia in dystonia-plus syndromes and heredodegenerative diseases is variable. Dopa-responsive dystonia shows an excellent and sustained response to levodopa therapy and off-period dystonia in Parkinson’s disease may be effectively treated with levodopa or dopamine agonists. Limb dystonia in neurodegenerative disorders is frequently associated with other disabling neurologic symptoms and prognosis depends largely on the course of the underlying disorder.

Investigations

In all cases with a possible secondary cause of dystonia, a thorough clinical examination together
with neuroradiologic biochemical, or genetic testing should be performed depending on the suspected etiology.

Genetic testing for DYT1 mutations is recommended for patients with onset before age 26 years or in older patients having an affected relative with early-onset primary dystonia. Genetic testing is also indicated in suspected DRD and Huntington’s disease. Diagnostic testing for Wilson’s disease includes serum ceruloplasmin, 24-hour urinary copper excretion, slit-lamp examination, and perhaps liver biopsy as the most sensitive test. DAT-SPECT is indicated when Parkinson’s disease is suspected. Routine imaging studies using CT or MRI may serve to exclude symptomatic forms of limb dystonia due to contralateral basal ganglia pathology or central cortical atrophy.

A specific pharmacotherapy directed at the underlying biochemical defect exists only for a limited number of symptomatic limb dystonias. Wilson’s disease is effectively treated with drugs that deplete copper or interfere with copper absorption such as penicillamine or trientine. Patients with dopa-responsive dystonia show an excellent and sustained response to low-dose levodopa therapy. In patients with Parkinson’s disease, dopaminergic treatment should be optimized to handle off-period dystonia and prevent levodopa-induced dyskinesia.

In primary torsion dystonia, chronic bilateral globus pallidus internus stimulation seems to be the most effective treatment for limb dystonia. Patients with PKD may respond to treatment with anticonvulsants, those with PNKD to acetazolamide. For the remaining patients with focal limb dystonia, symptomatic treatment with botulinum toxin is the therapy of choice (see Chapter 18). Additional pharmacologic therapies, including anticholinergics, benzodiazepines, baclofen, or atypical neuroleptics, may also be tried similar to other types of dystonia.

REFERENCES

30. Odergren T, Stone-Elander S, Ingvar M. Cerebral and cerebellar


Laryngeal dystonia

Christy L Ludlow

FORMS OF LARYNGEAL DYSTONIA

The laryngeal dystonias are a subset of laryngeal motor control disorders affecting voice and/or breathing, including adductor and abductor spasmodic dysphonia (SD), voice tremor, and adductor breathing dystonia. A significant proportion, about one-third, of persons with SD also have voice tremor. Diagnosis is symptom-based and dependent upon excluding other laryngeal disorders such as those secondary to neurologic diseases/disorders and those laryngeal dysfunction disorders thought to be behavioral in origin (Table 11.1). The laryngeal dystonias are relatively rare, affecting 1 in 100,000 persons.1

Among those laryngeal disorders that are secondary to neurologic disease that need to be separated from SD are vocal fold paralysis in the bulbar form of amyotrophic lateral sclerosis causing dysphonia and dysphagia,2 airway obstruction due to loss of vocal fold opening in multiple system atrophy,3 hypophonia in Parkinson’s disease,4 and abductor vocal fold paralysis in familial polyneuropathy.5

Two poorly understood disorders, muscular tension dysphonia6 and paradoxical vocal fold function,7 are thought to have a behavioral component because a large proportion of persons affected respond well to behavioral management.7,8

Although previously, the laryngeal dystonias were often misdiagnosed as psychogenic disorders,9 more recently, these disorders tend to be overdiagnosed. When voice disorder is an early symptom of other underlying neurologic disorders, misdiagnosis can lead to injection of the laryngeal muscles with botulinum toxin in patients who might be not benefit, such as a early-onset bulbar amyotrophic lateral sclerosis (ALS).10 Accurate diagnosis is important, although the symptom complexes among these disorders are not always distinct.11

DIAGNOSIS

Spasmodic dysphonia

SD is usually focal to the laryngeal musculature and may involve tone abnormalities in only a few of the laryngeal muscles. As the name implies, spasmodic dysphonia involves intermittent involuntary laryngeal muscle spasms12 rather than constantly abnormal levels of muscle tone.13 Adductor spasmodic dysphonia (ADSD) is characterized by intermittent voice stoppages in vowels in the middle of words and difficulty initiating voice on words beginning with vowels.14 During voice breaks, the vocal folds squeeze together or hyperadduct to such a degree that voicing is stopped.15 These breaks are due to involuntary spasms in the vocal fold closing muscles, the thyroarytenoid and lateral cricoarytenoid muscles, although spasms can be seen in other muscles such as the cricothyroid in some patients with ADSD.16,17

Abductor spasmodic dysphonia (ABSD) occurs in between 10% and 15% of persons with SD.18 The speech symptoms are breathy breaks due to prolonged voiceless consonants such as ‘s’, ‘h’, ‘p’, ‘t’, ‘k’, and ‘f’ before a vowel. During the break, the vocal folds have prolonged involuntary opening, preventing rapid voice onset for the following vowel. Vocal fold opening and lengthening muscles, the posterior cricoarytenoid and cricothyroid, respectively, may be involved in ABSD, although some patients have breathy breaks in the middle of vowels as a result of uncontrollable decreases in tone in the thyroarytenoid muscle during a vowel.

Patients with either ADSD or ABSD are symptomatic only during voice for speech, while non-speech tasks such as breathing, sighing, laughter, and crying are unaffected. Singing is usually less affected than speech and most patients can shout better than they can speak.19 These task-specific differences were previously interpreted as
CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA

an indication that the disorder was psychogenic; however, it is now recognized that innate laryngeal gestures may be under separate control in the human brain from learned laryngeal gestures such as those that occur during speech.20

The most common complaint of persons with SD is the effort required to speak. Patients also develop fears with speaking on the telephone and in public because of embarrassment caused by their voice problems. Persons with ABSD often also complain of difficulty coordinating breathing with speaking.

Voice tremor

Action-induced voice tremor, only present during speech, often co-occurs with SD.21,22 In vocal tremor, intermittent hyperadduction of the vocal folds regularly produces breaks in vowels at around 5 Hz.23 In the abductor form, which is quite rare, breathy modulations or pitch changes are most notable. Because syllables are usually produced at 4 per second in conversational speech, a 5 Hz tremor may not be evident until the patient is asked to produce a prolonged vowel for at least 10 seconds or more.

Adductor breathing dystonia

During breathing, the vocal folds act as a valve in the midline of the upper airway, opening during inspiration and partly closing during exhalation.25 Patients with a breathing dystonia only have uncontrolled vocal fold closure during inspiration but move their vocal folds normally during speech. Increases in thyroarytenoid muscle during inspiration results in stridor or obstruction.26 Adductor breathing dystonia is usually continuously present while the patient is awake, reduced during speech, and absent during sleep. Obstruction is exacerbated during forced inspiration when the negative pressure produced by air flow through the glottis sucks the vocal folds together. Adductor breathing dystonia is rare and usually has its onset in middle age. It can be associated with oral–mandibular dystonia. In some patients the obstruction is not at the level of the larynx but rather involves the posterior pharynx. Involuntary tongue retraction and contraction of the superior pharyngeal constrictor can cause the epiglottis to obstruct the hypopharynx. Obstruction occurs as the patient breathes in, producing a negative pressure sucking the walls of the pharynx together.

Adductor breathing dystonia is one form of paradoxical vocal fold dysfunction (PVFD) and differs from other vocal fold breathing dysfunctions, because the dystonic form is continuous while the patient is awake while the other vocal fold dysfunctions are usually episodic, associated with a trigger such as laryngopharyngeal reflex, an airway irritant, asthma, or psychological stressors.7 PVFD occurring at night may be associated with laryngopharyngeal reflex when gastric juices with a low pH stimulate a glottic closure reflex, or during the day when bending over also causes regurgitation of gastric contents into the larynx.28 Other patients, often adolescents, develop episodes of PVFD that may be related to psychological triggers or asthma.7

Table 11.1 Affected and unaffected tasks in the laryngeal dystonias

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Type</th>
<th>Affected tasks</th>
<th>Unaffected tasks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasmodic Adductor Vowels during speech</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spasmodic Abductor Voiceless consonants during speech</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voice tremor Action-induced Prolonged vowels and voice during speech</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Voice tremor Essential tremor Rest, voice, and speech</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adductor breathing dystonia Laryngeal obstruction Inspiration during breathing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adductor breathing dystonia Pharyngeal obstruction Inspiration during breathing, garbled speech</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ASSESSMENT

Identification of the laryngeal dystonias requires a medical history and physical examination, speech testing, a psychosocial history, and viewing the larynx during breathing, conversational speech, whistling, and phonation using flexible nasolaryngoscopy to visualize the laryngeal movement abnormalities (Table 11.2).

The speech and breathing history can be informative to determine if the disorder is episodic, or constant and chronic for a particular task. Although the severity of SD can wax and wane with ‘good days and bad days’ if the patient reports that the voice disorder completely abates for days at a time, this is not typical of SD, and may indicate a functional voice disorder, either muscular tension dysphonia or a psychogenic voice disorder.

Complaints of effort are also typical of SD and may include complaints of problems with breathing control while speaking. Patients with psychogenic dysphonia rarely complain of effort, have poor insight into their voice disorder, and discuss it as something occurring independent of themselves, taking little ownership or responsibility for their voice production. On the other hand, patients with SD can often provide a great deal of information on their speaking difficulties and may have considerable insight into their disorder.

The patient’s report of the degree of effort on different types of speech sounds is also useful in identifying the type of SD. Sentences or syllable repetitions loaded with glottal stops (words beginning with vowels requiring the vocal folds to close tightly together and then release into vibration) are very difficult for patients with ADSD. Examples are repetition of the vowel ‘ee-ee-ee . . . ’ and sentences such as ‘we eat eels everyday’, ‘we mow our lawn all year’, and ‘Sam wants to be in the army’ are difficult for patients with ADSD with prolonged voice offsets at the underlined vowels.

In contrast, in ABSD, repetitions of syllables containing voiceless consonants are difficult, such as ‘he-he-he . . . ’, ‘see-see-see . . . ’ ‘pea-pea-pea . . . ’ or ‘key-key-key . . . ’ and sentences such as, ‘he had half a head of hair’, ‘a mahogany highboy is heavy’, ‘the puppy bit the tape’, or ‘she speaks pleasingly’.

When patients with ADSD and ABSD are asked to repeat different syllables, including those with glottal stops (i-i-i-i-i), voiceless consonants (see-see-see-see), and some decoy phrases involving nasal sounds (me-me-me-me-me), they can reliably identify which type is most effortful. Patients with muscular tension

<table>
<thead>
<tr>
<th>Table 11.2 Assessment of symptoms in the laryngeal dystonias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disorder</td>
</tr>
<tr>
<td>Abductor</td>
</tr>
<tr>
<td>Voice tremor</td>
</tr>
<tr>
<td>Essential tremor</td>
</tr>
<tr>
<td>Adductor breathing dystonia</td>
</tr>
<tr>
<td>Pharyngeal obstruction</td>
</tr>
</tbody>
</table>
dysphonia or psychogenic dysphonia usually find all syllable types equally difficult.

**Nasolaryngoscopy examination**

Flexible nasolaryngoscopy is essential for examining patients with laryngeal motor control disorders so that the vocal fold movement abnormalities can be visualized during connected speech when symptoms are most evident. This examination is also necessary to exclude vocal fold paralysis or weakness that may also produce voice and/or breathing abnormalities. On entry into the nasal passages, the superior surface of the velum can be viewed and the degree of closure of the velopharyngeal port during speech tasks can be assessed. The velum should raise to close off the nasopharynx during the vowel ‘ee’ and a whisper such as ‘shhhhh’ will be lower at rest and during humming and nasal sounds such as ‘mama’. Patients with voice tremor may have tremor in the velum during a prolonged vowel such as ‘eeeeddddd’. Sentences containing nasal and non-nasal sounds can assess the speed and extent of velar movement, such as ‘Mama made some lemon jam’ and ‘Susie sews socks’. Some patients with ABSD have abnormal movement of the velum during speech, although it is normal for pronged vowels and rises normally during swallowing.

After entering the oropharynx, vocal fold movements can be visualized during both speech and non-speech tasks. During speech, high tongue position vowels (‘ee’ as in ‘tree’ and ‘oo’ as in ‘blue’) will provide the best view of the larynx. Low back vowels produce posterior tongue positions, which move the epiglottis backwards, obscuring the view of the larynx (e.g. ‘ah’ as in ‘saw’).

The vocal folds should be examined for spontaneous movement during quiet respiration to identify tremor or adduction during inspiration for breathing dystonia. Examination of the speed of vocal fold movement for abduction (opening) and adduction (closing) should include speech and non-speech tasks. A rapid ‘sniff’ followed by an ‘ee’ at least 3 times in rapid succession allows for examination of the adequacy of opening and closing movements of the vocal folds for speech. Whistling ‘Happy Birthday’ produces rapid and frequent opening and closing of the vocal folds for non-speech tasks for assessing movement range and symmetry. Most persons will say they can’t whistle but the rapid opening and closing of the vocal folds occurs regardless of their skill in whistling a tune.

To examine for symptoms of ADSD, repetitions of vowels, as in ‘ee-ee-ee-ee-ee’, can assess prolonged vocal fold closing while producing a glottal stop between vowels, resulting in longer voice offsets than normal. Also, sentence production can assess intermittent breaks in all voiced sentences with glottal stops between vowels such as ‘we eat gels every day’, and counting upwards beginning with ‘eighty’.

To examine for symptoms of ABSD, repetition of ‘see-see-see-see-see’ or ‘he-he-he-he-he’ will detect prolonged vocal fold opening during voiceless consonants for longer periods than normal. Sentences to examine intermittent spasmodic movements, include ‘he had half a head of hair’ and ‘Peter will keep at the geak’ and counting upwards beginning with ‘sixty’.

In vocal tremor, the prolonged vowel ‘ee’ should be produced at different pitches and in glides; usually, tremor is greatest in the low-pitch speaking voice range and reduced at high pitches and in falsetto voice. To determine if tremor is action induced, no tremor will be seen at rest but it may appear during expiration and as soon as the patient goes to speak. In benign essential tremor affecting the larynx, tremor may occur at rest, during both inspiration and expiration, as well as during speaking. If tremor involvement is limited to the vocal folds, then only the intrinsic laryngeal muscles are involved and can be injected with botulinum toxin. On the other hand, if there is a constant superior–inferior (bobbing) motion of the entire larynx, some of the extrinsic laryngeal muscles may also be involved. Finally, if the pharyngeal walls, posterior tongue, and velum are also involved, it will be difficult to manage symptoms using only botulinum toxin injection, and medications may also be needed.

When assessing adductor breathing dystonia, nasolaryngoscopy is important to determine if the range and speed of vocal fold movement are normal during other tasks such as sniffing and whistling, to identify whether stridor is due to abductor vocal fold paralysis or paresis rather than dystonia. Observing vocal fold and pharyngeal movement is important to determine if there is active vocal fold closing during inspiration or whether the obstruction is above the glottis. An otorlaryngologist can also examine the laryngeal tissues for signs of laryngopharyngeal reflux to determine if a history of an episodic breathing disorder might be due to gastric reflux stimulating a vocal fold adductory reflex.

**Non-dystonic laryngeal movement disorders**

Asymmetries in vocal fold movements between the two sides on the whistling task would be indicative of an adductor or abductor paralysis/paresis. Sometimes, asymmetries in movement between the right and left sides are seen during speech in ABSD but are not evident during non-speech tasks such as ‘whistling’ and ‘sniffing’, indicating that the disorder is part of the dystonia and not due to vocal fold paralysis. Patients with thinning of the vocal folds or vocal fold bowing can have many different disorders: either Parkinson’s disease,
whereas those with SD do not.8,35 Often benefit from manual circumlaryngeal therapy, suggested that response to voice therapy is diagnostic in control involuntary movements. Some clinicians have increased tension in their laryngeal muscles in an attempt to speak (termed the isometric larynx34), without intermittent voice breaks, is more typical of muscular tension dysphonia, considered a ‘functional’ voice disorder. Differentiating muscular tension dysphonia from ADSD is a frequent dilemma because often patients with ADSD have a constant harshness in addition to their intermittent spasmodic breaks. These SD patients may have an overlaid muscular tension dysphonia as a result of using tent spasmodic breaks. These SD patients may have psychogenic voice disorders. Total aphony rarely, if ever, occurs in ABS. Humming and other task manipulations involving distractions, counting backwards in sevens, along with circumlaryngeal manipulation can sometimes resolve psychogenic voice disorders.36,37

If a patient has a constant breathy voice without prolonged voiceless consonants which are heard as intermittent breathy breaks, the disorder is more likely a ‘functional’ voice disorder than ABS. Patients who are constantly aphonically, but have normal vocal fold movements for cough, whistle, throat clear, and swallow, often have psychogenic voice disorders. Total aphony rarely, if ever, occurs in ABS. Humming and other task manipulations involving distractions, counting backwards in sevens, along with circumlaryngeal manipulation can sometimes resolve psychogenic voice disorders.36,37

PVFD, due to gastric reflux or in association with anxiety and masquerading as asthma, is usually episodic and therefore has very different features from adductor breathing dystonia. Episodes of stridor that occur in the middle of the night or after bending over in the middle of the day suggest gastric reflux. These can be managed by an otolaryngologist using proton pump inhibitors while education by a speech–language pathologist can help the patient understand what is causing the problem and help to reduce the patient’s anxiety. If the disorder is exercise-induced, having the patient perform the exercise before the nasolaryngoscopy can be helpful in viewing the laryngeal movement abnormality and can be used to show the patient how to control the symptoms by using short light breaths and avoiding deep inspirations.

TREATMENT OF LARYNGEAL DYSTONIAS

None of the currently available treatments for laryngeal dystonias will reverse the central disorder; all are aimed at only peripheral control of the muscle spasms, either through denervation or muscle excision. The treatments available manage the symptoms for different time windows and with side effects of varying degrees.

Treatments for spasmodic dysphonia

Botulinum toxin injections into the thyroarytenoid muscle or combined with the lateral cricoarytenoid muscle benefit 90% of ADSD patients38–40 (Table 11.3). Although most patients report significant benefit, even those with a good response do not have a normal voice; the voice is usually ‘thin’ and reduced in resonance.41 Small bilateral injections with a starting dose of 1.5–2.5 units on each side42 were shown effective in a small double-blind trial.43 Other clinicians have used unilateral injections, producing a unilateral paresis/paralysis.44 No consistent differences have been found between the two approaches.45–48 Some clinicians report that unilateral injections can be better controlled to meet patients’ needs without producing considerable swallowing and breathlessness as side effects.48 Accurate placement of the toxin in the thyroarytenoid muscle is essential and, usually, placement errors are the basis for a poor result.49 Continued treatment with botulinum toxin injection is beneficial using outcome measures.50 However, some patients lose their benefit over time; in such cases, alternating between unilateral and bilateral injections or between injection to the right and then the left can better control symptoms without increasing the dosage.51 A few patients have developed antibodies to botulinum toxin following laryngeal injections after dosage increases.52 Surgical approaches to laryngeal muscle denervation have been used for treatment of SD. The initial success often fades, however, as the central disorder often returns with reinnervation of the laryngeal muscles. Recurrent laryngeal nerve resection was introduced by Dedo51 in the 1970s but a return of symptoms occurred within a few years in 60% of patients.54 A recurrent laryngeal nerve avulsion, a more extensive procedure, although used in a smaller number of patients, may have a better long-term rate of symptom control.55,56 More recently Berke et al developed a denervation–reinnervation procedure, sectioning the branch of the recurrent nerve going to the thyroarytenoid muscle on both sides and then reinnervating with the ansa cervicalis.57 The procedure initially produces swallowing problems and loss of voice, which then resolve with a resulting voice benefit. The results have recently been replicated in a small series by a second group58 and a long-term follow-up of patients showed benefit in several patients based on a questionnaire completed by the patients.59 Isshiki introduced a laryngeal framework approach (midline lateralization thyroplasty type 2) to produce a gap between the vocal folds with a wedge in the anterior commissure. This was reported in six cases, with no postoperative voice evaluation. If such surgical procedures are successful, they might provide patients with longer-term benefits by permanently altering laryngeal structure and function.
CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA

Treating abductor spasmodic dysphonia

Treatment for ABSD has not been as successful as for ADSD using either botulinum toxin injection or surgery. Most efforts using botulinum toxin have focused on the posterior cricoarytenoid, the only muscle that opens the vocal folds. About 60% of patients benefit\(^60,61\) and their benefit is less and shorter than in ADSD.\(^47\) One reason may be technical: greater skill and experience is needed to inject the posterior cricoarytenoid and few centers see large numbers of these patients. Secondly, great care must be taken to prevent stridor and bilateral airway obstruction, requiring a tracheostomy if both sides are injected. Therefore, most centers inject only one side at a time with 3–5 units and have the patient return in 2 weeks to re-evaluate before deciding to inject the other side. Some centers only inject one side with a dosage of 10 units.

Some patients may not have involuntary spasms of the posterior cricoarytenoid muscles. In one series of patients with spasmodic bursts seen in the cricothyroid muscle during speech, bilateral cricothyroid injections reduced symptoms.\(^62\) An electromyographic study of patients with ABSD not benefited by botulinum toxin found decreases in tone in the thyroarytenoid muscle on one side during speech.\(^30\)

Surgical options have been few. To prevent excessive abduction, one approach combined a myotomy of the posterior cricoarytenoid with a thyroplasty.\(^63\) In a preliminary report, this was performed in three patients with partial success, making the approach experimental.

Voice tremor

A variety of muscles can be affected in vocal tremor\(^23\) and the types of tremor may be either action-induced or continuously present. In addition, the tremor may be focal to just the thyroarytenoid muscle, or involve the muscles of the entire upper airway. This may explain why results have been unreliable when only the thyroarytenoid muscle is injected in the same fashion as in ADSD.\(^64-66\) In general, about 50% of patients are benefited and the degree of benefit has been limited. A combined approach of medication (beta blockers) and botulinum toxin injection is often used. Further

---

Table 11.3 Treatment dosages with botulinum toxin for the laryngeal dystonias

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Type</th>
<th>Muscle</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spasmodic dysphonias</td>
<td>Adductor</td>
<td>Bilateral thyroarytenoid</td>
<td>1.5–2.5 U initial injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unilateral thyroarytenoid</td>
<td>0.5–2.0 U reinjection</td>
</tr>
<tr>
<td>Abductor</td>
<td></td>
<td>Bilateral posterior cricoarytenoid</td>
<td>7.5–15 U initial injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only inject one side at a time, 5 U one side, 5 U, 1–2 weeks later, on opposite side</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unilateral posterior cricoarytenoid</td>
<td>10 U one side only</td>
</tr>
<tr>
<td>Voice tremor</td>
<td>Adductor</td>
<td>Bilateral thyroarytenoid</td>
<td>1.5–2.5 U initial injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unilateral thyroarytenoid</td>
<td>0.5–2.0 U reinjection</td>
</tr>
<tr>
<td>Abductor</td>
<td></td>
<td>Bilateral posterior cricoarytenoid</td>
<td>7.5–15 U initial injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Only inject one side at a time, 5 U one side, 5 U, 1–2 weeks later, on opposite side</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Unilateral posterior cricoarytenoid</td>
<td>10 U one side only</td>
</tr>
<tr>
<td>Adductor breathing dystonia</td>
<td>Laryngeal obstruction</td>
<td>Bilateral thyroarytenoid</td>
<td>1.5–2.5 U initial injection</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.5–2.0 U reinjection</td>
</tr>
</tbody>
</table>
research is needed to more carefully categorize patients according to which muscles are affected to produce a more reliable result using botulinum toxin in voice tremor.

**Treating adductor breathing dystonia**

Patients with an adductor breathing dystonia must be carefully distinguished from those with episodic PVFD, as the treatment regimen differs. Adductor breathing dystonia is rare and only large centers are likely to see enough of these patients for accurate diagnosis. If a patient is shown to have laryngeal obstruction rather than pharyngeal involvement, botulinum toxin injection of the thyroarytenoid muscles, similar to treatment for ADSD, is the best approach to treatment.\(^{26}\) Injecting the thyroarytenoid muscle bilaterally can reduce the degree of obstruction or stridor; however, there is a trade-off between an improvement in breathing and loss of voice volume and swallowing difficulties.\(^{26,67}\) Patients with pharyngeal obstruction cannot be managed using botulinum toxin injection, because of the potential for swallowing difficulties. Therefore, the use of medications for management of the dystonia is currently the only approach available for this disorder.

**PATHOPHYSIOLOGY AND PATHOGENESIS OF THE LARYNGEAL DYSTONIAS**

Very little is understood about these disorders – most research has focused on controlling symptoms through peripheral changes in muscle activation in the larynx. In the 1970s came the first recognition that these were neurologic disorders.\(^{68,69}\) During the 1980s it was recognized that the symptomatology was similar to other focal dystonias, and the term ‘laryngeal dystonia’ was first used.\(^{70}\) Studies on the pathophysiology in the 1990s demonstrated similar abnormalities in central suppression of laryngeal adductor reflexes in both ADSD and ABSD.\(^{71,72}\) Little attention has been given to the neurologic abnormalities underlying the involuntary muscle spasms. A few studies in the 1990s, using the techniques available at that time, had equivocal findings.\(^{73-75}\)

With more recent brain imaging techniques, better insight should soon become available on the central abnormalities of these patients. Recently, two neuroimaging studies have been published on SD: both studies compared patients with healthy volunteers before receiving botulinum toxin and then examined changes in the patients’ brain activation after receiving botulinum toxin.\(^{76,77}\) Although the two studies had methodologic differences, one used positron emission tomography and \(O_2\)\(^{15}\) and examined connected speech,\(^{76}\) while the other used blood oxygen level-dependent changes in functional magnetic resonance imaging (fMRI) and examined extended phonation on a vowel.\(^{77}\) However, both studies had a similar finding of reduced activity in the most lateral M1-S1 regions in the SD patients versus controls, possibly those regions associated with laryngeal sensorimotor control. In one study, however, the hypoactivity in laryngeal sensory regions did not normalize with botulinum toxin injection but was less apparent during whispering.\(^{77}\) In the other study, the unimodal and heteromodal sensory hypoactivity was reduced in SD but increased with botulinum toxin, and increases in blood flow in the left hemisphere sensory regions were highly correlated with the degree of symptom improvement.\(^{76}\) These two studies both demonstrate functional neurologic abnormalities that are associated with symptoms of SD in left hemisphere sensorimotor processing for laryngeal control during phonation and whispered speech.

Nothing is known about the etiology of the laryngeal dystonias. Dedo et al first proposed that pathologic changes could be found in the recurrent laryngeal nerve that might indicate a peripheral etiology for the disorder;\(^{68}\) however, other clinicians could not replicate these findings.\(^{78}\) More recently, similar studies have yielded conflicting results\(^{79,80}\) and concluded that the disorder is central in origin.

Only a small percentage of patients have a familial background of either idiopathic torsion dystonia or other focal dystonias;\(^{81}\) the most frequent condition is writer’s cramp, which is found in 11% of patients with SD.\(^{82}\) The disorder is predominant in females (between 60–80% of those affected)\(^{18,82,83}\) and develops later than many forms of focal primary dystonia with mean age of onset in one study of 50.7 years.\(^{84}\) This is in keeping with other adult onset primary cranial dystonias. Events commonly reported preceding the onset of symptoms include a severe upper respiratory infection with an associated voice disorder which does not remit in 30%, with a period of severe stress in 21%.\(^{82}\) One study found a childhood incidence of measles or mumps in 65% of patients but there was no control group.\(^{82}\) Onset is usually gradual; the initial voice symptoms may fluctuate over the first 2–6 months before stabilizing and becoming chronic after a year. Improved understanding of the central mechanisms involved in symptom generation in SD is needed to develop new and effective treatment approaches aimed at altering the central abnormality responsible for the generation of spasms. Furthermore, knowledge of risk factors and the mechanisms involved in the pathogenesis might lead to prevention of the disorder. The field has a long way to go to meet these objectives.
REFERENCES


INTRODUCTION

In recent classifications of the dystonias, several disorders have been distinguished from ‘idiopathic’ or ‘primary’ torsion dystonia based on characteristic clinical features or pharmacologic responses. These diseases have been grouped into a category of ‘dystonia-plus syndromes’.1 This distinction is useful from a nosologic point of view, as dystonia-plus syndromes frequently have distinct genetic etiologies. However, as in most genetically complex disorders, clinical and genetic classifications are not entirely concordant. Not all patients diagnosed according to a given set of clinical criteria prove to have a discernible genetic defect. If they do, the clinical presentation may be highly variable, even within single families, regardless of the underlying genetic cause, and may overlap with other genetic or non-genetic disease entities.

For example, an occasional patient with genetically proven myoclonus-dystonia (M-D, DYT11) may present with pure writer’s cramp in his forties2 and may therefore be misclassified as ‘primary dystonia’. Lightning-like myoclonic jerks, which are the clinical hallmark of M-D and which may be found in other members of his family, may only be reported to have prevailed until late adolescence.

On the other hand, myoclonic jerks in affected body parts of patients with primary torsion dystonia (PTD) are quite common. This is reflected in the term ‘myoclonic dystonia’,3 which has been coined to draw attention to this fact. To avoid confusion, this term should now only be used to describe this feature of primary dystonia, and not the disease of ‘myoclonus-dystonia’, which denotes the genetic disorder described in more detail below.

Patients with another dystonia-plus syndrome, dopa-responsive dystonia (DRD, DYT5), may be indistinguishable from those with PTD unless treated with L-dopa. And even then, occasional patients with PTD often show transient or partial therapeutic benefit to L-dopa (although usually not as striking as in DRD), and anticholinergic medication may also be beneficial in both groups.4 For several of the dystonia-plus syndromes, the respective genetic loci have been mapped, and a few of the genes have been identified. Although the proteins encoded by these genes appear to serve completely distinct cellular functions, the similarities between the different entities exemplified above may point to common molecular pathways in their pathogenesis.

In this chapter, the molecular and genetic basis of three dystonia-plus syndromes is discussed in detail.

– dopa-responsive dystonia, myoclonus-dystonia, and rapid-onset dystonia-parkinsonism.
– Other dystonic syndromes with specific distinguishing clinical features, such as the paroxysmal dystonias, are discussed in other chapters of this book.

DOPA-RESPONSIVE DYSTONIA (DYT5)

The syndrome of DRD was first delineated by Segawa et al in 1976.5 Since then, the analysis of this syndrome and the underlying molecular biochemical alterations have not only helped to elucidate the molecular pathogenesis of this disease but also provided many valuable insights into the motor function of the basal ganglia.

Clinical presentation

Patients with typical DRD usually present with gait disturbance due to foot dystonia between the ages of 1 and 12 (mean ~6) years. Dystonia often becomes progressively severe during the day (diurnal variation) and is relieved by sleep or rest. The course of the condition is variable, sometimes evolving to severe generalized dystonia that renders the patient wheelchair-bound. Features suggestive of lower extremity spasticity (brisk
deep-tendon reflexes, ankle clonus, and/or dystonic extension of the big toe [the striatal toe] are present in many patients. Parkinsonian symptoms commonly develop later during the disease. In some patients, mild parkinsonism may also be the only manifestation of the disorder (although DRD is certainly a very rare cause in an otherwise-unselected group of patients with adult-onset parkinsonism). Atypical manifestations have been described, such as adult-onset limb, cervical, and craniofacial dystonia,1,6,7 and some patients may resemble spastic paraplegics.8 On rare occasions, patients present with myoclonic jerks of the neck accompanying cervical dystonia and the condition could be therefore confused with myoclonic jerks of the neck accompanying cervical dystonia and the condition could be therefore confused with myoclonus-dystonia.9 Minimal manifestations, such as stiffness of a leg upon exertion, can also be seen. As in other forms of dystonia, site and age at presentation are interdependent. Onset before the age of 10 years occurs usually in the lower limb, whereas other manifestations, including postural tremor, are commonly seen in cases with later onset.

The most striking clinical feature is the marked and sustained responsiveness to relatively small doses (usually 50–200 mg, but in some cases up to 450 mg may be necessary) of L-dopa/decarboxylase inhibitor.10 Fluctuations and dyskinesias, often seen as troublesome complications of long-term L-dopa treatment in Parkinson’s disease, are rare and, if they occur, only mild in DRD.11 Treatment should be initiated with slowly increasing doses, and a response is usually seen within days or a few weeks. Rapid dose increases may result in choreic, myoclonic, or tic-like hyperkinesias, which disappear upon dose reduction. Patients have been followed for over 30 years without loss of efficacy. Anticholinergics are also quite effective, although not as completely and consistently as L-dopa. Some patients, particularly those with severe tetrahydrobiopterin (BH4) deficiency due to compound heterozygous mutations (see below), may require supplementation of 5-hydroxytryptophan (the precursor of serotonin, as phenylalanine hydroxylase also uses BH4 as a cofactor) and BH4. Imaging studies using ligands for the pre- and postsynaptic dopaminergic terminals ([11C]-methyphenidate and [11C]-raclopride, respectively) showed that those structures are not compromised in DRD.12–14 However, a marked increase in the uptake of [11C]-dihydrotetrabenazine (DTBZ), a ligand of the vesicular monoamine transporter (VMAT2), has been interpreted as reflecting the decrease in the intravesicular concentration of dopamine and/or a compensatory up-regulation of VMAT2 expression.15 Pathologically, a normal number of neurons in the substantia nigra has been found. These neurons, however, are poorly melanized,16 possibly reflecting the lower rate of dopamine turnover and hence autooxidation.

Recent observations point towards a possibility of discriminating DRD from juvenile-onset parkinsonism by transcranial ultrasound: DRD patients fail to show increased areas of substantia nigra hyperechogenicity.17

Genetic and molecular basis

Inheritance of DRD is in most cases autosomal dominant with incomplete penetrance. Apparently sporadic cases with proven mutations occur and may be due to incomplete penetrance in other family members or to new mutational events (which is not uncommon in DRD). Many series showed a higher penetrance (~2.5-fold) in females compared to males. Personal examination of the parents of reportedly sporadic children with DRD often reveals mild parkinsonism of adult onset in a mutation-carrying parent.

The gene for dominant DRD has been mapped to chromosome 1418 and the causative mutations were identified in the gene for GTP cyclohydrolase I (GCH1).19 The encoded protein, GTPCH1, catalyzes the first step of BH4 synthesis, which is in turn a crucial cofactor for tyrosine hydroxylase (TH), the rate-limiting key enzyme in the biosynthesis of dopamine and other amine neurotransmitters.

More than 85 different mutations scattered over all 5 exons of the gene have been found so far,20 including missense and nonsense mutations, but also mutations affecting splice sites,21 mutations in the 5’-untranslated region,22 or large genomic deletions.23 In as many as 40% of patients with otherwise typical DRD (both familial and sporadic) no mutation can be detected in the coding region, even in some cases with proven linkage to the DRD locus on chromosome 14.19,22,24 It is assumed that mutations in the introns or regulatory regions of the gene may be responsible in these cases.

Molecular pathogenesis

The molecular pathogenesis of DRD is still not entirely clear. Heterozygous mutations in the GCH1 gene result in a reduction of enzyme activity beyond what would be expected by a simple loss of function of one allele. Brain levels of total biopterin, neopterin, and dopamine are decreased by more than 80–90% in symptomatic individuals with DRD.25 Also, activity of GTPCH1 in phyohemagglutinin-stimulated mononuclear blood cells of patients with this type of DRD is decreased to less than 20% of that of normal controls.19 This phenomenon can probably be explained, at least in part, by a classic ‘dominant negative’ effect: GTPCH1 normally functions as a homodecameric complex. The integration of abnormal polypeptides derived from the mutant allele into this complex will therefore lead to dysfunction
of a large proportion of catalytic peptides, as only a few will exist entirely of wild-type peptides. Other mechanisms, however, may also play a role. In fact, there is now direct experimental evidence that dominant mutations of GCH1 may exert their dominant negative effect by also decreasing the level of wild-type protein in the cell: cotransfection of HEK cells with vectors encoding both the mutant and wild-type gene led to accelerated protein degradation.26

The deficiency of GTPCH1 activity results in reduced levels of total biopterin (the bulk of which is present as tetrahydrobiopterin (BH4) in the brain) and neopterin. BH4 deficiency in turn leads to a reduction of enzymatic activity of TH and other BH4-dependent enzymes. As a consequence, the concentration of dopamine and its metabolite homovanillic acid (HVA) is reduced in the striatum, which is also measurable in the cerebrospinal fluid (CSF).27 However, decreased dopamine levels are not only due to low enzymatic activity of TH in the presence of low cofactor concentrations but also to a loss of the TH protein. In fact, a reduction of TH protein content by as much as 97% in the putamen has been found in patients with typical DRD.27 As levels of TH protein and mRNA in the substantia nigra are normal, it has been hypothesized that the loss of striatal TH is due to increased instability and degradation of the protein in the absence of its cofactor BH4, within the nigrostriatal processes.

The pattern of striatal dopamine depletion in DRD and idiopathic Parkinson’s disease (PD) differs in some respect and its analysis may well provide interesting insights into the function of the basal ganglia. In both DRD and PD, the dopamine deficiency is greater in the putamen than in the caudate nucleus. However, there is evidence that the distribution along the ventrodorsal axis of the striatum may differ between the two disorders, the ventral area being more affected in DRD, while the dorsal portions are more heavily involved in PD. As there is also a differential distribution of relative abundance of D1 and D2 receptors in these areas, which in turn are linked to the direct and indirect striatopallidal pathways, respectively, it is possible that the relative difference in dopamine efficiency in D1 vs D2 pathways may account, in part, for the different clinical presentation of the two disorders.28

Another interesting aspect is the age dependence of clinical symptoms related to dopamine depletion: young-onset cases tend to present with dystonia, whereas later onset is more commonly associated with parkinsonism, both in DRD and in PD. It has been hypothesized that this age effect may be related to differential maturation of dopamine receptors.29

Not only TH but also phenylalanine hydroxylase and tryptophan hydroxylase use BH4 as a cofactor. However, in dominant DRD, only dopamine seems to be deficient to a clinically relevant degree, but not serotonin, the product of tryptophan hydroxylase. The reason for this observation is not entirely clear. It is possible that different expression levels of the respective enzymes in dopaminergic vs serotonergic neurons may play a role. It is also possible that the higher Ka value of TH for BH4 may contribute to the fact that TH enzymatic activity appears to be much more impaired compared to that of the other two hydroxylases.

Heterozygous, dominant negative mutations in the GCH1 gene cause a spectrum of clinical manifestations of DRD, as described above. In contrast, patients with homozygous (two identical) or compound heterozygous mutations in the GCH1 gene in trans (a different mutation in each of the two copies of the gene) have a more severe loss of enzyme activity, and suffer from BH4-deficient hyperphenylalaninemia (HPA), a disorder presenting in infancy with severe neurologic dysfunction (mental retardation, developmental delay, convulsions, truncal hypotonia, and limb hypertonia).30 Patients with an intermediate phenotype carrying (presumably less deleterious) homozygous or compound heterozygous mutations have been described with a dopa-responsive extrapyramidal syndrome beginning in infancy.31 The parents, as heterozygous carriers of these recessive mutations, remain clinically asymptomatic.

Diagnosis and differential diagnosis

As more than 85 different mutations have been described that are scattered over the entire gene,20 the practical role of molecular diagnosis is limited. Fortunately, a suspicion of dopa-responsive dystonia can usually be confirmed by the excellent response to L-dopa treatment, so that molecular analysis is frequently not necessary. A slowly increasing dose up to 300–400 mg/day of L-dopa/decarboxylase inhibitor is given; the effect can usually be seen within days, but may occasionally take weeks. Alternatively, low CSF levels of total biopterin and neopterin,20 a pathologic phenylalanine loading test,32 or a reduced activity of GTPCH1 in phytohemagglutinin (PHA)-stimulated peripheral mononuclear cells can be used to substantiate the diagnosis.

Relevant differential diagnoses in childhood-onset DRD include spastic paraplegia and cerebral palsy. A trial of L-dopa/decarboxylase inhibitor (up to 200 mg t.i.d. for 4–6 weeks) should be performed in doubtful cases. Early-onset parkinsonism (EOPD), particularly with parkin mutations may present with dystonia at onset and can be clinically very similar to DRD.33 These patients also show a very good response to L-dopa; however, fluctuations and hyperkinesias appear subsequently during the course of the disease. EOPD can also
be distinguished from DRD by abnormal imaging studies using markers of the presynaptic dopaminergic terminals and positron emission tomography (PET) ([18F]-fluorodopa; [11C]-methylphenidate) or single-photon emission computed tomography (SPECT) ([123I]-β-CIT)\textsuperscript{13,14} or by transcranial ultrasonography.\textsuperscript{17}

**DRD due to TH deficiency**

A recessive form of dopa-responsive dystonia has been described in patients with a genetic deficiency of TH.\textsuperscript{34,35} A complete loss of function of the TH protein appears to be lethal, as judged from knock-out (TH\textsuperscript{−/−}) mice. Mutations causing a severe TH deficiency, with enzyme activities <5% of normal lead to a syndrome of developmental motor delay, truncal hypotonia, rigidity, and hypokinesia,\textsuperscript{36} a disorder which has been termed ‘infantile parkinsonism’. Other mutations have been described, however, with enzymatic activities in the range of 10–20% of normal, with a phenotype more closely resembling DRD.\textsuperscript{37}

**Dystonia occurring with other defects of pterin synthesis**

Homzygous mutations in the genes for 6-pyrovoyl-tetrahydropterin synthase and sepiapterin reductase, encoding the enzymes catalyzing the subsequent two steps of BH\textsubscript{4}-biosynthesis, cause HPA and a severe neurologic syndrome including mental retardation, developmental delay, and seizures. Dystonia is usually not a part of this syndrome, although some patients do show dystonic movements with diurnal fluctuations. Such patients may partially respond to l-dopa therapy, but also need replacement of 5-hydroxytryptophan, the precursor of serotonin, and BH\textsubscript{4}.\textsuperscript{38}

**DRD linked to chromosome 14q31 (DYT14)**

In a single family with dopa-responsive dystonia, linkage to a novel locus, termed DYT14, has been located to chromosome 14q13 between D4S283 and D4S70 (maximum lod score of 3.28), clearly distinct from the GCH1 gene on chromosome 14q22. The clinical picture and pathologic findings closely resemble typical GCH1-deficient DRD.\textsuperscript{39} To date, linkage to DYT14 has not been confirmed in other families and the gene remains to be discovered.

**MYOCLONUS-DYSTONIA**

Myoclonus-dystonia is a dystonia-plus syndrome characterized by brief lightning-like myoclonic jerks and dystonia.\textsuperscript{40-42}

In its familial form, M-D follows an autosomal dominant inheritance pattern. Families with these clinical features have previously been described under the terms of (familial) essential myoclonus,\textsuperscript{43-45} myoclonic dystonia,\textsuperscript{46-47} and hereditary dystonia with lightning jerks responsive to alcohol.\textsuperscript{48} Affecteds in families from all of these categories have been found to carry mutations in the gene for ε-sarcoglycan, the major gene in this disorder.

It is important to distinguish inherited M-D from inherited and sporadic primary dystonia with concomitant myoclonic jerks in the dystonic limb, a condition which has also been called myoclonic dystonia.\textsuperscript{3} Occationally, this distinction may be difficult, and discriminating electrophysiologic criteria have not yet been established.

**Gene mapping and cloning**

After the initial mapping of a locus in large M-D pedigree to the long arm of chromosome 7 (7q21-31) by Nygaard et al,\textsuperscript{49} this finding has been confirmed by several other groups.\textsuperscript{50-52} Asmus and coworkers narrowed the critical region to approximately 3 cM. Using a classic positional cloning approach, Zimprich et al then identified five different heterozygous loss-of-function mutations in the gene for ε-sarcoglycan (SGCE) in six German families with M-D.\textsuperscript{53} Subsequently, many additional mutations were reported.\textsuperscript{41,54,55}

The fact that mutations in the ε-sarcoglycan gene are causative in a dystonia-plus syndrome was unexpected, as four other known members of the sarcoglycan family of genes (α-, β-, γ- and δ-sarcoglycan) had already been associated with autosomal recessive limb girdle muscular dystrophies.\textsuperscript{56}

By contrast to the other sarcoglycans, which are expressed predominantly or exclusively in muscle, SGCE expression is found in a wide variety of embryonic and adult tissues, including several brain regions.\textsuperscript{57} In the periphery, the sarcoglycans form a complex, together with other proteins, which links intracellular structural proteins like dystrophin to the extracellular matrix. The function of ε-sarcoglycan in brain is still unknown.

The SGCE gene consists of 13 exons (exons 1–11, plus alternatively spliced exons 9b and 11b). Exon 9b contains an Alu-element and can only be detected in traces in mRNA from human leukocytes. The major splice variants either lack exon 2 or exon 8. The use of exon 11b leads to a brain-specific SGCE splice variant with an altered C-terminus.\textsuperscript{58,59} The gene encodes a ubiquitously expressed 438-amino acid protein, which has a single transmembrane domain and is 68% homologous to α-sarcoglycan.

Exon deletions, as well as different nonsense and missense mutations of the SGCE gene in patients with
M-D, have been published (Figure 12.1). From the limited information available to date, there is no indication of a major difference in the phenotype between different types of mutations.

The vast majority of published heterozygous SGCE mutations presumably lead to a premature termination of protein translation (nonsense mutations or exon deletions resulting in a premature stop codon, or small deletions or insertions leading to a shift of the reading frame, or splice-site mutations, resulting in aberrant splicing of exons). However, a few mutations have been found to result in single amino acid changes only.

Heterozygous loss-of-function mutations are usually associated with autosomal recessive inheritance, as a single allele is usually sufficient to sustain the function of the encoded protein. Exceptions are dominant negative effects, as described above for GCH1-deficient DRD. In M-D, the most likely explanation for the dominant pattern of inheritance is the inactivation of the 'healthy' allele in affected individuals by a process called parental genomic imprinting, which is a well-described mechanism of gene regulation in some chromosomal areas, among them the human 7q21 region bearing the SGCE gene.

There is both genetic and direct experimental evidence for this hypothesis.

The most common mechanism for genomic imprinting is the specific inactivation of one of the parental alleles by methylation of cytosine residues in the promoter region. In the case of SGCE, the maternal allele is inactivated; hence, this process is called ‘maternal’ imprinting. The selective methylation of maternal alleles of the SGCE gene could be demonstrated by bisulfite sequencing in cell lines with uniparental disomy of chromosome 7q21, and by analysis of DNA from blood lymphocytes and from brain tissue. In addition, sole expression of the paternal allele could be detected in blood lymphocytes by reverse transcription polymerase chain reaction (RT-PCR); (Asmus et al, unpublished observations). Imprinting of the maternal allele explains the marked difference in penetrance of the disease, which depends on the sex of the transmitting parent: less than 5% of mutation carriers manifest the disease if the disease allele is passed on by the mother, while penetrance approaches 95% following paternal transmission. If the mutated allele is inherited from the mother, the intact paternal allele is sufficient to sustain ε-sarcoglycan function (as in most cases of...

Figure 12.1 Published heterozygous mutations in the SGCE gene in M-D patients. All except one mutation (R372X) are located in the extracellular and transmembrane domains of ε-sarcoglycan. Mutations in gray boxes denote nonsense mutations, dashed lines indicate splicing mutations. Missense mutations are given in ovals.
loss-of-function mutations) and the mutation carrier remains healthy. If, on the other hand, the mutated allele is inherited from the father, inactivation of the maternal allele due to imprinting leads to complete ε-sarcoglycan deficiency, and hence to the manifestation of clinical symptoms. Maternal imprinting of the SGCE gene has also been demonstrated in the mouse.65

**Clinical picture**

The clinical signs and symptoms of M-D usually develop during childhood or early adolescence and after that take a fluctuating, but usually not progressive course.40 The predominant symptom at presentation (mean age at onset 5.4 years, range 0.5–38 years41), as well as during the course of the disease in most patients, is myoclonic jerks, affecting predominantly axial muscles (neck and trunk) but also muscles of the upper more than lower extremities, with proximal muscles being more affected than distal ones. Jerks are very brief, ‘lightning-like’, and are precipitated or aggravated by action and psychological stress, but also occur at rest. More sustained, dystonic movements are observed in about two-thirds of patients, with torticollis and writer’s cramp being the most common manifestations. Dystonia of the lower limbs is occasionally seen, leading to dystonic gait disturbances. Usually, dystonia of the extremities accompanies myoclonus and has the characteristics of an action dystonia. Torticollis as the sole manifestation has only been found in a single individual in an M-D pedigree with an otherwise classical phenotype.41

Electroencephalographic (EEG) abnormalities and epileptic seizures in several individuals of a single M-D pedigree with an SGCE mutation have been reported recently.61 Additional neurologic manifestations, such as (cerebellar) ataxia, spasticity, or dementia, have not been found so far in M-D patients, unless explained by additional pathology such as perinatal hypoxia.

Most patients experience substantial symptomatic relief by alcohol or benzodiazepines but effective doses may vary considerably and patients can experience a heavy rebound of motor symptoms after single doses of alcohol or benzodiazepines. In contrast to cortical or posthypoxic myoclonus, valproic acid, piracetam, and levetiracetam provide neither significant nor lasting improvement of motor symptoms, although controlled therapeutic trials in M-D have not been performed. In severe cases of M-D, bilateral deep brain stimulation (DBS) to the ventral intermediate (Vim) nucleus of the thalamus or to the internal pallidum have been shown to confer substantial and lasting symptomatic relief.62,66 In patients with marked limb dystonia accompanying myoclonus, the internal globus pallidus (Gpi) is the preferred target.

**Psychiatric features of M-D**

Several reports on M-D pedigrees mentioned non-motor features like panic attacks, personality disorders, and alcohol abuse.41,49,67,68

In a more systematic investigation of possible psychiatric manifestations, Saunders-Pullman et al assessed three families with linkage to the 7q21 locus.

Symptoms of obsessive-compulsive disorder (OCD) were found to be more common in carriers of the disease-associated haplotype, both with and without motor symptoms, as compared to non-carriers, suggesting that these symptoms may be a primary manifestation of the disease. Recently, this association has been confirmed by the same authors in an extended sample of SGCE mutation carriers (Hess et al., 2007). By contrast, alcohol and benzodiazepine abuse were only detected in patients who experienced motor symptom control by these substances.

**Genetic heterogeneity in M-D**

Several studies of families and sporadic patients with M-D could only detect SGCE mutations in a proportion of the patients tested.41,60 Whereas in familial cases with a typical phenotype, SGCE is certainly the major gene, it seems to play a minor role in sporadic patients. SGCE mutations have never been described in patients with an onset of symptoms above 35 years of age.

Prior to the identification of linkage to chromosome 7q21, Klein et al reported a missense change (Val154Ile) in the gene for the dopamine D2 receptor (DRD2), cosegregating with the phenotype in a single family with M-D.68 However, in this particular family, a heterozygous SGCE mutation was later detected, also cosegregating with the M-D phenotype. As cell culture studies did not show functional effects of the sequence alteration in the D2 receptor, it is likely that the disease in this family is caused by the SGCE mutation, and not by the D2DR variant.

Leung et al identified a novel 18 bp deletion in the TOR1A gene (the causative gene in primary torsion dystonia) in an M-D sib pair.71 As both affecteds also carried a heterozygous SGCE mutation, the relevance of the 18 bp TOR1A deletion for the clinical phenotype remains uncertain.

The mapping of a second locus on chromosome 18p (lod score 3.96) in a family with a typical M-D phenotype and no indication of maternal imprinting was reported by Grimes et al (DYT15).72 Clinical features in this pedigree are indistinguishable from the classical SGCE phenotype. Interestingly, this genetic region had
been implicated in dystonic syndromes before: patients with a deletion of part of chromosome 18p, among other disturbances, dystonia (18p deletion syndrome,\textsuperscript{73}) and one form of adult-onset craniocervical dystonia (DYT7) was mapped to this region,\textsuperscript{74} although this finding had not been confirmed in other families.

Occasionally, other conditions such as dopa-responsive dystonia\textsuperscript{8} or vitamin E deficiency\textsuperscript{75} may mimic M-D.

**RAPID-ONSET DYSTONIA-PARKINSONISM (DTY12)**

Rapid onset dystonia-parkinsonism (RDP) is a rare, autosomal dominantly inherited movement disorder with incomplete penetrance, characterized by the abrupt or subacute onset of both dystonic symptoms and parkinsonism with prominent bulbar features.\textsuperscript{69} To date, 21 families with this condition\textsuperscript{95–100} and five possible sporadic cases\textsuperscript{96,101–103} have been reported.

**Clinical presentation**

Most patients experience sudden to subacute onset, over hours to days, of dystonic posturing of the limbs (upper more than lower), bradykinesia with prominent bulbar involvement, postural instability, dysarthria, and dysphagia.\textsuperscript{84} In some cases, the acute onset is preceded by stable mild limb dystonia over the course of several years. Onset usually occurs in adolescence or young adulthood, but can also occur in early childhood or late adulthood (as early as 4 and as late as 58 years). Subsequently, symptoms typically remain stable with little or no progression, sometimes even with moderate improvement in some cases. In one family,\textsuperscript{78} psychiatric manifestations such as social phobia and depression were noted in five out of eight affected family members and in one obligate gene carrier. In a few cases, seizures and paroxysmal dystonia have also been observed.\textsuperscript{76,77} Whereas dystonic features usually predominate, RDP may rarely also present as l-dopa-unresponsive parkinsonism.\textsuperscript{83}

In the majority of patients, trigger factors such as emotionally traumatic events, extreme heat or physical exercise, or infection could be identified. Symptoms do not respond significantly to dopaminergic medication. Bilateral pallidal DBS failed to improve symptoms in one sporadic patient.\textsuperscript{82}

The differential diagnosis of combined symptoms of generalized dystonia and parkinsonism includes DRD, X-linked dystonia, and parkinsonism (XDP, Lubag),\textsuperscript{85} and early-onset autosomal recessive parkinsonism due to mutations in the parkin gene.\textsuperscript{86}

**Biochemical and imaging studies**

Although reduced levels of dopamine metabolites in the CSF have been found in some patients, these levels did not correlate with severity of the disease and were also observed in unaffected at-risk individuals and obligate gene carriers.\textsuperscript{84} Cranial imaging studies using magnetic resonance imaging (MRI), computed tomography (CT), and PET imaging of presynaptic dopamine uptake sites\textsuperscript{87} were normal, suggesting that RDP is not a neurodegenerative disease, but that symptoms result from neuronal dysfunction. Consistent with this notion, a pathologic study in one patient\textsuperscript{78} who had previously undergone unilateral pallidotomy did not reveal evidence of nerve cell loss or gliosis other than that related to surgery.

**Genetic studies and molecular pathogenesis**

Linkage to an 8 cM region on chromosome 19q13.2 (DYT12) has been established in three families\textsuperscript{88} and refined to a 5.9 cM critical interval.\textsuperscript{89} Subsequently, six missense mutations in the gene for the Na\textsuperscript{+}/K\textsuperscript{+}-ATPase \(\alpha_3\) subunit (ATP1A3), including de-novo mutations, have been identified in four families and three sporadic patients.\textsuperscript{90} The ATP1A3 protein catalyzes the active transport of cations across cell membranes and is responsible for maintaining the electrochemical gradient. All six mutations are located in phylogenetically highly conserved regions of the protein, and five out of six are found in the transmembrane domain. Functional studies and structural predictions suggest that they act as loss-of-function mutations by impairing enzyme activity or stability, presumably leading to a change of cellular Na\textsuperscript{+} homeostasis.\textsuperscript{91} Differences in protein expression levels of mutant compared to wild-type subunits in transfected cells further suggest that ATP1A3 activity is reduced in RDP patients, with a result equivalent to haploinsufficiency. However, the molecular mechanisms by which these mutations cause an acute non-progressive neuronal phenotype triggered by external factors, followed by continuous specific dysfunction of certain neuronal populations, remain to be determined.

The expression of the ATP1A3 gene in humans is confined to excitable tissues, i.e. developing and adult brain and heart, and is observed throughout the brain, with the exception of corpus callosum, pituitary gland, and spinal cord.\textsuperscript{92} Interestingly, haploinsufficiency due to mutations in the gene encoding the closely related ATP1A2 isoform leads to familial hemiplegic migraine\textsuperscript{93} and benign familial infantile convulsions.\textsuperscript{94} The fact that mutations in different Na\textsuperscript{+}/K\textsuperscript{+}-ATPase isoforms cause clinically distinct neurologic syndromes suggests
that expression of these isoforms in the brain is temporally and spatially highly regulated and essential for normal brain function.

Recently, genetic studies in another large RDP family, which ruled out linkage to the DYT12 locus, demonstrated genetic heterogeneity, suggesting at least one additional RDP gene.79 A comprehensive study of the phenotypic spectrum of RDP in 49 subjects from 21 families (Brashear et al., 2007) provided further evidence for genetic heterogeneity, excluding ATP1A3 mutations in 13 individuals from 11 families, and recommended genetic testing for the ATP1A3 gene when abrupt onset, rostrocaudal gradient and prominent bulbar findings are present.

REFERENCES


57. Scheidtmann K, Muller F, Hartmann E, Koenig E. [Familial myoclonus-dystonia syndrome associated with panic attacks]. Nervenarzt 2000; 71(10):839–42. [in German]


85. Nolte D, Niemann S, Muller U. Specific sequence changes in multiple transcript system DYT3 are associated with X-linked dystonia parkinsonism. Proc Natl Acad Sci USA 2003; 100(18): 10347–52.
INTRODUCTION

In primary generalized dystonia and idiopathic adult-onset focal dystonia, dystonia occurs in isolation, usually the result of identified or unknown genetic mutations. Dystonia also presents after structural brain injury, exposure to toxins, or in the setting of a progressive neurodegenerative illness. These secondary forms of dystonia form the focus of this chapter. Infarcts, tumors, vascular malformations, and traumatic injuries to the basal ganglia are well-known triggers of dystonia. Exposure to drugs or toxins may cause either acute or chronic dystonia. Dystonia also occurs in a wide range of heredodegenerative illnesses, diseases characterized by progressive neuronal loss with accompanying neurologic symptoms and signs.

The most common causes of secondary dystonia are summarized in Table 13.1: most involve the basal ganglia directly, but secondary dystonia may also occur after injury to cortical or brainstem structures, spinal cord, and even peripheral nerve. Hemidystonia almost always occurs as the result of contralateral basal ganglia injury. Perinatal injury may cause dystonia at the time of brain injury, or with delay. So-called delayed-onset dystonia may begin years after injury, and may progress.1 Infectious, post-infectious, and inflammatory syndromes associated with dystonia usually present in combination with other movement disorders, including parkinsonism, chorea, athetosis, and tics. Medications such as dopamine receptor antagonists, levodopa, and dopamine agonists may also cause transient dystonia. Toxins such as manganese and carbon monoxide that directly affect the basal ganglia also result in dystonia.

Heredodegenerative causes of dystonia (summarized in Table 13.2) are extremely varied and best classified by etiology: disorders of metabolism, mitochondrial diseases, trinucleotide repeat disorders, parkinsonian disorders, and other degenerative processes without defined cause.

DIAGNOSTIC APPROACH

A brief perusal of Tables 13.1 and 13.2 should convince anyone that arriving at an etiologic diagnosis in a patient with a secondary or heredodegenerative dystonia is a formidable challenge. The differential diagnosis is broad, and there is a natural tendency to adopt a ‘shotgun’ approach, casting as wide a net as possible with multiple ancillary tests in the hope that one test will secure the diagnosis.

In contrast to this time-consuming and costly approach, we offer an alternative strategy, summarized in Figures 13.1 and 13.2. Age of symptom onset is critically important in guiding the evaluation. The most common causes for dystonia in different age groups are summarized in Table 13.3. Typical age ranges are listed, although there is variability in age of presentation. Brain imaging directs the next step: we routinely rely on magnetic resonance imaging (MRI). Hemidystonia almost always indicates a contralateral structural lesion, and all patients with acute hemidystonia should be promptly imaged to exclude a mass lesion, stroke, or tumor. Characteristic patterns of signal abnormality may aid in the diagnosis, including the ‘eye of the tiger’ sign in neurodegeneration with brain iron accumulation type I, ‘face of the giant panda’ in the midbrain of patients with Wilson’s disease, and basal ganglia calcification in Fahr’s disease.

If radiographic studies are normal, Wilson’s disease should be excluded, as this disorder is treatable when diagnosed early and uniformly fatal when missed. Slit-lamp examination by an experienced ophthalmologist, serum ceruloplasmin, and measurement of 24-hour urine
### Table 13.1 Causes of secondary dystonia

<table>
<thead>
<tr>
<th>CNS lesions</th>
<th></th>
<th>CNS lesions (Continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital malformations:</td>
<td></td>
<td>Buspirone</td>
</tr>
<tr>
<td>● Arteriovenous malformations</td>
<td></td>
<td>Cocaine</td>
</tr>
<tr>
<td>● Pachygyria</td>
<td></td>
<td>Monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>Brain tumor</td>
<td></td>
<td>Flecainide</td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td><strong>Toxins</strong></td>
</tr>
<tr>
<td>Hypoxia</td>
<td></td>
<td>Manganese</td>
</tr>
<tr>
<td>Head trauma</td>
<td></td>
<td>Carbon monoxide</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td></td>
<td>Carbon disulfide</td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td></td>
<td>Wasp sting</td>
</tr>
<tr>
<td>Brainstem lesion, including</td>
<td></td>
<td>Cyanide</td>
</tr>
<tr>
<td>central pontine myelinolysis</td>
<td></td>
<td>Methanol</td>
</tr>
<tr>
<td>Electrical injury</td>
<td></td>
<td>Disulfiram</td>
</tr>
<tr>
<td>Cervical cord lesion,</td>
<td></td>
<td>3-Nitropropionic acid</td>
</tr>
<tr>
<td>including syringomyelia</td>
<td></td>
<td><strong>Metabolic disorders</strong></td>
</tr>
<tr>
<td>Spinal stenosis</td>
<td></td>
<td>Hypoparathyroidism</td>
</tr>
<tr>
<td><strong>Peripheral nerve injury</strong></td>
<td></td>
<td><strong>Chromosomal abnormality</strong></td>
</tr>
<tr>
<td><strong>Perinatal cerebral injury</strong></td>
<td></td>
<td>18q or p deletion</td>
</tr>
<tr>
<td>Cerebral palsy</td>
<td></td>
<td><strong>Psychogenic</strong></td>
</tr>
<tr>
<td>Delayed-onset dystonia</td>
<td></td>
<td>Conversion disorder</td>
</tr>
<tr>
<td>Perinatal hypoxia</td>
<td></td>
<td>Somatization disorder</td>
</tr>
<tr>
<td>Kernicterus</td>
<td></td>
<td>Malingering</td>
</tr>
<tr>
<td><strong>Infectious, post-infectious, and inflammatory</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subacute sclerosing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>panencephalopathy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reye’s syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viral encephalitis, including</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creutzfeldt–Jakob disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paraneoplastic syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>brainstem encephalitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiphospholipid antibody</td>
<td></td>
<td></td>
</tr>
<tr>
<td>syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sjögren’s syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple myeloma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rasmussen’s syndrome</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Drug-induced</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopaminomimetic:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Levodopa</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Dopamine receptor agonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dopamine receptor antagonists</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(primarily D2 receptors)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Neuroleptics</td>
<td></td>
<td></td>
</tr>
<tr>
<td>● Prochlorperazine,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>metoclopramide</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiepileptic medications</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective serotonin reuptake</td>
<td></td>
<td></td>
</tr>
<tr>
<td>inhibitors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ergots</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* (Continued) copper excretion are usually sufficient to exclude the diagnosis. Once Wilson’s disease is excluded, the history should be carefully probed for evidence of perinatal hypoxia or exposure to any drug with affinity for the dopamine receptor.

At this point in the work-up, metabolic disorders and heredodegenerative disorders become more likely. Many metabolic disorders can be diagnosed by testing for serum amino acids and organic acids, or documenting specific enzymatic deficiencies in cultures of fibroblasts or leukocytes. These are the most challenging conditions to diagnose, because unique identifying features are absent.

In the remainder of this chapter, we summarize the clinical features and pathogenesis of these disorders, and briefly discuss their treatment.

**DISORDERS OF METAL AND MINERAL METABOLISM**

**Wilson’s disease**

Wilson’s disease, hepatolenticular degeneration, is caused by a mutation in the \(\text{ATP7B}\) gene (13q14) which encodes...
<table>
<thead>
<tr>
<th>Metabolic disorders</th>
<th>Defect</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metal and mineral metabolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Copper metabolism defect ATP7B gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 13</td>
<td></td>
</tr>
<tr>
<td>Neurodegeneration with brain iron accumulation type I (formerly Hallervorden–Spatz disease)</td>
<td>PANK2 gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 20</td>
<td></td>
</tr>
<tr>
<td>Neuroferritinopathy</td>
<td>Ferritin light-chain gene</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>Chromosome 19</td>
<td></td>
</tr>
<tr>
<td>Idiopathic basal ganglia calcification (Fahr’s disease)</td>
<td>IBGC1 gene</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>Chromosome 14</td>
<td></td>
</tr>
<tr>
<td><strong>Lysosomal storage disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Niemann–Pick disease type C</td>
<td>Unesterified cholesterol accumulation NPC1 and HE1 genes</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosomes 18 and 14</td>
<td></td>
</tr>
<tr>
<td>GM₁ gangliosidosis</td>
<td>β-Galactosidase gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 3</td>
<td></td>
</tr>
<tr>
<td>GM₂ gangliosidosis</td>
<td>Hexosaminidase A gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 15</td>
<td></td>
</tr>
<tr>
<td>Metachromatic leukodystrophy</td>
<td>Arylsulfatase A ASA/ARSA gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 22</td>
<td></td>
</tr>
<tr>
<td>Krabbe’s disease</td>
<td>Galactosylceramide β-galactosidase GALC gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 14</td>
<td></td>
</tr>
<tr>
<td>Pelizaeus–Merzbacher disease</td>
<td>Proteolipid protein PLP gene</td>
<td>X</td>
</tr>
<tr>
<td>Neuronal ceroid-lipofuscinosis (Batten disease)</td>
<td>Intranuclear accumulation of granular lipopigment</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>6 gene mutations found</td>
<td></td>
</tr>
<tr>
<td>Fucosidosis</td>
<td>Alpha-1-fucosidase FUCA1 gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 1</td>
<td></td>
</tr>
<tr>
<td><strong>Inborn errors of metabolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesch–Nyhan syndrome</td>
<td>HGPRT</td>
<td>X</td>
</tr>
<tr>
<td>Aromatic amino acid decarboxylase deficiency</td>
<td>AADC</td>
<td>AR</td>
</tr>
<tr>
<td>Triose-phosphate isomerase deficiency</td>
<td>Triose-phosphate isomerase</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 12</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Metabolic disorders</th>
<th>Defect</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guanidinoacetate methyltransferase</td>
<td>GAMD</td>
<td>AR</td>
</tr>
<tr>
<td>deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Molybdenum cofactor deficiency</td>
<td>MCD and in sulfite oxidase deficiency</td>
<td>AR</td>
</tr>
<tr>
<td>Glucose transport defects</td>
<td>GLUT1 gene</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>Chromosome 1</td>
<td></td>
</tr>
<tr>
<td><strong>Amino and organic acidurias</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glutaric academia type I</td>
<td>Glutaryl-CoA dehydrogenase gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 19</td>
<td></td>
</tr>
<tr>
<td>Homocystinuria</td>
<td>Cystathionine β-synthase gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 21</td>
<td></td>
</tr>
<tr>
<td>Prionionic acidemia</td>
<td>Propionyl-CoA carboxylase genes</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosomes 13 and 3</td>
<td></td>
</tr>
<tr>
<td>Methylmalonic aciduria</td>
<td>Methylmalonyl CoA mutase gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 6</td>
<td></td>
</tr>
<tr>
<td>4-Hydroxybutyric aciduria</td>
<td>Succinic semialdehyde dehydrogenase gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 6</td>
<td></td>
</tr>
<tr>
<td>3-Methylglutaconic aciduria</td>
<td>3-Methylglutaconyl-CoA hydratase, among</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>other deficiencies</td>
<td></td>
</tr>
<tr>
<td>2-Oxoglutaric aciduria</td>
<td>2-Oxoglutarate dehydrogenase</td>
<td>AR</td>
</tr>
<tr>
<td>Hartnup disease</td>
<td>Neutral amino acid transporter defect</td>
<td>ND</td>
</tr>
<tr>
<td><strong>Mitochondrial disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leigh disease</td>
<td>Mitochondrial respiratory chain enzyme</td>
<td>AR, X,</td>
</tr>
<tr>
<td></td>
<td>defects</td>
<td>maternal</td>
</tr>
<tr>
<td></td>
<td>SURF1 gene</td>
<td></td>
</tr>
<tr>
<td>Leber's hereditary optic neuropathy</td>
<td>Mitochondrial respiratory chain complexes</td>
<td>Maternal</td>
</tr>
<tr>
<td></td>
<td>I, III, or IV defects</td>
<td></td>
</tr>
<tr>
<td>Mohr–Tranebjaberg syndrome – dystonia,</td>
<td>Deafness/dystonia peptide (DDP) gene</td>
<td>X</td>
</tr>
<tr>
<td>deafness</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Trinucleotide repeat disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Huntington's disease</td>
<td>Huntingtin gene</td>
<td>AD</td>
</tr>
<tr>
<td></td>
<td>Expanded CAG repeat</td>
<td></td>
</tr>
<tr>
<td></td>
<td>in IT15 gene</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Chromosome 4</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Table 13.2 (Continued)

<table>
<thead>
<tr>
<th>Metabolic disorders</th>
<th>Defect</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinocerebellar ataxia type 3 (Machado–Joseph disease)</td>
<td>Expanded CAG repeat in ataxin gene</td>
<td>AD</td>
</tr>
<tr>
<td>and other SCAs</td>
<td>Chromosome 14 (SCA3)</td>
<td></td>
</tr>
<tr>
<td>Parkinsonian syndromes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Familial; parkin, synuclein, and DJ1 genes</td>
<td>Variable</td>
</tr>
<tr>
<td>Progressive supranuclear palsy</td>
<td>Tau</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Multiple system atrophy</td>
<td>synuclein</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Corticobasal ganglionic degeneration</td>
<td>Tau</td>
<td>Sporadic</td>
</tr>
<tr>
<td>Juvenile-onset parkinsonism</td>
<td>parkin gene</td>
<td>AR</td>
</tr>
<tr>
<td>X-linked dystonia-parkinsonism (Lubag)</td>
<td>DYT3 gene</td>
<td>X</td>
</tr>
<tr>
<td>Rapid-onset dystonia-parkinsonism</td>
<td>Chromosome 19</td>
<td>AD</td>
</tr>
<tr>
<td>Other degenerative processes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>ATM gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 11</td>
<td></td>
</tr>
<tr>
<td>Chorea-acanthocytosis</td>
<td>Chorein gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 9</td>
<td></td>
</tr>
<tr>
<td>Rett syndrome</td>
<td>MECP2 gene</td>
<td>X</td>
</tr>
<tr>
<td>Infantile bilateral striatal necrosis</td>
<td>ND</td>
<td>AR, maternal</td>
</tr>
<tr>
<td>Neuronal intranuclear inclusion disease</td>
<td>Ubiquinated intranuclear inclusions with polyglutamine tracts</td>
<td>ND</td>
</tr>
<tr>
<td>Ataxia with vitamin E deficiency</td>
<td>α-Tocopherol transfer protein gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 8</td>
<td></td>
</tr>
<tr>
<td>Progressive pallidal degeneration</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td>Sjögren–Larsson syndrome</td>
<td>Fatty alcohol dehydrogenase gene</td>
<td>AR</td>
</tr>
<tr>
<td></td>
<td>Chromosome 17</td>
<td></td>
</tr>
<tr>
<td>Ataxia–amyotrophy–mental retardation–dystonia syndrome</td>
<td>ND</td>
<td>AR</td>
</tr>
</tbody>
</table>

AD = autosomal dominant; AR = autosomal recessive; ND = not determined; X = X-linked.

a copper transporter. It is inherited in autosomal recessive fashion, and numerous point mutations have been described. Certain mutations occur more frequently in particular ethnic groups, such as the H1069Q mutation in those of European descent, R778L found in Asian populations, and H714Q and delC2337 in the Russian population. Mutations in the Wilson’s disease gene result in abnormal copper metabolism, with accumulation...
Imaging

Structural abnormality
Stroke, tumor, AVM or congenital malformation

T2 hyperintensity in white matter
consider leukodystrophies

MLD Krabbe's disease
Consider fibroblast culture

PANK2 mutation

T2 hypodensity in striatum
consider Infantile bilateral striatal necrosis

CT hypodensity in globus pallidus
consider Infantile bilateral striatal necrosis

T2 hyperintensity in basal ganglia

Signal abnormality
T2 hyperintensity in white matter
consider leukodystrophies

Eye-of-the-tiger T2 signal change in globus pallidus
consider NBIA-I

CT calcifications and +FH IBGC1 mutation

CO, Mn, MeOH, etc.

Perinatal hypoxia or ischemia

Infection
Encephalitis, post-infectious

Drug-induced dystonia
Exposure to DRBs

Developmental delay

Chorea
Juvenile-onset HD
mutation analysis

Parkinsonism
consider ARJPD
parkin mutation
PMH and FH

Ataxia
consider NA
consider SCA

Mutations

- MR

- GM1 GM2

- NCL

- Leber's syndrome

- Lesch-Nyhan syndrome

- GM3

- fibrinogen

- GM4

- Hand-wringing

- Rett syndrome

- VITAMIN E DEFICIENCY

- check level, ATTP mutation analysis

- SCA

- NPC

- NIDD

- cholesterol esterification

- filipin staining

Associated signs and symptoms

Figure 13.1 Flow chart detailing investigations for secondary dystonia with onset in childhood. AADC = aromatic amino acid decarboxylase deficiency; ARJPD = autosomal recessive juvenile-onset Parkinson's disease; AT = ataxia-telangiectasia; AVM = arteriovenous malformation; CO = carbon monoxide; CP = cerebral palsy; CT = computed tomography; DRBs = dopamine receptor blocking drugs; FH = family history; HD = Huntington's disease; K–F = Kayser–Fleischer; MeOH = methanol; MLD = metachromatic leukodystrophy; Mn = manganese; NBIA-I = neurodegeneration with brain iron accumulation type I; NCL = neuronal ceroid-lipofuscinosis; NIID = neuronal intranuclear inclusion disease; NPC = Niemann–Pick disease type C; PMH = past medical history; PTH = parathyroid hormone; RODP = rapid-onset dystonia-parkinsonism; SCA = spinocerebellar ataxia.
Figure 13.2 Flow chart detailing investigations for secondary dystonia with onset in adulthood. AVM = arteriovenous malformation; CBGD = corticobasal ganglionic degeneration; CO = carbon monoxide; CP = cerebral palsy; CT = computed tomography; DRBs = dopamine receptor blocking drugs; FH = family history; K–F = Kayser–Fleischer; MeOH = methanol; MLD = metachromatic leukodystrophy; Mn = manganese; MSA = multiple system atrophy; NBIA-I = neurodegeneration with brain iron accumulation type I; NCL = neuronal ceroid-lipofuscinosis; NIID = neuronal intranuclear inclusion disease; NPC = Niemann–Pick disease type C; PD = Parkinson’s disease; PMH = past medical history; PSP = progressive supranuclear palsy; PTH = parathyroid hormone; RODP = rapid-onset dystonia-parkinsonism; SCA = spinocerebellar ataxia.
Clinical manifestations may begin from age 3 to 58 years, typically presenting with hepatic (40%), neurologic (40%), or psychiatric (20%) symptoms and signs.6–8 Three neurologic presentations have been identified: parkinsonism, generalized dystonia, and a tremor-predominant form. Dystonia is common, often affecting cranial structures, with prominent dysarthria, risus sardonicus or a fixed pseudosmile (see Chapter 9, figure 9.11), and a high-pitched whining on inspiration. Kayser–Fleischer rings are visible in 90–95% of patients with neurologic manifestations of the illness.7,9 Systemic manifestations of Wilson’s disease are common, including hemolytic anemia, renal impairment, pancreatitis, cardiomyopathy, endocrinopathy, osteoarthritis, and osteoporosis.5

The diagnosis of Wilson’s disease is supported by decreased serum ceruloplasmin (typically less than 20 mg/dl), a 5–10-fold increase in 24-hour urinary copper excretion, and the presence of Kayser–Fleischer rings on slit-lamp examination. Quantification of hepatic copper on liver biopsy is rarely necessary. Mutation analysis is available on a research basis; however, the large number of mutations prevents routine screening.10,11 Approximately 300 mutations in the ATP7B gene have been found to date (http://www.medicalgenetics.med.ualberta.ca/wilson/index.php). A scoring system has been developed based on the clinical signs and symptoms and laboratory testing results. A score of ≥4 suggests that a diagnosis of Wilson’s disease is very likely.10

### Table 13.3 Age at onset of secondary dystonia

<table>
<thead>
<tr>
<th>Birth</th>
<th>&lt;1 year</th>
<th>1–10 years</th>
<th>10–20 years</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perinatal injury</td>
<td>Infectious causes</td>
<td>Cerebral palsy</td>
<td>Infectious causes</td>
<td>Stroke, tumor, AVM, hemorrhage</td>
</tr>
<tr>
<td>Congenital malformations</td>
<td>GM subgansiosidosis</td>
<td>Delayed-onset dystonia</td>
<td>Wilson’s disease</td>
<td>Hypoxia, head trauma</td>
</tr>
<tr>
<td>Infectious causes</td>
<td>GM subgansiosidosis</td>
<td>Infectious causes</td>
<td>Niemann–Pick type C</td>
<td>Infectious, inflammatory causes</td>
</tr>
<tr>
<td>Chromosomal deletion</td>
<td>Leukodystrophy</td>
<td>Wilson’s disease</td>
<td>GM subgansiosidosis</td>
<td>Drug-induced, toxins, psychogenic</td>
</tr>
<tr>
<td>NCL (Batten disease)</td>
<td>Niemann–Pick type C</td>
<td>Leukodystrophy</td>
<td>NCL (Batten disease)</td>
<td>Wilson’s disease</td>
</tr>
<tr>
<td>Inborn errors of metabolism</td>
<td>GM subgansiosidosis</td>
<td>Leigh disease</td>
<td>Fahr’s disease</td>
<td>Neuroferritinopathy</td>
</tr>
<tr>
<td>Amino and organic acidurias</td>
<td>Leukodystrophy</td>
<td>Leber’s syndrome</td>
<td>Niemann–Pick type C</td>
<td></td>
</tr>
<tr>
<td>Bilateral striatal necrosis</td>
<td>NCL (Batten disease)</td>
<td>Juvenile HD</td>
<td>Leukodystrophy</td>
<td></td>
</tr>
<tr>
<td>NCL (Batten disease)</td>
<td>ARJP Parkinson’s disease mutation</td>
<td>RODP</td>
<td>NCL (Batten disease)</td>
<td>Leber syndrome</td>
</tr>
<tr>
<td>Leigh syndrome</td>
<td>Vitamin E deficiency</td>
<td>NIID</td>
<td>HD, SCA3</td>
<td></td>
</tr>
<tr>
<td>Deafness-dystonia</td>
<td>Ataxia-telangiectasia</td>
<td>Rett syndrome</td>
<td>PD, PSP, MSA, CBGD</td>
<td></td>
</tr>
<tr>
<td>NCL (Batten disease)</td>
<td>Juvenile HD</td>
<td>ARJP Parkinson’s disease mutation</td>
<td>RODP</td>
<td></td>
</tr>
<tr>
<td>NCL (Batten disease)</td>
<td>Leber syndrome</td>
<td>Vitamin E deficiency</td>
<td>NIID</td>
<td></td>
</tr>
<tr>
<td>Ataxia-telangiectasia</td>
<td>Rett syndrome</td>
<td>Vitamin E deficiency</td>
<td>NIID</td>
<td></td>
</tr>
<tr>
<td>Deafness-dystonia</td>
<td>Ataxia-telangiectasia</td>
<td>Rett syndrome</td>
<td>Vitamin E deficiency</td>
<td>NIID</td>
</tr>
</tbody>
</table>

ARJPD = autosomal recessive juvenile-onset Parkinson’s disease; AVM = arteriovenous malformation; CBGD = corticobasal ganglionic degeneration; HD = Huntington’s disease; MSA = multiple system atrophy; NBIA-I = neurodegeneration with brain iron accumulation type I; NCL = neuronal ceroid-lipofuscinosis; NIID = neuronal intranuclear inclusion disease; PD = Parkinson’s disease; PSP = progressive supranuclear palsy; RODP = rapid-onset dystonia-parkinsonism; SCA = spinocerebellar ataxia.
Imaging of the brain typically shows T2 hyperintensity in the basal ganglia and thalamus. A characteristic pattern, the ‘face of the giant panda’, is occasionally visible in the midbrain. On pathologic examination, caudate and putamen are often atrophic, with neuronal loss extending to globus pallidus, subthalamic nucleus, thalamus, and brainstem. Alzheimer type II astrocytes are prominent in the cortex, basal ganglia, brainstem nuclei, and cerebellum. Opalski cells may be found in the globus pallidus.

Missing the diagnosis of Wilson’s disease is one of the worst errors a neurologist can make. Administration of copper chelators such as penicillamine, trientene, tetrathiomolybdate, or 2,3-dimercaptopropanol, or agents that bind intestinal copper such as zinc sulfate or zinc acetate, is effective in treatment of this disease. There is debate in the literature whether penicillamine or tetrathiomolybdate should be used as initial treatment, as there is a significant risk of worsening of neurologic symptoms when penicillamine is used. Penicillamine’s potential side effects also limit the drug’s effectiveness. Patients who do not respond to medical treatment, or in whom hepatic injury is severe, may need liver transplantation, which is curative.

**Neurodegeneration with brain iron accumulation type I (formerly Hallervorden–Spatz disease)**

This neurodegenerative disorder is transmitted in an autosomal recessive fashion, typically with age of onset between 2 and 10 years. The majority of affected patients possess mutations in a gene on chromosome 20p13 encoding pantothenate kinase 2, a regulatory enzyme important in the biosynthesis of coenzyme A, and the disorder has also been termed pantothenate kinase-associated neurodegeneration (PANK). Dystonia is a prominent presenting sign, present in 87% of patients in one study. Cranial and limb dystonia occur early, followed later by axial dystonia. Other neurologic manifestations include chorea, athetosis, rigidity, dysarthria, and dementia. Seizures and retinitis pigmentosa may also occur. The disease is progressive, leading to death in 15–20 years, although atypical forms with later onset and slower progression occur.

Clinical presentation and MRI findings of low T2 signal intensity in the globus pallidus with a central area of increased intensity (the characteristic ‘eye of the tiger’ sign) should suggest the diagnosis. Recent studies suggest that all cases with a mutation in PANK2 also possess the ‘eye of the tiger’ finding on MRI. Pathologic examination reveals iron deposition and cell loss in the pallidum and substantia nigra, associated with axonal spheroids and gliosis. Although there are no treatments proven to affect the natural history of the disease, it is reasonable to treat with pantothenate in order to bypass the enzymatic defect.

**Neuroferritinopathy**

Neuroferritinopathy is a recently described neurodegenerative disorder in which iron accumulates in the brain due to mutations in the gene encoding the ferritin light chain (chromosome 19q13.3). This dominantly inherited disorder typically presents in the fourth to sixth decades of life with dystonia, chorea, and parkinsonism. Dystonic dysarthria is common, and dystonia may also affect the limbs. Laboratory testing reveals a low ferritin level, typically ≤20 mg/dl. Histopathology reveals iron and ferritin deposition extracellularly in the basal ganglia, forebrain, and cerebellum. Cysts may be seen in the globus pallidus. MRI reveals increased T2 signal in the putamen and globus pallidus. Treatment at this time is symptomatic.

**Idiopathic basal ganglia calcification (Fahr’s disease)**

Calcification of the basal ganglia is an incidental finding in 0.3–1% of routine head computed tomography (CT) scans. However, in idiopathic basal ganglia calcification (IBGC), also known as Fahr’s disease, progressive neurologic and psychiatric dysfunction are caused by calcium deposition within the brain. Parkinsonism, chorea, dystonia, ataxia, dyskinesias, seizures, cognitive impairment, and psychosis have been described. The disorder is usually autosomal dominant with an age of onset of 30–50 years. A locus, IBGC1, has been identified on chromosome 14q. Calcification is commonly seen in the globus pallidus, putamen, caudate, thalamus, and dentate nucleus. Pathology reveals perivascular iron deposits in the basal ganglia and dentate nucleus.

**LYSOSOMAL STORAGE DISORDERS**

**Niemann–Pick type C**

Niemann–Pick type C (NPC) is an autosomal recessive disorder with progressive neurologic and hepatic dysfunction secondary to accumulation of endocytosed unesterified cholesterol. Ninety-five percent of cases are caused by mutations in the NPC1 gene located on chromosome 18q11, which encodes a protein important for cholesterol trafficking. Other cases have been associated with mutations in the HET gene on chromosome 14q24, which encodes a lysosomal protein. Onset is typically in late childhood, and the
clinical manifestations include organomegaly, vertical supranuclear gaze palsy, progressive dystonia, ataxia, and dementia. Dystonia is initially focal but often generalizes. Adult-onset cases progress more slowly, whereas infantile onset is characterized by hypotonia and motor delay. The diagnosis relies on demonstration of abnormal cholesterol esterification and filament staining in cultured fibroblasts. Foamy cells and sea-blue histiocytes are present in bone marrow, spleen, liver, lung, lymph nodes, and tonsils. Cholesterol and other lipids accumulate in the brains of patients with NPC, particularly in the large pyramidal neurons, and ballooned neurons are found in the basal ganglia and thalamus. Axonal spheroids are present in the thalamus, brainstem, and cerebellum. Neurofibrillary tangles are found in the hippocampus, entorhinal cortex, thalamus, and basal ganglia in adults with the disease.

**GM₁ gangliosidoses**

Mutations in the gene encoding the lysosomal enzyme β-galactosidase result in GM₁ gangliosidosis. This disorder manifests shortly after birth with poor feeding, organomegaly, and failure to thrive. Dystonia may be a prominent feature, or it may be absent. An adult-onset form has been described in which dystonia is more prominent. A macular cherry-red spot is present in 50% of patients. The disorder is autosomal recessive, and the diagnosis can be made enzymatically using cultured fibroblasts, white blood cells, or serum. On pathologic examination, multilamellated neuronal inclusions are found primarily in the basal ganglia.

**GM₂ gangliosidoses**

GM₂ gangliosides are autosomal recessive lysosomal storage diseases that may present during infancy, childhood, or adulthood. They are caused by mutations in the genes encoding hexosaminidase A (chromosome 15) or B, or the GM₂ activator of hexosaminidase A (both on chromosome 5). There are many forms of GM₂ gangliosidoses, including Tay–Sachs and Sandhoff’s diseases. Dystonia is present in many forms of hexosaminidase deficiency and may be prominent in the adult-onset form. Motor regression, ataxia, seizures, myoclonus, dementia, and macular cherry-red spots also occur. Ganglioside GM₂ accumulates in neuronal lysosomes, and ‘meganeurites’ are observed throughout the cortex.

**Leukodystrophies (MLD, Krabbe’s disease, and Pelizaeus–Merzbacher disease)**

Metachromatic leukodystrophy (MLD) is an autosomal recessive disorder caused by mutations in the ASA/ARSA gene (chromosome 22q13), which encodes the lysosomal protein arylsulfatase A. There are three variants of MLD: late-infantile, juvenile, and adult. Dystonia may occur in any form of MLD but typically occurs later in the disease. Ataxia, spasticity, and seizures are frequent concomitant findings. Brain MRI demonstrates diffuse demyelination, and the diagnosis is made by documenting decreased arylsulfatase A activity in leukocytes or cultured fibroblasts. On pathologic examination, there is demyelination and metachromatic granule deposition in oligodendrocytes, macrophages, and neurons.

Krabbe’s disease, also known as globoid cell leukodystrophy, is also an autosomal recessively inherited disorder with presentation either in the first year of life, childhood, or adulthood. Mutations have been found in the GALS gene on chromosome 14q31 encoding the lysosomal enzyme galactosylceramide β-galactosidase. Typically, psychomotor regression, frequent vomiting, and seizures are the initial manifestation of disease. Progression of disease is rapid, with marked dystonia, optic atrophy, and frequent seizures leading to death within 2 years. In late-onset disease, the clinical features are more variable and the rate of progression may be slower. Brain MRI demonstrates diffuse demyelination. Diagnosis is made by demonstrating the enzyme deficiency in leukocytes or cultured fibroblasts. Pathology reveals extensive demyelination and globoid cells throughout the white matter.

Pelizaeus–Merzbacher disease is a recessive X-linked disorder caused by mutations in the gene that encodes proteolipid protein (PLP). Demyelination is the cardinal feature, and age of onset and disease progression vary. Disease manifestations include dystonia, ataxia, spasticity, nystagmus, and psychomotor retardation. Brain MRI demonstrates diffuse demyelination. Diagnosis is made by direct mutation analysis. Neuropathology demonstrates central demyelination and axonal loss.

**Neuronal ceroid-lipofuscinosis (Batten disease)**

Neuronal ceroid-lipofuscinosis (NCL) (Batten disease) is a group of lysosomal storage disorders including eight distinct forms. These disorders are inherited in an autosomal recessive manner and vary in the age of onset. They were originally classified into four groups: infantile NCL or Haltia–Santavuori disease; late-infantile NCL or Jansky–Bielschowsky disease; juvenile NCL or Spielmeyer–Vogt–Sjögren disease; and adult NCL or Kufs’ disease. Forms of NCL are distinguished by their characteristic neuronal inclusions: granular osmiophilic deposits, curvilinear profiles, fingerprint profiles, and mixed inclusions, respectively. The pathologic hallmark of NCL is accumulation of a granular lipopig-
ment in neurons. Diffuse neuronal loss is also evident. Recent advances have led to the identification of six different gene mutations linked to NCL, termed CLN1, 2, 3, 5, 6, and 8. The first two genes code for lysosomal enzymes, while CLN3, 5, 6, and 8 encode transmembrane proteins.57

NCLs are characterized by progressive vision loss, cognitive decline, and seizures. Dystonia may occur, and has been described in all forms of the disorder.58-61 The diagnosis of NCL can be made by the demonstration of lysosomal inclusions on skin biopsy and confirmed by electron microscopy. Biochemical and genetic studies are also available.

**Fucosidosis**

Fucosidosis is an autosomal recessive disease caused by a deficiency of the lysosomal enzyme α-1-fucosidase. Mutations in the α-fucosidase gene (FUCA1) located on chromosome 1 are responsible.62 The disorder typically manifests during infancy, with progressive psychomotor retardation, dysostosis multiplex, organomegaly, angiokeratoma, seizures, and spasticity.63 An individual homozygous for a Q422X mutation was reported to have progressive generalized dystonia.64 The diagnosis is made by demonstrating abnormal enzyme activity in cultured fibroblasts or leukocytes. Electron microscopy reveals the presence of vacuoles in multiple tissues, including brain and liver.65

**INBORN ERRORS OF METABOLISM**

**Lesch–Nyhan syndrome**

Lesch–Nyhan syndrome is an X-linked disorder resulting from deficiency of hypoxanthine–guanine phosphoribosyltransferase. Clinical manifestations include movement disorders such as dystonia, choreoathetosis, spasticity, self-mutilation, hyperuricemia, and developmental retardation.66 Symptoms typically begin after 6 months of age. The diagnosis is suggested by elevated levels of uric acid in serum and urine, and secured by absent hypoxanthine guanine phosphoribosyltransferase activity in cultured fibroblasts. No consistent abnormalities have been described on central nervous system (CNS) histopathology.

**Aromatic amino acid decarboxylase deficiency**

The first patients with aromatic L-amino acid decarboxylase (AADC) deficiency were described by Hyland and Clayton in 1992, and several cases have been subsequently reported.67-69 Lack of AADC results in reduced levels of the biogenic amines dopamine, serotonin, nor epinephrine, and epinephrine. The disorder is inherited in autosomal recessive fashion with typical onset, between 2 and 9 months of age, of characteristic paroxysmal dystonia of the limbs and oculogyric crises. These spells increase in frequency and severity over time. Between spells, bradykinesia, athetosis, myoclonic jerks, tongue thrusting, and flexor spasms may be seen. The diagnosis rests on the demonstration of high levels of plasma levodopa and low levels of plasma dopamine and norepinephrine metabolites. Alternatively, cerebrospinal fluid (CSF) neurotransmitter analysis demonstrates low levels of homovanillic acid and 5-hydroxyindoleacetic acid and elevated 3-O-methyldopa.70 Direct genetic analysis is available on a research basis to confirm the diagnosis.

**Triose-phosphate isomerase deficiency**

This autosomal recessive disorder is caused by mutations in triose-phosphate isomerase (TPI) (chromosome 12), a glycolytic enzyme that interchangeably converts glyceraldehyde phosphate and dihydroxyacetone phosphate.71 Age of onset is typically 2 years, with clinical features of dystonia, tremor, muscular atrophy secondary to anterior horn cell disease, and corticospinal signs.72 Chronic hemolytic anemia may also occur. The disorder is inherited in an autosomal recessive fashion, and the diagnosis is made by assaying triose-phosphate isomerase levels in red blood cells.

Guanidinoacetate methyltransferase deficiency, molybdenum cofactor deficiency, and glucose transporter protein type 1 deficiency have also been reported to exhibit dystonia as part of their clinical phenotypes.73-76

**AMINO AND ORGANIC ACIDURIAS**

**Glutaric acidemia type I**

Glutaric acidemia type I is an autosomal recessive disorder caused by mutations in the mitochondrial enzyme glutaryl-coenzyme A dehydrogenase (chromosome 19).77 Affected patients develop normally during the first months of life, and symptoms may begin acutely or insidiously. Severe generalized dystonia is common, often accompanied by spasticity and seizures.78 The diagnosis is made by demonstrating elevated glutaric and 3-hydroxyglutaric acids in urine. The enzyme deficiency may also be demonstrated in cultured fibroblasts. Neuronal loss and decreased γ-aminobutyric acid (GABA) levels have been demonstrated in the putamen and caudate.79,80
Homocystinuria

Deficiency of cystathionine β-synthase causes homocystinuria, which typically features global developmental delay, cerebral thromboembolism, and anterior dislocation of the optic lens. The disorder is inherited in an autosomal recessive fashion, and many different mutations have been identified in the gene located on chromosome 21. When present, dystonia usually occurs due to infarction of the basal ganglia, although this idea has been challenged. Diagnosis is confirmed by documenting the enzyme deficiency in liver or in cultured fibroblasts.

Propionic acidemia

Mutations in the gene encoding propionyl-CoA carboxylase cause propionic acidemia, an autosomal recessive disorder. Symptoms typically begin in infancy, with episodes of ketosis and metabolic acidosis. Infarction of the basal ganglia may be responsible for the movement disorders that occur, which often include dystonia and choreoathetosis. Seizures and developmental delay are also common. The diagnosis is made by measurement of organic acids and demonstration of a decrease in propionyl-CoA carboxylase.

Dystonia has been described in various other disorders of amino acid and organic acid metabolism, including methylmalonic aciduria, 4-hydroxybutyric aciduria, 3-methylglutaconic aciduria, 2-oxoglutaric aciduria, and Hartnup disease. Measurement of serum and urine amino and organic acids is indicated in children with no other identifiable cause of dystonia.

MITOCHONDRIAL DISORDERS

Leigh disease

Leigh disease, or subacute necrotizing encephalomyelopathy, typically occurs as the result of mutations in the gene encoding SURF1, important for cytochrome oxidase assembly. Other mitochondrial enzymatic abnormalities have been described, including defects in pyruvate dehydrogenase and respiratory complexes I, II, IV, and V. Leigh disease may be inherited in a maternal, X-linked or autosomal recessive fashion. Onset is typically in infancy or childhood, with developmental regression, seizures, brainstem dysfunction, dystonia, ataxia, and optic atrophy. The diagnosis is supported by finding elevated levels of lactate and pyruvate in serum and CSF, abnormal pattern of cytochrome c oxidase expression on muscle biopsy, and abnormal MRI signal and necrosis in the basal ganglia, thalamus, and brainstem.

Leber’s hereditary optic neuropathy

Mutations in mitochondrial respiratory chain complexes I, III, or IV may lead to Leber’s hereditary optic neuropathy, a disorder characterized by rapid vision loss beginning between 18 and 23 years old. Dystonia, ataxia, or spastic paraplegia may accompany the visual changes. Transmission is maternal and the diagnosis is supported by an elevated serum lactate and microangiopathic changes in the optic fundus. Direct DNA mutation analysis is available.

Human deafness-dystonia syndrome (Mohr–Tranebjaerg syndrome)

This unusual disorder results from mutations in the genes encoding DDP1 or DDP2, proteins involved in mitochondrial transport. It is inherited in a recessive X-linked fashion and is characterized by sensorineural deafness, dystonia, cortical blindness, dysphagia, and paranoia. Symptoms usually begin in childhood.

TRINUCLEOTIDE REPEAT DISORDERS

Huntington’s disease

Huntington’s disease (HD) is an autosomal dominant movement disorder caused by an abnormal CAG triplet repeat expansion in the huntingtin gene, encoded on chromosome 4. Classically, the disease is characterized by a progressive movement disorder accompanied by cognitive decline and psychiatric abnormalities. Chorea is thought to be related to the early and preferential loss of the enkephalinergic striatal projection neurons to the external segment of the globus pallidus. As the disease progresses and projections to the globus pallidus interna are also affected, rigidity and dystonia predominate. In juvenile-onset cases, dystonia is common early. Striatal and cortical atrophy are prominent, and pathologic examination reveals striatal neuronal loss. Cell loss is also demonstrable in the cortex.

Spinocerebellar ataxia

Machado–Joseph disease or spinocerebellar ataxia type 3 (SCA3) is an autosomal dominant, adult-onset disorder caused by CAG triplet repeat expansions in the gene ataxin, encoded on chromosome 14q32.1. Similar to HD, increased repeat length correlates with earlier disease onset and more severe symptoms. Dystonia is a frequent finding in SCA3, particularly in the juvenile-onset form. Progressive ataxia, parkinsonism, and external ophthalmoparesis are the cardinal manifestations.
An updated list of the identified spinocerebellar ataxias is available at http://www.neuro.wustl.edu/neuromuscular/ataxia/domatax.html.

**PARKINSONIAN SYNDROMES**

Dystonia is not uncommon in parkinsonism. It occurs commonly during ‘off’ periods in patients with Parkinson’s disease (PD) with motor fluctuations, and is also seen in patients with multiple system atrophy. Corticobasal ganglionic degeneration classically features a dystonic hand or foot, and retrocollic dystonia of the neck is common in progressive supranuclear palsy.105,106

Approximately 10% of patients with Parkinson’s disease have an inherited form of the disease. Mutations identified in families with PD include H9251-synuclein (chromosome 4q21), DJ1 (chromosome 1p36), parkin (chromosome 6q25–27), UCH-L1 (ubiquitin C-terminal hydrolase L1, chromosome 4p14), pink1 (PTEN-induced kinase 1, chromosome 1p35), and LRRK2 (leucine-rich repeat kinase 2, chromosome 12). 107–113 Dystonia is common in autosomal recessive juvenile Parkinson’s disease.114,115

**X-linked dystonia-parkinsonism (Lubag)**

This X-linked disorder was reported in men originating from the island of Panay in the Philippines.116 Dystonia or parkinsonism may define the clinical presentation. The disorder is linked to the centromere of the X chromosome, and is called DYT3.117 Female heterozygotes can manifest mild dystonia or chorea. Positron emission tomography (PET) scans reveal decreased striatal glucose metabolism, without decrease in nigrostriatal dopaminergic projection.118 Neuronal loss and gliosis are observed in a mosaic distribution throughout the striatum, preferentially affecting the lateral putamen.119

**Rapid-onset dystonia-parkinsonism (see Chapter 12)**

This unusual disorder is characterized by the abrupt onset (over hours to weeks) of dystonia, dysarthria, dysphagia, bradykinesia, and postural instability.120 Symptoms typically begin between the ages of 14 and 45 years, and the disorder often remains stable. It is inherited in an autosomal dominant fashion, linked to chromosome 19q13.121

**OTHER NEURODEGENERATIVE PROCESSES**

**Ataxia-telangiectasia**

Ataxia-telangiectasia is an autosomal recessive disorder caused by mutations in the ATM gene which encodes a member of the phosphoinositol 3-kinase family important for cell cycle regulation and DNA repair.122 Symptoms typically begin between the ages of 2 and 4 years old, and cerebellar ataxia is the initial and most prominent finding on examination.123 Telangiectasias are a diagnostic hallmark, found commonly in the conjunctivae, and dystonia is usually seen only in later stages of the disease.124,125 Cerebellar Purkinje cell loss is characteristic, and degeneration of the posterior and lateral columns of the spinal cord is also seen.126

**Chorea-acanthocytosis**

Chorea-acanthocytosis or neuroacanthocytosis is an autosomal recessive disorder caused by mutations in the gene encoding chorein (chromosome 9), a protein involved in intracellular protein trafficking.127 Symptoms typically begin in the third to fourth decade of life with prominent and progressive chorea, tics, dystonia, behavioral disinhibition, and cognitive decline.128 The chorea commonly affects the mouth and tongue, with frequent lip and tongue biting, dysphagia, and dysarthria. Imaging reveals atrophy and signal abnormality of the basal ganglia, particularly the striatum. Neuronal loss is found in the basal ganglia on postmortem examination.129

**Rett syndrome**

Females with Rett syndrome, an X-linked disorder, typically manifest symptoms after the first year of life, with regression of language and motor skills and autistic behavior.130 Stereotyped wringing of the hands is very characteristic. Spasticity and dystonia may occur.131,132 Direct mutation analysis of the Rett gene is now available.

**Infantile bilateral striatal necrosis and familial striatal necrosis**

Infantile bilateral striatal necrosis usually occurs acutely and is characterized by chorea, dystonia, rigidity, and ballismus, and a stereotyped cry, grimace, and hyperextension of the neck in response to stimuli.133 Often, symptoms begin after a respiratory infection. Most cases are sporadic, but some are inherited in an autosomal recessive or maternal pattern. The characteristic findings include spongy degeneration of caudate and putamen, which can be detected on CT or MRI as either hypodensities or T2 hyperintensities, respectively.134

**Neuronal intranuclear inclusion disease**

Clinical manifestations of this disorder typically begin in childhood, but adult onset has been reported. Ataxia, spasticity, parkinsonism, autonomic dysfunction, and
cognitive deficits are the core features, but other neurologic deficits occur, including dystonia, chorea, and motor neuropathy.135–137 Neuronal intranuclear inclusion disease typically occurs sporadically but inherited forms have been described. Intranuclear inclusions composed of eosinophilic, ubiquinoned material are found in the central, peripheral, and autonomic nervous systems.138

Ataxia with vitamin E deficiency

Approximately 13% of patients with ataxia with vitamin E deficiency exhibit dystonia.139 This autosomal recessive disorder is caused by mutations in the gene encoding α-tocopherol transfer protein (chromosome 8q).140 Age of onset is typically under 20 years old, and clinical features include cerebellar ataxia, dysarthria, loss of vibration sense, and deep tendon reflexes. Vitamin E supplementation may retard progression of the disease.

REFERENCES

58. Cooper JD. Progress towards understanding the neurobiology of Batten disease or neuronal ceroid lipofuscinosis. Curr Opin Neurol 2003; 16: 121–8.


INTRODUCTION

Soon after the introduction of dopamine receptor blocking drugs (DRBs) in the early 1950s it was observed that dystonia could occur acutely with first exposure. It was later that a dystonic syndrome was recognized in association with the chronic use of DRBs, and later still that acute dystonic reactions were observed to occur with non-DRB prescription drugs and drugs of abuse. Dystonia associated with drug administration is now a common problem encountered in clinical practice. In this chapter we review current knowledge regarding the clinical features, epidemiology, pathophysiology, and treatment of acute dystonic reactions (ADRs) and tardive dystonia (TD).

ACUTE DRUG-INDUCED DYSTONIA

Definition and clinical features

Acute dystonic reactions occur in the period shortly after the introduction of particular drugs, usually DRBs. Although the time to onset of ADRs following drug exposure is variable, over 50% of patients will develop symptoms within 48 hours of exposure, and over 90% will show symptoms within 5 days.1

Clinical features of ADRs are variable, but can be severe and dramatic in nature. Typical presentations are pronounced dystonia of the oromandibular region, often causing mouth-opening spasms. Axial dystonia with hyperextension of the spine, retrocollis, or laryngospasm (which can be life threatening) can also be seen. A sideways twisting of the trunk, Pisa syndrome, is also described as a clinical presentation of ADR.2 However, this syndrome not only occurs as an ADR but also is seen in Parkinson’s disease, progressive supranuclear palsy, and tardive dystonia.2 Oculogyric crises are characterized by tonic conjugate ocular deviation, which can be associated with psychotic features, including obsessional thoughts and hallucinations.3 Oculogyric crises are also observed outside the setting of ADRs: e.g. in patients with postencephalitic parkinsonism.3

Drugs that cause acute dystonic reactions

DRBs, which are commonly used for the treatment of psychosis, are the drugs most frequently associated with ADRs. As with tardive dystonia (see below), the older DRBs are thought to be the most likely offenders, but it is not entirely certain whether this represents a bias given the longer length of time that such drugs have been available for use in clinical practice compared to the newer ‘atypical’ antipsychotics. What is clear, however, is that nearly all DRBs are capable of causing ADRs.4

This also includes DRBs used for treatment of non-psychiatric conditions such as metoclopramide and prochlorperazine in the treatment of nausea and vomiting and also dopamine-depleting and blocking drug such as tetrabenzine.5

A growing number of non-DRB drugs have also been associated with ADRs. These include antidepressants (serotonin reuptake inhibitors,6 monoamine oxidase inhibitors,7) calcium antagonists,8 benzodiazepines,9 general anesthetic agents,10 anticonvulsants,11 and triptans.12 ADRs also occur with drugs of abuse, including cocaine,13 crack cocaine,14 and Ecstasy (3,4-methylenedioxymethamphetamine).15 A list of the most commonly implicated drugs is given in Table 14.1. Clinically, the ADRs seen with these non-DRB drugs appear to be similar to that seen in association with DRBs.

ADRs can also be seen in patients with parkinsonian disorders when treated with dopaminergic agents.16 In Parkinson’s disease, this typically occurs as the drug level drops (‘off-period dystonia’), but is also sometimes seen when the drug level is at its peak (‘peak-dose dystonia’) or is rising. Alterations in the frequency, dose, and type of dopaminergic drug can be helpful in the
treatment of these symptoms.\textsuperscript{16} In the atypical parkinsonian condition multiple system atrophy, levodopa administration can give rise to unusual dystonic spasm of the face, and can be helpful as a differentiating feature of this condition from idiopathic Parkinson’s disease.

### Risk factors for the development of acute dystonic reactions

Risk factors for the development of ADRs have been mainly studied in psychiatric populations treated with DRBs. In such individuals, male gender, young age under 30 years old, mental retardation, history of electroconvulsive therapy, dose of DRB, and use of injectable DRBs are all associated with a higher risk of developing ADRs.\textsuperscript{17,18} The relative risk associated with male gender and young age may be erroneous, simply reflecting the higher incidence of schizophrenia in young males, and therefore a higher rate of exposure to DRBs.\textsuperscript{17,18}

The notion that ADRs occur more frequently in individuals with bipolar disorder as opposed to other psychiatric conditions\textsuperscript{19} has been challenged by a prospective study of such patients, where peak DRB dose and age were found to be most predictive of ADRs, as opposed to psychiatric diagnosis.\textsuperscript{20} It may be that higher doses of DRBs are more commonly used in those with bipolar disorder (particularly in the manic phase), and that this is responsible for the apparent high prevalence of ADRs in patients with this condition.

Abuse of drugs known to cause ADR (e.g. cocaine) can lead to an increase in the incidence of ADRs when such patients are treated with DRBs.\textsuperscript{21} Likewise, patients with HIV (human immunodeficiency virus) or AIDS (acquired immunodeficiency syndrome) have a higher risk of developing ADRs when treated with DRBs,\textsuperscript{22} perhaps in some cases due to antiretroviral therapy impairing the normal metabolism of DRBs.\textsuperscript{23}

### Pathophysiology of acute dystonic reactions

The pathophysiologic mechanism of ADR is unclear. One possibility that has been suggested is that drugs causing ADRs do so by disturbing the balance of dopaminergic and cholinergic neuronal activity in the basal ganglia.\textsuperscript{24} Obviously, DRBs are likely to alter this balance due to dopaminergic hypoactivity, but other drugs causing ADR could equally well affect cholinergic neurons. The response of most patients with ADR to anticholinergic drugs supports the hypothesis that relative or actual cholinergic hyperactivity is the mechanism whereby ADRs are produced. A second related hypothesis is that DRBs can cause a paradoxical increase in dopaminergic activity by preferentially blocking presynaptic dopamine receptors.\textsuperscript{25} In addition, DRBs may cause an increase in the synthesis and release of dopamine, as well as up-regulation of postsynaptic dopamine receptors.\textsuperscript{25} It is informative to note that in patients with Parkinson’s disease, ADR can occur at peak or trough dopamine levels. It may therefore be the case that it is the relative balance (or imbalance) of dopaminergic neuronal function that is important in the generation of ADR, rather than the actual level itself.

Sigma receptors, which are widely expressed in motor areas of the brain, have been implicated in the genesis of acute dystonia. The unilateral injection of sigma ligands into the red nucleus of the rat can cause torticollis.\textsuperscript{26} Sigma 1 and 2 ligands can both be associated with the production of acute dystonia in animal studies,\textsuperscript{27} which can be ameliorated by anticholinergic drugs.\textsuperscript{28}

There has been recent interest as to whether dopamine receptor polymorphisms (particularly those of the D\textsubscript{2} receptor) might be important in the pathophysiology of ADR. Although no indication has been found that dopamine receptor polymorphisms are predictive of ADR, an association has been found in one small study between CYP2D6 polymorphisms (a cytochrome P450 enzyme) and ADR.\textsuperscript{29} However, this finding was not confirmed by a separate study.\textsuperscript{30}

### Treatment of acute dystonic reactions

Treatment of ADRs can be clinically urgent, not only as symptoms can be very distressing to the patient but also as serious consequences can occur, including respiratory arrest\textsuperscript{31} and rhabdomyolysis.\textsuperscript{32} Fortunately, the majority of ADRs can be successfully treated with injectable anticholinergic drugs. Typically, 1–2 mg of benztropine

### Table 14.1 Drugs commonly associated with ADRs

<table>
<thead>
<tr>
<th>Dopamine receptor blocking drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressants: serotonin reuptake inhibitors, monoamine oxidase inhibitors</td>
</tr>
<tr>
<td>Calcium antagonists</td>
</tr>
<tr>
<td>Benzodiazepines</td>
</tr>
<tr>
<td>General anesthetic agents</td>
</tr>
<tr>
<td>Anticonvulsants (carbamazepine, phenytoin)</td>
</tr>
<tr>
<td>Triptans</td>
</tr>
<tr>
<td>Ranitidine</td>
</tr>
<tr>
<td>Cocaine</td>
</tr>
<tr>
<td>Ecstasy</td>
</tr>
</tbody>
</table>

---

\textsuperscript{16} In the atypical parkinsonian condition multiple system atrophy, levodopa administration can give rise to unusual dystonic spasm of the face, and can be helpful as a differentiating feature of this condition from idiopathic Parkinson’s disease.

\textsuperscript{17} Risk factors for the development of ADRs have been mainly studied in psychiatric populations treated with DRBs. In such individuals, male gender, young age (under 30 years old), mental retardation, history of electroconvulsive therapy, dose of DRB, and use of injectable DRBs are all associated with a higher risk of developing ADRs.\textsuperscript{17,18} The relative risk associated with male gender and young age may be erroneous, simply reflecting the higher incidence of schizophrenia in young males, and therefore a higher rate of exposure to DRBs.\textsuperscript{17,18}

\textsuperscript{18} The notion that ADRs occur more frequently in individuals with bipolar disorder as opposed to other psychiatric conditions\textsuperscript{19} has been challenged by a prospective study of such patients, where peak DRB dose and age were found to be most predictive of ADRs, as opposed to psychiatric diagnosis.\textsuperscript{20} It may be that higher doses of DRBs are more commonly used in those with bipolar disorder (particularly in the manic phase), and that this is responsible for the apparent high prevalence of ADRs in patients with this condition.

\textsuperscript{19} Abuse of drugs known to cause ADR (e.g. cocaine) can lead to an increase in the incidence of ADRs when such patients are treated with DRBs.\textsuperscript{21} Likewise, patients with HIV (human immunodeficiency virus) or AIDS (acquired immunodeficiency syndrome) have a higher risk of developing ADRs when treated with DRBs,\textsuperscript{22} perhaps in some cases due to antiretroviral therapy impairing the normal metabolism of DRBs.\textsuperscript{23}

\textsuperscript{20} Pathophysiology of acute dystonic reactions

The pathophysiologic mechanism of ADR is unclear. One possibility that has been suggested is that drugs causing ADRs do so by disturbing the balance of dopaminergic and cholinergic neuronal activity in the basal ganglia.\textsuperscript{24} Obviously, DRBs are likely to alter this balance due to dopaminergic hypoactivity, but other drugs causing ADR could equally well affect cholinergic neurons. The response of most patients with ADR to anticholinergic drugs supports the hypothesis that relative or actual cholinergic hyperactivity is the mechanism whereby ADRs are produced. A second related hypothesis is that DRBs can cause a paradoxical increase in dopaminergic activity by preferentially blocking presynaptic dopamine receptors.\textsuperscript{25} In addition, DRBs may cause an increase in the synthesis and release of dopamine, as well as up-regulation of postsynaptic dopamine receptors.\textsuperscript{25} It is informative to note that in patients with Parkinson’s disease, ADR can occur at peak or trough dopamine levels. It may therefore be the case that it is the relative balance (or imbalance) of dopaminergic neuronal function that is important in the generation of ADR, rather than the actual level itself.

\textsuperscript{21} Sigma receptors, which are widely expressed in motor areas of the brain, have been implicated in the genesis of acute dystonia. The unilateral injection of sigma ligands into the red nucleus of the rat can cause torticollis.\textsuperscript{26} Sigma 1 and 2 ligands can both be associated with the production of acute dystonia in animal studies,\textsuperscript{27} which can be ameliorated by anticholinergic drugs.\textsuperscript{28}

\textsuperscript{22} There has been recent interest as to whether dopamine receptor polymorphisms (particularly those of the D\textsubscript{2} receptor) might be important in the pathophysiology of ADR. Although no indication has been found that dopamine receptor polymorphisms are predictive of ADR, an association has been found in one small study between CYP2D6 polymorphisms (a cytochrome P450 enzyme) and ADR.\textsuperscript{29} However, this finding was not confirmed by a separate study.\textsuperscript{30}

\textsuperscript{23} Treatment of acute dystonic reactions

Treatment of ADRs can be clinically urgent, not only as symptoms can be very distressing to the patient but also as serious consequences can occur, including respiratory arrest\textsuperscript{31} and rhabdomyolysis.\textsuperscript{32} Fortunately, the majority of ADRs can be successfully treated with injectable anticholinergic drugs. Typically, 1–2 mg of benztropine
is injected intravenously, and will terminate the attack. Injectable antihistamines such as chlorpheniramine have also been used either in addition or as sole treatment. Benzodiazepines can sometimes be helpful as adjunctive treatment: e.g. 1–2 mg of clonazepam. For those with severe dystonia, relevant management of any systemic complications, particularly compromise of the airway, is essential.

There is evidence to suggest that pretreatment with anticholinergic drugs can reduce the incidence of ADR. This strategy should therefore be considered when DRBs are prescribed to those at particular risk of ADRs, such as cocaine users and those with HIV/AIDS.

TARDIVE DYSTONIA

Introduction and definition

Following the introduction of DRBs in 1952 for the treatment of psychosis, it soon emerged that abnormal involuntary movements could occur in association with chronic DRB administration. Initial reports were of rather rapid involuntary movements that tended to involve the mouth and face, leading to the use of the term tardive dyskinesia (TDK) to describe them. At around the same time as these early reports of TDK were appearing in the medical literature, there were others which reported dystonia related to the long-term use of DRBs. It was Keegan and Rajput, however, who first coined the term ‘dystonia tarda’ in 1973 when reporting a series of patients with torticollis and axial dystonia secondary to the use of DRBs. Other ‘tardive’ syndromes have been reported in association with DRB use, including tics and tremor.

There has been some confusion generated by the parallel development of the two terms tardive dystonia (TDT) and tardive dyskinesia (TDK). Although both can be caused by DRBs, there has been a tendency to call all DRB-associated movement disorders TDK. Many reports of movement disorders associated with DRBs have therefore mixed cases of TDT and TDK, making it difficult to separate out risk factors and epidemiologic features specifically related to TDT. This may explain why there have been so few case series of patients specifically with TDT. To date, only three large series to have been published (Burke et al, Kang et al, and Kiriakakis et al) with a combined total of over 200 patients.

In this regard, criteria have been suggested to aid the clinical definition of TDT. Burke et al defined TDT as:

an involuntary movement disorder predominated by dystonia and associated with the use of dopamine receptor antagonists. The dystonia must have been present for more than a month and occur either during treatment with DRBs or within 3 months of its discontinuation.

This definition allowed for the presence of choreiform movements, but dystonia had to be the dominant movement disorder. A family history of dystonia was an exclusion criterion, as was the presence of other possible causes for dystonia. A more recent clinical classification of TDT by Adityanjee and colleagues has attempted to stratify patients with TDT based on the dominance of dystonia over any other movement disorder. Under this system, patients are classified as:

- type I – pure TDT in the absence of any other movement disorder
- type II – dystonia coexists with dyskinetic movements of the same body part, but dystonia is predominant
- type III – dystonia coexists with dyskinetic movements in the same or different body parts, but dystonia is less prominent than dyskinesias
- type IV – dystonia coexists with a variety of movement disorders.

It may be useful in a research setting, as the authors of these criteria suggest, to use these criteria to separate out those patients with pure (type I) TDT from those with TDT associated with TDK, in order to aid research into risk factors and pathophysiologic features that are specific for TDT. In clinical practice, however, we would suggest that it is probably most useful to identify TDT (and therefore plan its treatment) by the observation of predominant dystonia in a patient with a history of DRB use when all other relevant causes have been excluded.

Clinical features

Onset of dystonia in TDT typically occurs in one body part, most commonly the neck or face, but spread to a contiguous body part may follow to cause segmental dystonia, or further to produce generalized dystonia. Onset in the arms, trunk, or legs is reported, but is less common. It is rare for TDT to remain as focal dystonia – only 16% of one series remained with focal involvement. There appears to be a relationship between age of onset and distribution of dystonia, mirroring the pattern observed in idiopathic primary dystonia (ID): thus, patients with young-onset disease typically have limb-onset disease, which can spread to become generalized; patients who present in mid-life have segmental
dystonia; and patients with an older age of onset tend to have craniocervical involvement. Progression of dystonia typically occurs over months to years: the largest clinical study of patients with TDT found a mean progression of 1.8 years, but with a wide range from 1 month to 14 years.\textsuperscript{43} The most rapid onset tends to be seen in younger patients.

Although, clinically, patients with TDT can look very similar to those with ID, there are some features that can be useful in distinguishing the two conditions. Retrocollis and axial extension dystonia causing marked hyperextension of the neck and trunk are quite characteristic of TDT. The extensor neck spasms can be so severe that they often lead to loss of hair, causing a bald patch at the back of the head due to constant friction of the head with the back rest. In contrast, simple torticollis, laterocollis, muscle hypertrophy, head tremor, and a positive family history are more commonly observed in ID.\textsuperscript{41,43,45,46} A sensory geste is less commonly observed in TDT but can be present.

Interestingly, typical writer’s cramp or other task-specific dystonias do not appear to occur as a manifestation of TDT. Leg and trunk involvement were seen, respectively, in 26\% and 44\% of patients with TDT in the large series of Kiriaiakakis et al.\textsuperscript{43} Adult onset of leg and axial dystonia is unusual in ID. Bruxism as the sole feature of TDT has been described.

Other movement disorders may be associated with TDT. Most common is the association with the typical stereotyped orofacial dyskinesias of TDK, and it appears that older patients have a greater propensity to develop this pattern of movement disorder. Parkinsonism, tremor, and akathisia can also occur with TDT.\textsuperscript{43}

### Differential diagnosis

One should bear in mind that there are conditions other than TDT where psychiatric disturbance and dystonia (which may affect the craniocervical region in the main) are encountered together. Most important amongst these (as the condition is treatable) is Wilson’s disease, a disorder in which psychiatric disturbance, various movement disorders including dystonia, and sometimes systemic complications can occur. Serum copper and ceruloplasmin, urinary copper excretion, slit-lamp examination for Kayser–Fleischer rings, and sometimes liver biopsy are necessary to make the diagnosis. Other conditions that can present with dystonia and psychiatric disturbance include Huntington’s disease, dentatorubral-pallidoluysian atrophy (DRPLA), and pantothenate kinase-associated neurodegeneration (PKAN) for which genetic tests are available, as well as a positive family history in some cases and imaging abnormalities (particularly in PKAN). Delayed-onset dystonia following birth injury and metachromatic leukodystrophy can be excluded by a careful history and cerebral imaging.

As mentioned above, coincidental idiopathic primary dystonia and psychiatric disturbance may be the cause of the clinical presentation rather than TDT, even given exposure to DRB. Although the clinical features outlined above provide a guide to distinguishing the two conditions, such a distinction can be difficult to make with certainty. In younger patients, particularly those with generalized dystonia, it can therefore be useful to perform a \textit{DYTI} gene test. This genetic abnormality is the commonest cause of early-onset primary generalized dystonia,\textsuperscript{47} and can therefore be a useful test in the differential diagnosis of certain patients with suspected TDT. The \textit{DYTI} gene has been found to be negative in a series of patients with TDT.\textsuperscript{48}

In the majority of patients with suspected TDT where clear exposure to DRB has occurred prior to the onset of the dystonia and the clinical phenotype is typical, testing for Wilson’s disease and cerebral imaging with computed tomography (CT) or magnetic resonance imaging (MRI) are sufficient as screening tests for alternative diagnoses.

### How common is tardive dystonia

It is difficult to be accurate regarding the true prevalence of TDT, because, as mentioned earlier, many epidemiologic studies have included patients with TDK and other DRB-associated movement disorders rather than pure TDT. Most studies have been retrospective and have taken place in a variety of settings, including in- and outpatient psychiatric services. However, a broad impression of the prevalence of TDT can be gained by examining data from the 10 cross-sectional studies into the prevalence of movement disorders in patients with psychiatric disease treated with DRB that have been performed.\textsuperscript{49–59} The prevalence of TDT in these studies ranges from 0.5\% to 21\%, with a mean of 3\%. The figure of 21\% is from a study by Sethi and colleagues,\textsuperscript{32} who explained the high prevalence of TDT they discovered by their systematic examination of patients in the study by neurologists specializing in movement disorders. This might indicate that other studies not employing this type of approach may have underestimated the prevalence of TDT within DRB-treated populations. When patients with all types of drug-induced movement disorders are studied, TDT is a relatively common phenotype: for example, it accounts for 24\% of a sample of 125 patients with drug-induced movement disorders reported by Miller and Jankovic.\textsuperscript{60}
Risk factors for the development of tardive dystonia

Type of drug

Despite the impression that the older generation of DRBs might be more likely to produce TDT, it is clear that there are no ‘safe’ DRBs. Even the newer ‘atypical’ DRBs are capable of producing TDT, including olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, and even clozapine. Chlorpromazine, thioridazine, and haloperidol are most commonly reported as associated with TDT, but this may simply reflect the length of time they have been in use in clinical practice, and the way in which they have been used (average dose, average length of treatment). It remains to be seen whether the modern trend towards the use of atypical DRBs for the treatment of psychosis will lead to a reduction in the incidence of DRB-induced movement disorders including TDT.

DRBs are not only prescribed for the treatment of psychosis. Such drugs are used for the treatment of other psychiatric conditions, including depression, anxiety, and acute confusional states. DRBs such as metoclopramide and prochlorperazine are commonly prescribed for the treatment of nausea and vertigo. In populations of patients with TDT, over 20% may have been prescribed DRBs for conditions such as these where alternative treatment might have been appropriate.

There is no evidence to suggest that the concurrent use of non-DRB drugs (such as anticholinergics) in patients taking DRBs increases (or decreases) their risk of developing TDT.

Duration of exposure

There is no clear relationship between duration of exposure to DRB and the subsequent occurrence or severity of TDT. Although mean exposure time prior to the onset of TDT is in the region of 6 years, there is clearly no ‘safe’ exposure time to DRB, and patients have been reported who have developed TDT after exposures as short as 4 days (Figure 14.1). Likewise, those on very long-term treatment cannot be considered to be safe from developing TDT: exposure times as long as 23 years have been reported before the onset of TDT. In this regard, there is some evidence that the onset of TDT can be triggered in patients on long-term stable DRB therapy by either a change in DRB, the addition of another DRB, or even a change in a stable dose of DRB.

Diagnosis

It is not surprising that the majority of those with TDT have psychiatric disorders, or that the majority of these patients have a diagnosis of schizophrenia, given that psychiatric disease, and schizophrenia in particular, are the major indications for DRB. There is no evidence that there is a particular psychiatric diagnosis that puts patients at an increased or decreased risk of developing TDT during treatment with DRB. Although there is less evidence available, patients without psychiatric disorders are clearly capable of developing TDT when exposed to DRB, and there is no reason to suspect that their risk of developing TDT with DRB exposure is any greater or less than those with psychiatric disorders.

Age and gender

There does appear to be an association between the age at onset of the DRB-associated movement disorder and the type of tardive movement disorder produced. An older age of onset is associated with the production of TDK rather than TDT, and if TDT does occur in older patients, lower limb involvement and generalized dystonia are less likely. There is a male predominance observed in studies of TDT (approximately 2:1), and men also tend to have a lower age at onset of TDT compared with women. This may simply reflect the differences between men and women regarding the prevalence and age at onset of schizophrenia, which is both more common in men than women, and also tends to occur at a younger age in men. It is likely, therefore, that men are more frequently prescribed DRB, and at a lower age, leading to an apparent male predominance.
younger age than women. Indeed, the age at first exposure to DRB was found to be 27 years for males and 36 years for females in one case series.43

Natural history of tardive dystonia – outcome and remission

Unfortunately, spontaneous remission of TDT is rare. Summarizing the six published case series (a total patient group of 231 patients),41–43,68–70 remission was only seen in 10% of cases, after a mean follow-up of 7 years (Table 14.2). The chance of remission occurring is not influenced by age at onset, type of DRB, gender, or the distribution and extent of dystonia. The two factors that do appear to be related to the chance of remission are the discontinuation of DRB therapy and the total duration of DRB exposure. Patients with TDT in whom DRBs have been discontinued are more likely to experience a remission of their TDT (12/54 patients vs 3/52 patients in one series43). Patients with TDT with an exposure to DRB of greater than 10 years are five times less likely to experience a remission than those with an exposure to DRB of less than 1 year.43

Pathophysiology of tardive dystonia

The majority of research into the pathophysiology of tardive syndromes has focused on TDK, rather than TDT. The clinical classification of subjects in such studies is not always clear, and it is therefore likely that a number of patients with TDT are included. The data presented below must therefore be considered with this in mind, as TDT and TDK may have different underlying mechanisms.

Dopamine receptor hypersensitivity is the leading pathophysiologic theory behind the origins of both TDK and TDT.25,71 It is suggested that enhanced D1 receptor stimulation by endogenous dopamine in the presence of D2 receptor blockade by DRBs might lead to a critical imbalance between direct and indirect pathway activity in the basal ganglia.71 A slowly developing sensitization of D1-mediated striatal output is consistent with the delayed onset of dystonia, and its persistence after DRB withdrawal. In addition, blockade of D1 receptors and stimulation of D2 receptors (by the D1 antagonist and D2 agonist bromocriptine) has been found to be beneficial in some patients with TDK.72 Conversely, up-regulation of D2 receptors due to dopamine receptor blockade has been identified in patients on long-term DRB therapy. Using [11C]raclopride positron emission tomography (PET), Silvestri and colleagues73 have demonstrated a decrease in [11C]-raclopride binding (consistent with an up-regulation of D2 receptors), in patients on long-term DRB treatment, although none of these patients had TDT/TKD.

It has been proposed that γ-aminobutyric acid (GABA) may play a role in the pathogenesis of TDT/TKD.74 Abnormalities in glutamic acid decarboxylase (GAD) – an enzyme involved in the synthesis of GABA – have been found in experimental animals treated with DRBs75 and in humans with TDK.76 Other clinicians have failed to replicate these findings, however.77 In keeping with a possible role for abnormalities in GABA in the pathogenesis of TDT/TKD, there is some clinical evidence to support the efficacy of GABA agonists in the treatment of TDT/TKD.78 However, a recent Cochrane review has concluded that insufficient evidence currently exists to truly determine the usefulness of such drugs.79

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n)</th>
<th>Follow-up from onset (years)</th>
<th>Follow-up from DRB withdrawal (years)</th>
<th>Remitting patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burke et al, 198241</td>
<td>42</td>
<td>3.1</td>
<td>1.5</td>
<td>5</td>
</tr>
<tr>
<td>Gimenez-Roldan et al, 198567</td>
<td>9</td>
<td>4.7</td>
<td>n.s.</td>
<td>0</td>
</tr>
<tr>
<td>Kang et al, 198642</td>
<td>67</td>
<td>4.8</td>
<td>2.8</td>
<td>5</td>
</tr>
<tr>
<td>Gardos et al, 1987,69</td>
<td>10</td>
<td>5.2</td>
<td>n.s.</td>
<td>0</td>
</tr>
<tr>
<td>Wojcik et al, 199168</td>
<td>29</td>
<td>7.3</td>
<td>n.s.</td>
<td>0</td>
</tr>
<tr>
<td>Kiriakakis et al, 199843</td>
<td>107</td>
<td>8.3</td>
<td>3.9</td>
<td>15</td>
</tr>
</tbody>
</table>

DRB = dopamine receptor blocking drug; n.s = not stated.
As with ADRs, recent interest has focused on the possible role of genetic polymorphisms in the genesis of TDT. Polymorphisms in a number of genes have been studied, including estrogen, opioid, and dopamine receptor genes, and genes involved in oxidative phosphorylation. The most promising finding is of an association between a serine polymorphism in the dopamine D3 receptor and TDK,\(^80\) not only has this polymorphism been identified in patients with TDK\(^80\) but also it has been found in a primate model of TDK which has a high susceptibility to DRB-induced side effects.\(^81\) The functional relevance of this polymorphism is unclear at the present time. This finding has not been confirmed by all investigators. For example, Mihara and colleagues found no association between TDT and polymorphisms in the D2 and D3 receptor genes, but numbers were small in this study, with only nine TDT patients.\(^82\)

Recent research has also proposed a possible role for oxidative stress in the pathogenesis of TDT. It is hypothesized that DRBs are a cause of oxidative stress in the basal ganglia. Evidence in support of this hypothesis comes from cerebrospinal fluid (CSF) studies in patients taking DRB in whom lipid peroxidation was higher than control subjects,\(^83\) and also from studies in animal models and humans showing that vitamin E administration may reduce DRB-induced changes in monoamine metabolism, protect against DRB-induced cell death, and perhaps even reduce TDK symptoms in some patients.\(^84\)–\(^86\) Controlled studies of vitamin E in TDK have not, however, been able to demonstrate a benefit.\(^87\) It is possible that DRBs may cause excitotoxicity in the basal ganglia. There is evidence that DRBs can increase the striatal release of glutamate,\(^88\) and this could, in turn, increase the chance of excitotoxic damage. These hypotheses open the way for further studies of neuroprotective and antioxidant agents, both in patients with TDT and in those at risk of developing TDT.

**Treatment of tardive dystonia**

Treatments available for TDT are symptomatic, and there is no evidence that any particular treatment can increase the chance of a remission occurring. The most important ‘treatment’ therefore is that of prevention, by ensuring that DRBs are used when absolutely necessary, and then for the shortest time possible.

For those with focal or segmental TDT, or in patients with more widespread dystonia, but with specific problems associated with a body part, botulinum toxin (BT) injections are often the most effective treatment. In one study of the use of BT in 34 patients with TDT, moderate to marked improvement was noted in 29 of 38 body parts injected.\(^89\) All of the patients in this study had failed to respond to standard drug treatment.

In those in whom botulinum toxin is unhelpful or not appropriate, a variety of drugs can be tried, including anticholinergics, baclofen, benzodiazepines, tetrabenazine, reserpine, and levodopa. There is no clear way of predicting individual response to such drugs, and often a combination of two or more agents is necessary. Unfortunately, all of these drugs can cause psychiatric side effects, particularly at high doses. It is common practice to use anticholinergic drugs first, which should be introduced slowly and cautiously. Using such an approach, it is sometimes possible to reach high doses, particularly in younger patients, without the emergence of side effects and with a beneficial effect on the dystonia. Tetrabenazine and reserpine can be used in addition to anticholinergics, or alone if anticholinergics are not tolerated, but depression is a notable side effect. Oral baclofen can be helpful, but can be associated with sedation and depression. Intrathecal baclofen is sometimes used for patients with axial dystonia with good results in some case reports. However, long-term problems with catheter displacement, infection, and pump failure can occur. Benzodiazepines (in particular clonazepam) are sometimes useful as adjunctive agents, but are associated with side effects, including sedation, mood disturbance, and dependence. Levodopa is rarely helpful, but at least can be trialed without a major risk of side effects.

There is increasing evidence that patients with TDT may paradoxically benefit from the reintroduction of a particular DRB. Clozapine is the drug most studied in this respect, and a number of open-label and double-blinded trials have demonstrated some moderate benefit, although not all trials have reached this conclusion (for a review see Reference 90). There are reports of other atypical DRBs being beneficial in the treatment of TDT, including risperidone,\(^91\)\(^92\) olanzapine,\(^93\) and quetiapine.\(^94\)\(^96\) It must be noted that treatment with clozapine requires strict monitoring of blood counts due to the risk of neutropenia. There is clearly a risk that the reintroduction of DRBs may worsen TDT, and therefore the treatment of TDT with atypical DRBs should be considered only after other treatment strategies have failed. As a caveat to this, some patients with TDT will clearly require ongoing DRB treatment for psychosis and, in such patients, trials of clozapine and perhaps other atypical DRBs are indicated.

Although recent studies in the pathophysiology of TDT have suggested that oxidative stress induced by DRB may play a role, a controlled study of vitamin E supplementation failed to produce a benefit.\(^88\) Additional treatments for which benefit has been claimed in open studies of small numbers of patients include morphine\(^97\) and electroconvulsive therapy.\(^98\)\(^99\) Dietary supplementation with branched-chain amino acids has been found
to significantly decrease TDK symptoms in one uncontrolled study, and encouragingly also in a recent placebo-controlled trial, but results of the use of such treatment has not been published in patients with TDT.

The recent interest and notable success of pallidal deep brain stimulation for patients with idiopathic primary dystonia has led to the use of this technique in a small number of patients with TDT. One patient with TDT reported by Trottenberg and colleagues was implanted with bilateral internal globus pallidus (GPi) and ventral intermediate thalamic (VIM) stimulators. Dystonic symptoms were improved by stimulation through the GPi electrodes, but stimulation via the VIM stimulators alone produced no benefit, and simultaneous stimulation via GPi and VIM electrodes produced no additional benefit over GPi stimulation alone. This group has more recently published a small series of five patients with TDT treated with GPi stimulation. They reported an average improvement of 87% in the Burke Fahn Marsden dystonia rating scale in these patients. Thalamotomy has also been applied to patients with TDT, with apparent benefit.

A small number of patients with TDT (usually those with generalized dystonia) develop sudden severe exacerbations of their dystonia, sometimes triggered by intercurrent illness. This not only occurs in patients with TDT but also has been reported in patients with other forms of dystonia. This syndrome of ‘status dystonicus’ or ‘dystonic storm’ is a medical emergency, as the severity of the dystonia can compromise bulbar function, and can result in myoglobinuria and renal failure. Such patients should be managed in an intensive care setting, but despite the severity of the symptoms, episodes are usually self-limiting.

CONCLUSIONS

1. ADRs can be associated with a variety of drugs, not just DRBs, and although, typically, symptoms are readily treated with injectable anticholinergic drugs, they can be severe, and even life threatening.
2. TDT is a disabling, chronic condition associated with DRB use.
3. There is no ‘safe’ DRB and no ‘safe’ exposure time.
4. Remission from TDT is rare, and symptomatic treatment is difficult. DRBs should therefore only be used in situations where no other therapeutic options are available.
5. Treatment of focal dystonia due to TDT is most often treated with botulinum toxin. A range of medications are available for those in whom botulinum toxin is not appropriate, but responses to such drugs vary widely between patients. In those with refractory, severe TDT, atypical DRB or deep brain stimulation are viable treatment strategies.

REFERENCES


27. Matsumoto RR, Pouw B. Correlation between neuroleptic binding to sigma(1) and sigma(2) receptors and acute dystonic reactions. Eur J Pharmacol 2000; 401(2): 155–60.


Paroxysmal dyskinesias are a rare heterogeneous group of conditions manifesting as abnormal involuntary movements that recur episodically and last only a brief duration.\(^1,2\) The abnormal movements may be choreic, dystonic, ballistic, or other, or a mixture of these. The conditions can be inherited or acquired. Between episodes, the patient is generally normal. Hence, conditions such as tic disorders, where there may be paroxysmal worsening, or task- or action-induced dystonias such as musicians or writing dystonia, are traditionally not considered as forms of paroxysmal dyskinesias.

Gower probably gave the first description of paroxysmal movement disorders but called it epilepsy. The term paroxysmal choreoathetosis entered the literature in 1940, when Mount and Reback gave the first clear descriptions of an episodic hyperkinetic condition describing a 23-year-old man who had episodes of “choreo-dystonia” which could last several hours.\(^3\) There were more than 20 other family members also affected, with a clear autosomal dominant pattern of inheritance. As more families with a similar disorder were described,\(^4-6\) it became clear that these episodes of paroxysmal choreoathetosis seemed to be precipitated by drinking alcohol, coffee or tea, and by fatigue and smoking. Phenytoin and phenobarbitone were not found helpful. Richards and Barnett,\(^6\) noting the torsion spasms and increased tone in the limbs added ‘dystonia’ to the description of Mount and Reback, and this disorder thus came to be known as paroxysmal dystonic choreoathetosis (PDC).

In 1967 Kertesz described an episodic disorder termed paroxysmal kinesigenic choreoathetosis (PKC).\(^7\) It was noted that attacks in those affected were induced by sudden movement, i.e. kinesigenic. However, Kertesz probably did not recognize this as a new disorder but felt that this may represent an entity within the previously described condition of PDC, as suggested by the title of the paper. As more cases and families were described, it became clear that this disorder was different from PDC as the attacks were relatively brief and the condition responded well to antiepileptic drugs.\(^8\)

A third form of episodic dyskinesia was described by Lance in 1977, reporting a family who had attacks lasting between 5 and 30 minutes provoked by prolonged exercise and not by sudden movement.\(^8\) Lance referred to this paroxysmal exercise-induced dyskinesia (PED) as the ‘intermediate type’ because the attack duration seemed longer than PKC but less than typical PDC. In the same paper, Lance also suggested a classification of the paroxysmal dyskinesias based primarily upon the duration of attacks, dividing them into three types:

- PKC, in which there were brief attacks of up to 5 minutes induced by sudden movement;
- PDC, in which attacks were not induced by sudden movement and were of long duration, up to 4–6 hours;
- PED, which was induced by exercise and the attack duration was between PKC and PDC.

These terms have been used widely in the literature over the years.

In 1995, Demirkiran and Jankovic\(^1\) pointed out that the attacks in these disorders were not necessarily choreic or dystonic and could be any form of dyskinesia. Hence, they suggested classifying these disorders broadly into two main groups: paroxysmal kinesigenic dyskinesia (PKD), if the attacks were induced by sudden movement; or paroxysmal non-kinesigenic dyskinesia (PKND), if they were not. These two groups broadly correspond to PKC and PDC of the earlier classification of Lance 1977.\(^8\) Apart from these two main forms, PED continued as a separate entity (Table 15.1). Each type was to be further classified as either idiopathic or secondary (‘symptomatic’), depending on
Table 15.1 Summary of clinical and genetic characteristics of the three main forms of paroxysmal dyskinesia

<table>
<thead>
<tr>
<th></th>
<th>PKD</th>
<th>PED</th>
<th>PKND</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration</strong></td>
<td>Very brief</td>
<td>2 minutes to 2 hours</td>
<td>30 minutes to 1 hour</td>
</tr>
<tr>
<td><strong>Triggering factors</strong></td>
<td>Sudden movements, increase in speed, amplitude, force, strength</td>
<td>Prolonged or sustained exercise</td>
<td>Alcohol, coffee, coke, tobacco, emotions, hunger, fatigue</td>
</tr>
<tr>
<td><strong>Age at onset</strong></td>
<td>7–15 years (6 months to 33 years)</td>
<td>2–30 years</td>
<td>2–79 years</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Carbamazepine</td>
<td>Gabapentin</td>
<td>Benzodiazepines</td>
</tr>
<tr>
<td><strong>Gene</strong></td>
<td>Chromosome 16p11 (RE-PED-WC)</td>
<td>Chromosome 16p11 (RE-PED-WC)</td>
<td>Chromosome 2q33-q35 (MR-1)</td>
</tr>
</tbody>
</table>

PKD = paroxysmal kinesigenic dyskinesia; PED = paroxysmal exercise-induced dyskinesia; PNKD = paroxysmal non-kinesigenic dyskinesia.

the etiology. In the idiopathic form, which is often familial, imaging and other investigations are unremarkable and there are no other signs to suggest a neurodegenerative or symptomatic cause.

A fourth form of paroxysmal disorder, referred to as paroxysmal hypnogenic dyskinesia (PHD), in which dyskinetic episodes occurred only at night during sleep has also been recognized and added to the main three. In addition, we propose that the term ‘paroxysmal dyskinesias plus’ could be applied (in the same way as it is used for idiopathic primary dystonia) to describe some rare families in the recent literature where those affected are said to have additional interictal neurologic features such as spasticity. These features are not the norm in the four typical forms mentioned above. Apart from the idiopathic forms, secondary (‘symptomatic’) paroxysmal dyskinesias would be those caused by environmental insults. A whole host of different etiologies can cause the secondary paroxysmal dyskinesias. Lastly, it must be recognized that certain cases may not fall easily into the current classification of the main four subtypes.

CLINICAL ASPECTS

Paroxysmal kinesigenic dyskinesia (paroxysmal kinesigenic choreoathetosis)

As was noted in the original description of 10 cases by Kertesz, those affected have brief dyskinetic episodes precipitated by sudden movement. The kinesigenic form usually occurs from early childhood and is more common in males. In one report of a series of 26 idiopathic cases, the mean age of onset was 13 years (range 1–39). In the same series, there was a notable predominance of males (7:1), which has also been mentioned by earlier authors. A preceding ‘aura’-like sensation in the limb which gets involved in an attack has been reported in 63% of cases with PKD. The attacks frequently manifest as dystonia or choreo-dystonia induced by a sudden change in position, classically from a sitting to standing position, or by a sudden change in velocity while walking or running. However startle, hyperventilation, and even continuous exercise can also trigger them. Rarely, episodes occur at rest and occasionally in sleep. Attacks commonly involve the hemi-body, which can either be the same side or alternating sides. Rarely, the episodes become generalized. Speech can be affected but consciousness is not lost. Typically, PKD attacks are very brief and frequently last for seconds. Although Demirkiran and Jankovic have mentioned that PKD attacks can last up to 5 minutes, in our experience the attacks in the idiopathic form are very brief and in the majority of cases do not exceed more than 1 minute. There can be dozens of attacks per day. Most cases are idiopathic and apparently sporadic. Family history is clearly present in about 25% of cases and usually follows an autosomal dominant pattern of inheritance. These findings have also been replicated in a large series by Bruno et al, who suggested the specific criteria for PKD (Table 15.2).

Overall, prognosis for the idiopathic form is good and in our experience the condition may often abate in adult life, as the attack frequency tends to decrease with age.
Table 15.2 Clinical criteria for paroxysmal kinesigenic dyskinesia (PKD) as proposed by Bruno et al\textsuperscript{13}

- Identified kinesigenic trigger for the attacks
- Short duration of attacks (<1 minute)
- No loss of consciousness or pain during attacks
- Exclusion of other organic diseases and normal neurologic examination
- Control of attacks with phenytoin or carbamazepine, if tried
- Age at onset between 1 and 20 years, if no family history of PKD

The association of PKC/PKD with epilepsy

Recently, epilepsy has been recognized to be an associated feature in both sporadic and familial cases with PKC. There have also been a few reports describing families with ‘benign’ infantile convulsions and later onset of episodes of paroxysmal choreoathetosis (called the infantile convulsions and choreoathetosis – ICCA syndrome).\textsuperscript{14–19} The first description was by Szepetowski et al\textsuperscript{17} of four French families said to have the ICCA syndrome, as those affected had afebrile infantile seizures and paroxysmal involuntary movements. Lee et al soon followed, with a report of a Chinese family who had a similar condition.\textsuperscript{20} Although clinical details were somewhat sparse (in retrospect), the attacks of paroxysmal choreoathetosis in the ICCA syndrome resembled PKC in being very brief, frequent and induced by sudden exertion and, interestingly, also by ongoing exercise.\textsuperscript{17,20} Other families with epilepsy and PKD have also been recently recognized. Hattori et al described seven Japanese families and two sporadic cases with benign infantile convulsions and paroxysmal dyskinesias.\textsuperscript{15,20} Seventeen individuals developed afebrile complex partial infantile convulsions between 12 months and 3 years of age, followed later by brief paroxysmal dyskinesia resembling PKC. Most families were autosomal dominant, but in some only siblings were affected, suggesting a possible recessive inheritance and genetic heterogeneity. Another family with PKC and epilepsy has been described recently.\textsuperscript{21} In this autosomal dominant family from India, individuals with PKC did not have infantile convulsions. However, some had sporadic episodes of generalized tonic-clonic seizures in teenage years with spontaneous remission of their epilepsy a few years later, although the PKC attacks continued.\textsuperscript{22} PKD has also been associated with interictal myoclonus.\textsuperscript{23}

Paroxysmal exercise-induced dyskinesia

In this condition, episodes of involuntary movements occur after exercise such as walking or swimming. The dystonic episodes usually cease in 10–15 minutes after stopping the exercise. In the initial family described by Lance in 1977,\textsuperscript{8} affected members had attacks lasting between 5 and 30 minutes, provoked usually by walking. The inheritance pattern was autosomal dominant. Plant et al reported a mother and daughter with similar exercise-induced attacks, although attacks could also be initiated by repetitive passive movement of the limbs and by vibration. Munchau et al\textsuperscript{24} reported an autosomal dominant family with PED who also had associated migraine. In this, some members could have jaw dystonia due to chewing gum. Exposure to cold has also been reported to bring on attacks in affected individuals.\textsuperscript{25}

Sporadic examples of exercise-induced dystonia of the intermediate type of PDC are rare and only a few cases have been reported in the literature.\textsuperscript{25} Although, traditionally, PED was thought to be distinct from the kinesigenic form (as usually, the attacks come on after 10 or 15 minutes of continuing exercise rather than at the initiation of movement), recently there have been some familial cases with infantile convulsions and paroxysmal dyskinesias resembling PKD (the so-called ICCA syndrome) in whom the episodes were induced by sudden movements or ongoing exercise.\textsuperscript{14–19}

**PED plus syndrome**

Recently, a family with an apparently recessive disorder characterized by rolandic epilepsy, paroxysmal exercise-induced dystonia, and writers’ cramp (RE-PED-WC syndrome) affecting three members of the same generation, has been linked to chromosome 16p 12-11.\textsuperscript{26} in the same region as the families with the ICCA syndrome\textsuperscript{17,20} and PKD (see Genetics section), suggesting an overlap between these disorders. There is also a syndrome of exercise-induced dystonia associated with atypical absences, alternating hemiplegia, and ataxia that was improved by corticosteroid treatment.\textsuperscript{27}

**Paroxysmal non-kinesigenic dyskinesia (paroxysmal dystonic choreoathetosis)**

Since the initial description by Mount and Reback,\textsuperscript{3} a number of families have been reported with an autosomal dominant inheritance with a fairly similar clinical description between families.\textsuperscript{6,28,29} PNKD is characterized by attacks of dyskinesia which are frequently precipitated by alcohol, caffeine, stress, or fatigue.
Patients with PNKD have longer (10 minutes to 6 hours) and less frequent attacks (1–3/day) than patients with PKD/PKC, followed by long attack-free intervals. The dyskinesia may be of any form, but often tends to be more dystonic or choreic in nature. More males than females are affected (1.4:1), and onset is usually in childhood, with a tendency for the attacks to diminish with age.

Details of typical clinical features of a large English family with 18 affected members were described by Jarman et al. In all cases the onset of symptoms was very early in life, in the second year in seven individuals and as early as age 6 months and 2 months in two other individuals. Witnessed attacks consisted of generalized choreoathetosis in two individuals. In one case there was associated dysarthria in the attack. Attacks started in one limb or one side and progressed to become generalized. The attack duration varied from 10 minutes to 12 hours; however, the majority of attacks were between 30 and 180 minutes. All adults reported a decline in attack duration and frequency with age. One individual who was 85 years old had only 1 attack a year and that was very mild. Coffee, alcohol, anger and excitement, hunger and sleep deprivation were general precipitants, as well as cold and exercise in two individuals. All affected individuals reported a remarkable response to sleep, with 5–10 minutes of sleep being sufficient to abort an attack while some found drinking cold fluids or vigorous exercise while the attack was still mild could abort it. There was some diurnal fluctuation, with a tendency to attacks in the afternoon or evening but not in the morning. Recently, Bruno et al have confirmed these findings in 14 kindreds with classic PNKD.

There has been speculation as to why alcohol and coffee precipitate attacks in PNKD. Fink et al postulated a surge of dopamine release induced by alcohol, for example, followed by relative dopamine deficiency could cause the dystonia. This notion is supported by the fact that some patients with PNKD respond to L-dopa with sleep benefit. A surge in cerebrospinal (CSF) dopamine metabolites has been noted, supporting the theory of Fink et al in another family with PNKD.

Generally, PNKD cases have no detectable abnormalities between attacks, although there has been one report of a patient with PNKD who also had some interictal dystonia. There has also been a family with PNKD with additional myokymia.

With regard to investigations, routine tests as well as electroencephalograms (EEGs) and brain imaging in the idiopathic cases are normal. Pathologic examination at autopsy in two cases also revealed no abnormalities.

**PNKD associated with spasticity**

A large German family in whom affected members had choreo-dystonic attacks induced by alcohol, fatigue, and exercise (and thus similar to PNKD) was reported by Auburger et al. However, some affected individuals also had marked spastic paraparesis and other clinical features, including perioral paresthesias, double vision, headache, and generalized myoclonic jerks, and seizures were also present. This condition is therefore different from typical PNKD and can be considered as a PNKD plus syndrome.

**Paroxysmal hypnogenic dyskinesia**

In PHD, the attacks of paroxysmal dyskinesia occur at night in sleep (hence, hypnogenic), and this disorder is often erroneously suspected to represent night terrors or some other sleep disorder. In a typical PHD attack, the patient awakens with a cry followed by involuntary dystonic and ballistic limb movements that are very brief, lasting seconds and rarely over 1 minute. The movements often involve the legs. There is no loss of consciousness. Usually there are no detectable concurrent EEG abnormalities. Several attacks (sometimes even 20–25) can occur each night.

Lugaresi and Cirignotta gave one of the first clear descriptions of this condition in five patients who had attacks in sleep almost every night. Lee et al and others also described similar familial cases with a clear autosomal dominant inheritance pattern. It has now become clear that in a large proportion of these cases, especially the familial variety, these nocturnal dyskinesias are due to mesial frontal lobe seizures which are difficult to pick up on surface EEG recordings. Describing the salient features in six families from Canada, Australia, and the UK, Scheffer et al suggested the eponym autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) to describe this disorder. The gene responsible for ADNFLE has been discovered in a few families (see Genetics section).

**Benign paroxysmal torticollis in infancy**

BPT is a relatively rare disorder with onset in infancy and episodes of torticollis with or without tortipelvis. The duration is hours, rarely up to a few days. The episodes are infrequent, with 1–2 occurring in a day at times. There have been some suggestions of a relationship to migraine (basilar variety) and kinestostsis. This is because, with time, episodes of head tilt become less prominent, and are replaced by vertigo, vomiting, lassitude, and migraine-like headaches. Recently, two
cases with BPT were described from families with familial hemiplegic migraine linked with calcium channel gene (CACNL1A). This is interesting, given the hypothesis (see Pathophysiology section) that the paroxysmal dyskinesias may be caused by ion channel abnormalities.

Secondary (‘symptomatic’) paroxysmal dyskinesias

Secondary paroxysmal dyskinesias are probably more common than initially thought. In a series by Blakeley and Jankovic, 17 of 76 patients with paroxysmal dyskinesias (22%) had an identifiable cause. Secondary cases are notable for their variability in age of onset, the presence of both kinesigenic and non-kinesigenic symptoms in some patients, the prevalence of sensory precipitants, and most importantly, the reversal of symptoms when the underlying etiology is treated in some patients. The association of PKC/PDC with multiple sclerosis is the most common. Other causes include stroke, transient cerebral ischemia, antiphospholipid syndrome, central and peripheral trauma, hypoglycemia, hyperglycemia, hypoparathyroidism, pseudohypoparathyroidism, thyrotoxicosis, basal ganglia calcifications, keratitis, meningovascular syphilis, HIV (human immunodeficiency virus) infection, and cytomegalovirus encephalitis. Clinically, there may be some clues about the cause; for instance, in multiple sclerosis the attacks are often precipitated by hyperventilation. On examination, we can find some signs such as spasticity which would suggest multiple sclerosis or phalangeal shortening suggesting pseudohypoparathyroidism. Since there are multiple possible causes of secondary paroxysmal dyskinesias, most individuals with this movement disorder would therefore required basic investigation, including brain imaging, preferably magnetic resonance imaging (MRI) scan, and appropriate blood tests or other investigations.

GENETICS OF PAROXYSMAL DYSKINESIAS

Paroxysmal non-kinesigenic dyskinesia

Two groups separately linked families with PNKD to chromosome 2q. Fink and co-workers performed a genome-wide search in a large American kindred of Polish descent with 28 affected members and mapped PNKD on chromosome 2q33-q35. Fouad et al also showed tight linkage between PNKD and microsatellite markers on distal 2q (2q31-q36) in a five-generation Italian family with 20 affected members. The smallest region of overlap of the candidate intervals identified by these two groups placed the PNKD locus in a 6-cM interval. In a six-generation British family, Jarman and co-workers confirmed linkage to distal chromosome 2q and narrowed the candidate region to a 4-cM interval. Linkage to the same genetic location, designated FPD1 (familial paroxysmal dyskinesia type 1), was also confirmed by Hofele et al in a German family, originally described by Przuntek and Monninger as classical Mount and Reback type of PNKD, and other typical PNKD families, including one from North America of German descent as well as a Japanese family. These studies suggest a level of genetic homogeneity for classical familial PNKD/PDC.

After a number of candidate genes were excluded, the gene for responsible for PNKD was discovered to be the myofibrillogenesis regulator 1 (MR-1) gene. Mutations in this gene cause paroxysmal dystonic choreoathetosis. This gene encodes an enzyme in a stress response pathway. Lee et al found that the mutations cause changes (Ala to Val) in the N-terminal region of two MR-1 isoforms. The MR-1L isoform is specifically expressed in brain and is localized to the cell membrane, whereas the MR-1S isoform is ubiquitously expressed and shows diffuse cytoplasmic and nuclear localization. Bioinformatic analysis reveals that the MR-1 gene is homologous to the hydroxyacetylglutathione hydrolase (HAGH) gene. HAGH functions in a pathway to detoxify methylglyoxal, a compound present in coffee and alcoholic beverages and produced as a by-product of oxidative stress, thus suggesting a possible mechanism (Figure 15.1) whereby alcohol, coffee, and stress precipitate attacks in PNKD. Mutations in the MR-1 gene have been confirmed to be the cause of PNKD in numerous families all over the world and as far apart as Oman and Serbia.

PKD/PKC, the ICCA syndrome, and PED (RE-PED-WC syndrome)

These three disorders have to be considered together as they are all linked to the small arm of the pericentromeric region of chromosome 16. Szepetowski et al linked four French families with infantile convulsions and paroxysmal choreoathetosis (the ICCA syndrome) called to a 10-cM interval around the pericentromeric region of chromosome 16. Linkage to the same locus was confirmed in a Chinese ICCA family. Since the clinical characteristics of the paroxysmal dyskinetic episodes in the ICCA syndrome were very similar to those described for PKD, it was not surprising that eight Japanese families, as well as an African-American kindred with typical PKC, were mapped by linkage...
analysis to the same pericentromeric region of chromosome 16. The PKC region in the Japanese families spanned 12.4 cM and overlapped by 6.0 cM the ICCA region. The fact that there was an increased prevalence of afebrile infantile convulsions in the Japanese families with PKC87 suggested the possibility that the same one gene may be responsible for both PKC and ICCA. However, the PKC interval identified in the African-American family in which individuals have PKC alone (and no infantile seizures) overlaps by 3.4 cM with the ICCA region and by 9.8 cM with the PKC region identified in Japanese families. Thus, it was unclear whether there were two (or more) genes giving rise to both ICCA and PKC in these families or a single gene in this interval. Furthermore, the autosomal recessive family with RE-PED-WC syndrome described by Guerrini et al26 (see above in Clinical aspects) was also linked to chromosome 16 within the ICCA region but outside the 3.4 cM overlap between ICCA and PKC. Thus, it appears that the RE-PED-WC syndrome might also be allelic to ICCA but is probably not allelic to PKC. In addition, as epilepsy is the most striking feature of both the ICCA and RE-PED-WC syndromes and some of the ICCA attacks were induced by exercise, it has been suggested that there are common underlying genes for these two conditions which may be different from that giving rise to isolated PKC.

Swoboda et al19 highlighted a role for locus heterogeneity when reporting linkage data on 11 families with PKD, with infantile convulsions also present in nine families. Ethnic background was diverse, including two Afro-American, Taiwanese, Ashkenazi Jewish, Dutch, Mexican, and mixed European ancestry. Linkage was confirmed to chromosome 16 and overlapped the ICCA region, which the authors narrowed down to 3.2 cm. However, one family with classic PKC and infantile convulsions failed to share a common haplotype, thus suggesting heterogeneity. It is also interesting to note the paper by Valente et al21 in this context. They identified a family with PKC from India and linked it to a second locus on the long arm of chromosome 16, distinct from the locus of the Japanese families with PKC, hence this is referred to as episodic kinesigenic dyskinesia 2 locus (EKD2). The localization of PKC in the African-American family overlaps with both these regions.88 The African-American PKC locus may thus be allelic with either the Japanese or Indian PKC locus or represent yet another gene altogether. In addition, there are also families with PKD not linked to chromosome 16 at all, suggesting evidence of yet another locus.89

The gene(s) causing these disorders are as yet unknown but there are a group of ion channel genes which lie in this pericentromeric region of chromosome 16. The PKC region in the Japanese families spanned 12.4 cM and overlapped by 6.0 cM the ICCA region. The fact that there was an increased prevalence of afebrile infantile convulsions in the Japanese families with PKC suggested the possibility that the same one gene may be responsible for both PKC and ICCA. However, the PKC interval identified in the African-American family in which individuals have PKC alone (and no infantile seizures) overlaps by 3.4 cM with the ICCA region and by 9.8 cM with the PKC region identified in Japanese families. Thus, it was unclear whether there were two (or more) genes giving rise to both ICCA and PKC in these families or a single gene in this interval. Furthermore, the autosomal recessive family with RE-PED-WC syndrome described by Guerrini et al (see above in Clinical aspects) was also linked to chromosome 16 within the ICCA region but outside the 3.4 cM overlap between ICCA and PKC. Thus, it appears that the RE-PED-WC syndrome might also be allelic to ICCA but is probably not allelic to PKC. In addition, as epilepsy is the most striking feature of both the ICCA and RE-PED-WC syndromes and some of the ICCA attacks were induced by exercise, it has been suggested that there are common underlying genes for these two conditions which may be different from that giving rise to isolated PKC.

Swoboda et al19 highlighted a role for locus heterogeneity when reporting linkage data on 11 families with PKD, with infantile convulsions also present in nine families. Ethnic background was diverse, including two Afro-American, Taiwanese, Ashkenazi Jewish, Dutch, Mexican, and mixed European ancestry. Linkage was confirmed to chromosome 16 and overlapped the ICCA region, which the authors narrowed down to 3.2 cm. However, one family with classic PKC and infantile convulsions failed to share a common haplotype, thus suggesting heterogeneity. It is also interesting to note the paper by Valente et al21 in this context. They identified a family with PKC from India and linked it to a second locus on the long arm of chromosome 16, distinct from the locus of the Japanese families with PKC, hence this is referred to as episodic kinesigenic dyskinesia 2 locus (EKD2). The localization of PKC in the African-American family overlaps with both these regions.88 The African-American PKC locus may thus be allelic with either the Japanese or Indian PKC locus or represent yet another gene altogether. In addition, there are also families with PKD not linked to chromosome 16 at all, suggesting evidence of yet another locus.89

The gene(s) causing these disorders are as yet unknown but there are a group of ion channel genes which lie in this pericentromeric region of chromosome 16.
16, within the ICCA and PKC intervals, which are good candidates and are being currently investigated.

Finally, it is also interesting to note that a recent paper described linkage of seven families with benign neonatal infantile convulsions (without paroxysmal dyskinesias) to the same region as ICCA on 16p12-q12,14 thus suggesting that there may be a family of genes causing different paroxysmal disorders on the pericentromeric region of chromosome 16.

**Paroxysmal hypnogenic dyskinesia**

One ADNFLE locus was first mapped by Phillips et al90 on chromosome 20q13.2 in an Australian family. The obvious candidate was the α4 subunit of the neuronal acetylcholine receptor, a ligand gated channel gene. Two different mutations in two families in the α4 subunit of the neuronal acetylcholine receptor (CHRNA4) on 20q13.2 were found. The mutations observed were missense mutations in an Australian family and a Japanese family and a three base pair insertion in the case of a Norwegian family.91–93 However, a British family with ADNFLE was not found to be linked to CHRNA4 on chromosome 20q but to a locus on chromosome 15q24 close to a CHRNA3/CNRNA5/CHRNB4 nicotinic acetylcholine receptor gene cluster.94

Also, seven other families with ADNFLE and seven sporadic cases were unlinked to these loci on chromosomes 20q13.2 and 15q24, thereby suggesting the existence of at least a third ADNFLE locus and genetic heterogeneity of this disorder. This has been confirmed by the finding of mutations of a β subunit of the nicotinic acetylcholine receptor gene causing nocturnal frontal lobe epilepsy.95,96

**Paroxysmal dyskinesias plus**

The genetics of the PED plus syndrome (RE-PED-WC syndrome) have been discussed above together with PKD/PKC and the ICCA syndrome.

The German family with PNKD associated with spasticity was linked to a locus different to typical PNKD on chromosome 1p which has been designated CSE (choreoathetosis/spasticity episodic).9 Linkage analysis in this family placed the disease locus in a 12-cM interval on chromosome 1p21 between flanking markers. The gene is yet to be determined, but several potassium channel genes have been mapped to this region and lie in a cluster. Further investigations are needed to determine the gene for this disorder. No other similar families have been reported so far.

**PATHOPHYSIOLOGY**

Over the years, the pathophysiology of these disorders has been debated. The main arguments have been whether these conditions are a form of epilepsy or whether they represent a basal ganglia disorder. It has been suggested by some that the primary pathophysiologic process may be of epilepsy, perhaps at a subcortical level, given the paroxysmal character of attacks, prodromic aura-like symptoms in many, the short duration of the attacks, and the response to antiepileptic drugs.97,98 In support of this hypothesis are several reports of families in which some individuals presented with either or both paroxysmal dyskinesias and epilepsy, with different age-related expressions.26,99 On the other hand, the occurrence of dystonia in 70–80% of paroxysmal dyskinesia episodes might indicate a pathophysiologic process similar to primary dystonia, where deficits in cortical, brainstem, and spinal inhibitory circuits, due to disordered basal ganglia modulation of cortical motor output, have been detected. Evidence to support the role of the basal ganglia in the pathophysiologic process suggests that the paroxysmal dyskinesias is based on the observation of secondary paroxysmal dyskinesias in association with focal basal ganglia lesions.10

Few studies to date have investigated the pathophysiology of paroxysmal dyskinesias. Franssen et al investigated the contingent negative variation (CNV) in one patient with PKD.99 The slow negative wave component of the CNV was more pronounced compared to control subjects (the opposite to the pattern observed in primary dystonia), but this was normalized after phenytoin treatment. Lee et al studied forearm reciprocal inhibition in 10 patients with PKD and found a paradoxical facilitation of H reflex size in the first phase of reciprocal inhibition (a pattern not routinely observed in primary dystonia).100 More recently, Mir et al assessed a number of electrophysiologic parameters in 11 patients with PKD, a proportion of them on and off treatment. A reduced short intracortical inhibition, a reduced early phase of transcallosal inhibition, and a reduced first phase of spinal reciprocal inhibition (RI) in subjects with PKD were identified. Cortical silent period, the startle response, and the second and third phases of RI were normal. Treatment with carbamazepine normalized the abnormalities in transcallosal inhibition, but had no effect on other parameters.

Invasive long-term electrode monitoring of a patient with secondary PKD was reported to show consistent ictal discharge recorded from the ipsilateral caudate nucleus with a concomitant discharge recorded from the supplementary sensory motor cortex, without significant spread to other areas.102 Invasive monitoring has also
been performed in a child with severe PNKD, which recorded an ictal discharge from the caudate nuclei with no cortical correlate. 18F-dopa and 11C-raclopride PET (positron emission tomography) scans in the same patient revealed a marked reduction in the density of presynaptic dopa decarboxylase activity in the striatum, together with an increased density of postsynaptic dopamine D2 receptors. Ictal and postictal SPECT (single-photon emission computed tomography) studies have shown basal ganglia hyperactivity associated with dyskinetic attacks in PKD.103,104 However, a study with 99mTc-HMPAO (hexamethyl propyleneamine oxime) SPECT has found the opposite pattern, with a decrease in cerebral blood flow in the basal ganglia on the contralateral side of choreoathetotic movements.105 Increase in cerebral blood flow in the left medial thalamus during a PKD attack has been observed in a study using 123I-IMP SPECT.106

It is possible that a common, genetically determined, pathophysio logic abnormality is variably expressed in the cerebral cortex and in basal ganglia.107 It has been hypothesized that this abnormality might be in ion channels. The paroxysmal dyskinesias have many similarities to other episodic disorders of the nervous system such as episodic ataxias and periodic paralysis.108 Many of these paroxysmal neurologic disorders are now known to be ‘channelopathies’ due to mutations of genes regulating ion channels.109–115 In this regard it is interesting to note the many similarities between PKD and episodic ataxia type 1 (EA1). Like PKD, the episodes of ataxia in EA1 are often provoked by kinesigenic stimuli, are brief (lasting seconds to a few minutes), and can occur several times a day.116 Both conditions have a early age of onset and there is tendency for both to abate in adulthood. EA1 typically responds to acetazolamide and also to anticonvulsants.116,117 Interestingly, PKD also has similarities to hereditary hyperekplexia, an inherited disorder of the glycine receptor gene (GLRA1), characterized clinically by continuous muscle stiffness in the first year of life, and later an exaggerated startle response.118 Discrete abnormalities in the first phase of RI in PKD that resemble the pattern observed in patients with hereditary hyperekplexia have been shown.104,119,120 There are also reports of families with multiple episodic disorders: for example, paroxysmal dyskinesia in a family with episodic ataxia, and association of episodic problems like migraine and epilepsy in families with paroxysmal ataxia or dyskinesias.21,24,121,122 Furthermore, paroxysmal dyskinesias are observed in the tottering mouse, which inherits a mutation in the P/Q-type calcium channel.123 Thus, the familial paroxysmal dyskinesias are also believed to be due to defects in genes regulating ion channels. However, as mentioned earlier, so far the only identified mutations in channel genes are in ADFNLE, where there is a mutation of a ligand gated ion channel gene, and BPT, where some cases with mutation in a calcium channel gene have been reported. Surprisingly, the gene for PNKD did not turn out to be an ion channel gene and this condition is caused by mutations in the MR-1 gene, which encodes an enzyme in a stress response pathway.83 However, the exact mechanism of how intermittent attacks of dyskinesias occur in PNKD remains unclear and it is possible that there is some associated interaction with ion channels. The genes for PKD and PED are still unknown.

TREATMENT OF PAROXYSMAL DYSKINESIAS
PKD responds dramatically to different antiepileptic drugs, but there appears to be a particularly good response to carbamazepine, even with relatively low doses.12,29,124,125 More recently, it has been reported that PKC patients have a good response to the newer antiepileptics, including gabapentin,126 lamotrigine,127,128 levetiracetam,129 and topiramate,130 but our own experience is that carbamazepine is the drug of choice. PNKD is thus more difficult to treat than PKD with drugs; however, over the years, many patients learn to avoid precipitants and thus either avoid or even abort attacks. Most patients with PNKD generally do not benefit from antiepileptic drugs. However, clonazepam can be helpful in some and clobazam was reportedly beneficial in one case. Anticonvulsants may be useful in some but not all cases of PED.25 Other drugs which may be helpful in some cases include l-dopa, acetazolamide, and trihexiphenidyl, which can be tried in turn. Generally, PED is more difficult to treat than PKC. In drug refractory cases, stereotactic surgery may be considered, particularly if attacks are predominantly one-sided. There has been a report of unilateral pallidotomy being useful in a case with PED.25 Regarding the treatment of PHD, antiepileptics, particularly carbamazepine, are very effective in most cases.36 In secondary, as in idiopathic paroxysmal dyskinesias, it is more difficult to control symptoms in PNKD and mixed disease than in PKD.131 The treatments that have been used have not been uniformly effective, but anticonvulsant drugs and clonazepam have been the most beneficial.10 Treatment of the underlying etiology has been reported to improve the symptoms in some cases. Botulinum toxin injections into the agonist muscle have been found effective in some patients with focal paroxysmal dystonia.22 It is interesting to note that acetazolamide is helpful for some patients with paroxysmal dyskinesias,19 as it also is in patients with known channelopathies such as periodic paralysis and episodic ataxias.
FUTURE DIRECTIONS

The discovery of the genes will also lead to the possibility of developing animal models and functional cellular studies. This has already become possible for ADNFLE, which is known to be caused by mutations of the brain nicotinic acetylcholine receptor gene, a ligand gated channel. How these mutations cause epileptogenesis is not clearly understood, but functional studies have been performed expressing the mutant gene in cell lines, and undertaking single cell recordings using patch-clamp techniques to compare with the wild type. By this method, several different effects for different mutations of the \( \alpha_2 \) or \( \beta_2 \) subunits of the nicotinic acetylcholine receptor gene have been observed, which include a decrease in maximal current amplitude\(^{123} \) or increase,\(^{134} \) decreases in acetylcholine affinity\(^{133} \) and reduction in calcium entry into cells.\(^{52,134} \) The pathophysiologic mechanisms of PNKD related to dysfunction of the MR-1 gene product have been speculated on (see Figure 15.1)\(^83 \) but further work is needed.

REFERENCES


170 CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA

134. Kuryatov A, Gerzanich V, Nelson M et al. Mutation causing autosomal dominant nocturnal frontal lobe epilepsy alters Ca\textsuperscript{2+} permeability, conductance, and gating of human α\textsubscript{2}β\textsubscript{2} nicotinic acetylcholine receptors. J Neurosci 1997; 17(23): 9035–47.
Psychogenic dystonia

Martin Cloutier, Tamara Pringsheim, and Anthony E Lang

BACKGROUND

The history of dystonia is marked by a swinging pendulum of thought: from psychogenic to organic, and there and back again. The controversy surrounding the history of dystonia has made clinicians approach the diagnosis of psychogenic dystonia with understandable caution.

Early descriptions of idiopathic torsion dystonia date back to the beginning of the 20th century. Although originally described as a manifestation of psychiatric disease, several turn of the century neurologists recognized the organic nature of dystonia.1–3 Attitudes toward dystonia changed in the 1940s and 1950s, perhaps as a result of the puzzling nature of the syndrome, and failure to understand its underlying pathology.4 Commonly, physicians once more thought of dystonia as a psychiatric disorder, and patients with dystonia were sent for psychiatric evaluation and management. Over the next 20 years, clinicians became increasingly convinced that a true disorder of neurologic function was responsible for dystonia, and discouraged the notion of psychogenic causes. A hard line, denying the occurrence of dystonia secondary to psychological dysfunction, was taken in large part as a reaction to the recognition of the harm that had been done to patients with ‘organic’ dystonia who had been previously diagnosed and treated as having a psychiatric disorder. However, the pendulum has moved away from this extreme, with the recognition that in a small but definite proportion of patients with dystonia primary psychological factors are causative.

In order to better understand why theories of dystonia have swung so dramatically from organic to psychogenic, one must closely consider some aspects of the disease and its manifestations. Idiopathic torsion dystonia typically begins as a highly focal, action-specific movement disorder. For example, patients describe plantar flexion and inversion of the foot while walking forward, but not while running or walking backward, or writing is impaired in the absence of interference with other manual tasks. Symptoms may later progress to affect other tasks and other body segments. The appearance of dystonia is often quite bizarre. For example, dystonia involving the trunk, pelvis, and legs can cause a very peculiar gait that is often mistaken as hysterical. Focal and segmental dystonias also have interesting features such as amelioration by unusual sensory tricks (‘gestes antagonistes’) which could suggest psychogenicity to the inexperienced clinician. Cranial dystonias such as blepharospasm may be aggravated by trying to read or watch television, whereas manifestations of oromandibular dystonia may be minimal until the person attempts to eat or speak. These symptoms, especially blepharospasm, are often markedly diminished by the stress or alerting effect of a visit to the physician’s office, resulting in suspicion of psychogenic disease in a patient who claims to be functionally blind at home. Some patients, especially those with cervical dystonia, may give a history of full spontaneous remission of symptoms in the past with later recurrence, sometimes precipitated by emotional upset. It is the variable nature of the dystonia that has made it most puzzling to clinicians, and has led to debate regarding the etiology of the symptoms. Experience and observation have proven that this is indeed an organic syndrome and often ‘unusual’ but characteristic features such as task specificity and the ameliorative effect of sensory tricks are used in support of the diagnosis. That said, psychogenic dystonia does exist, and must be recognized.

Much of this chapter is reproduced with approval by the editor from a previous review on the topic.5

EPIDEMIOLOGY

Although psychogenic dystonia makes up a significant percentage of psychogenic movement disorders seen at subspecialty clinics, it accounts for a small minority of
patients with idiopathic or symptomatic dystonia. Combined data on psychogenic movement disorders seen at Columbia-Presbyterian Medical Center, the Toronto Western Hospital (unpublished data), Cleveland Clinic Florida (unpublished data), and Albany Medical Center are presented in Table 16.1. Dystonia makes up the largest subgroup, accounting for 33% of psychogenic movement disorders seen at these clinics. This is mostly due to the large number of psychogenic dystonia cases seen at Columbia-Presbyterian Medical Center, which during the time of this data collection, served as a Dystonia Medical Research Foundation center of excellence and therefore probably had a strong referral bias. In the other groups, tremor was the most common psychogenic movement disorder, followed by dystonia. In our recent evaluation of 279 patients with psychogenic movement disorders, 89 (32%) had dystonia, while 91 (33%) had tremor, 51 (18%) had myoclonus, and the remainder had a variety of less common phenotypes.

Looking at the percentage of patients with dystonia who had a psychogenic origin of their symptoms, Marsden quotes a figure of 1% at the National Hospital for Neurology and Neurosurgery in London (21 of 2221 patients with idiopathic or symptomatic dystonia), while Fahn’s group at the Dystonia Clinical Research Center had a figure of 2.6% (21 of 814 patients). These numbers are all from tertiary-care movement disorders clinics and are probably higher than the true prevalence of psychogenic dystonia. Clearly, the vast majority of patients with dystonia have an organic basis for their symptoms.

### CLINICAL FEATURES AND DIAGNOSIS

Overall, a psychogenic movement disorder is not a diagnosis of exclusion. Several important historical and particularly clinical features are required in support of this consideration. Of all the psychogenic movement disorders, psychogenic dystonia is probably the most difficult to diagnose. This is based on skillful observation and examination of the patient by an experienced clinician, which will reveal inconsistencies suggestive of a psychogenic origin of the patient’s symptoms. Expertise in the evaluation of movement disorders is necessary to make a diagnosis of psychogenic dystonia since there is no biologic marker for the condition. Currently, neuroimaging and electrophysiologic testing are of limited use in the diagnosis of psychogenic dystonia, although that role is evolving.

Table 16.2 provides a list of important historical and clinical clues to the diagnosis of psychogenic movement disorders.
disorders in general. Importantly, none of these are definitive and many of these features may also be seen in organic movement disorders. For example, abrupt onset or rapid progression to maximum severity is a common feature of psychogenic dystonia (and other psychogenic movement disorders) but it can be seen in some heredodegenerative dystonias such as Wilson’s disease or rapid-onset dystonia-parkinsonism. Paroxysmal movement disorders are commonly psychogenic, but idiopathic and secondary paroxysmal dyskinesias and dystonias—kinesigenic or non-kinesigenic—must be ruled out before the definitive diagnosis is made.

Fahn and Williams developed a classification system for psychogenic dystonia which is now used to classify psychogenic movement disorders of all types. This classification system allows the neurologist to categorize the degree of diagnostic certainty as documented, clinically established, probable, or possible. Table 16.3 outlines the features of each diagnostic category. Williams and colleagues have subsequently combined the categories of documented and clinically established to form a category of clinically definite dystonia, as both categories imply a definite diagnosis.9

Psychogenic dystonia can be extremely difficult to diagnose given the unusual clinical features of organic dystonia, as previously mentioned. This diagnosis requires considerable experience in the assessment of various organic dystonic syndromes, since it is based on the presence of clinical inconsistencies and incongruities with organic dystonia. Incongruous features include:

- rapid onset and progression with fixed postures followed by static course
- paroxysms (often triggered)
- marked (‘active’) resistance to passive movement, often with the inability to activate the same muscles on command
- elaborate, bizarre, or complex abnormal movements
- extreme slowness of voluntary movements, clinically different from true bradykinesia, since there is often preserved amplitude of movement and a lack of fatiguing
- extreme pain with the dystonic spasms
- variable direction of ‘dystonic’ posturing
- foot dystonia (especially fixed), beginning in the adult.

Features that are generally inconsistent with organic dystonia include:

- being witnessed free of dystonia on surreptitious observation
- dystonia subsides on distraction
- dystonia changes or is precipitated with suggestion.

Although organic dystonia often does fluctuate over time, it usually behaves in a stereotyped pattern, whereas psychogenic dystonia can show inconsistent variation over time. Table 16.4 lists features which help distinguish psychogenic from organic dystonia. Once again, it is important to emphasize that these features are simply ‘suggestive’ clues and no more. Organic dystonias may also manifest any or all of these features, and the incongruities and inconsistencies listed above are critical in support of the diagnosis.

Fahn and Williams reported on the largest series of patients with psychogenic dystonia. Among a total of 39 cases of psychogenic dystonia, diagnosed with various degrees of certainty, 17 met the criteria for documented
psychogenic dystonia and 4 were considered clinically established. The authors reported on these 21 patients in detail.

There were 19 females and 2 males. Age of onset was between 8 and 58 years. They differentiated between the 14 patients with continual dystonia and 7 having only paroxysmal dystonia. The former group had a mean age of onset of 23 years and the latter 33 years. Many of the patients had clinical features that were considered suspicious of a non-organic etiology. Dystonia was considered incongruent or inconsistent in 19 of the 21 patients. Nine patients reported prominent pain; 14 patients had false weakness and 5 had false sensory signs; 8 had multiple somatizations; 11 had dystonia at rest from the onset, another atypical feature of organic dystonia; 5 had superimposed paroxysmal episodes that were vaguely similar to seizures; 7 had other movement disorders that were also considered psychogenic; 5 patients had excessive non-organic slowness of movements.

Onset was in lower limbs in 14 patients, including 7 of the 11 patients who were 25 years of age or older. It frequently evolved to generalized dystonia — again, even in adult-onset cases.

Before the authors’ assessment, none of the patients were diagnosed as having a pure psychogenic disorder, although some were believed to have a mixture of organic dystonia with superimposed psychogenic features. Some patients had invasive procedures before the correct diagnosis was made: 1 patient had a previous right thalamotomy, 1 patient had carotid arteriography, 1 patient underwent a tendon transplantation, and 1 patient had received intrathecal baclofen.

The duration of symptoms from onset to their assessment was between 1 month and 15 years. The 5 patients who had symptoms for less than 2 months before the diagnosis was made had a complete remission. Among all 21 patients, 9 had a complete and permanent remission and another 4 had a moderate or considerable relief of their symptoms. The duration of follow-up was not specified.

Lang reviewed 18 patients with a diagnosis of clinically definite psychogenic dystonia.10 According to the Fahn and Williams classification, 4 of these met the definition of documented psychogenic dystonia and 14 were clinically established. Thirteen of the 18 patients were female. The mean age of onset was 35.5 ± 12.7

### Table 16.3 Classification system for psychogenic movement disorders by Fahn and Williams

<table>
<thead>
<tr>
<th>Classification</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Documented&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Movement disorder is persistently relieved by psychotherapy, psychological suggestion, or administration of placebo</td>
</tr>
<tr>
<td></td>
<td>Absence of symptoms when unaware of being observed</td>
</tr>
<tr>
<td>Clinically established&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Movement disorder is inconsistent over time or is incongruent with the clinical presentation of an organic movement disorder</td>
</tr>
<tr>
<td></td>
<td>Supportive evidence is provided by the presence of other physical signs that are definitely psychogenic (e.g. false weakness, non-anatomic sensory loss), multiple somatizations, or an obvious psychiatric disturbance</td>
</tr>
<tr>
<td>Probable</td>
<td>Three categories of patients:</td>
</tr>
<tr>
<td></td>
<td>1. Movements are inconsistent or incongruent with an organic disorder but no other features exist to support a psychogenic origin</td>
</tr>
<tr>
<td></td>
<td>2. Abnormal movements are consistent and congruent with an organic disorder, but physical signs are present that are definitely psychogenic&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>3. Movements are consistent and congruent with an organic disorder, but multiple somatizations are present&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Possible</td>
<td>Obvious psychiatric disturbance present in a patient with abnormal movements that are consistent and congruent with an organic movement disorder</td>
</tr>
<tr>
<td></td>
<td>Supportive evidence includes inappropriate affect, discrepancy between the movement disorder and the reported disability, and the presence of secondary gain</td>
</tr>
</tbody>
</table>

<sup>a</sup>Documented and clinically established groups could be combined as clinically definite.

<sup>b</sup>These features are not uncommon in patients with organic movement disorders. We would not support using these criteria to give a diagnosis of a probable psychogenic movement disorder.
years, with a range between 17 and 59 years. The mean duration of symptoms before the first assessment was 3.8 ± 6.9 years, but one patient had symptoms for 30 years before the diagnosis was made. Fourteen patients had a known precipitant before the onset of dystonia; in 6 patients, this was a local injury and in 5 a motor vehicle accident, usually with a whiplash injury, was reported.

The onset of dystonia was sudden in 9 patients, progressed over days in 6 patients, whereas the temporal evolution of the symptoms remained uncertain in 3 patients. In most patients, the maximum severity was reached rapidly, either immediately or over days, certainly an atypical course for organic dystonia. Onset was in the lower limbs in 7 patients, and generalized dystonia from onset was present in 3 patients. Again, these features are very rare in adults with organic dystonia. After the onset, there was a progression to generalized dystonia in 5 other patients.

At first assessment, 12 of the patients had dystonia at rest. Ten patients reported superimposed paroxysmal changes in their dystonia, and in 4 patients these paroxysmal events were triggered by non-physiologic means during examination.

Prominent pain was a common feature, reported by 14 patients. There was pronounced tenderness of the muscles involved and exaggeration of pain with attempted passive manipulation; 10 patients had other psychogenic movement disorders and 15 had non-organic neurologic abnormalities on examination, usually give-way weakness or false sensory signs; 8 patients had multiple somatizations. Six patients were receiving financial benefits for their disabilities and 2 patients had pending litigation. Thirteen patients went through multiple investigations before their assessment, and 6 patients had therapeutic trials with at least three medications. One patient had two right-sided thalamotomies.

Follow-up was available for only 8 patients. One patient had a complete remission and 2 patients showed marked improvement. Another patient who had obvious generalized dystonia when first evaluated was seen later at a lay symposium on dystonia and appeared normal. One other patient had a moderate improvement and in 3 patients the dystonia persisted unchanged.

Factor and colleagues reported 28 patients with various psychogenic movement disorders, including 5 patients with dystonia.7 These 5 patients were aged between 22 and 50 years old, and 4 were female; 2 patients had left foot dystonia, 2 patients had blepharospasm, and 1 patient had paroxysmal generalized dystonia. As a group, they shared many of the features of the patients reported by Fahn and Williams and Lang, such as additional non-organic neurologic signs and potential secondary gains. Interestingly, 7 of the 28 patients with a psychogenic movement disorder also had a distinct organic movement disorder.7

Another not uncommon presentation of psychogenic dystonia is facial dystonia. Patients will typically present with unilateral eye closure, and contralateral mouth deviation. This presentation in considered incongruent with organic dystonia and cannot be explained by neuroanatomic pathways.

Bentivoglio and colleagues reported a patient with psychogenic dystonia who was also a carrier of the DYT1 mutation.11 Four other family members, over three generations, were affected with organic primary torsion dystonia. The adult-onset inconsistent episodes of severe dystonia, leading to a temporary wheelchair-bound state, followed by complete spontaneous remission, with the additional non-organic neurologic signs led the authors to the correct diagnosis. The sense of guilt of having transmitted a severe movement disorder to her son was believed to be the source of her conversion disorder.

<table>
<thead>
<tr>
<th>Table 16.4 Features suggestive of psychogenic dystonia &lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset with resting dystonia</td>
</tr>
<tr>
<td>Adult onset with leg involvement</td>
</tr>
<tr>
<td>Fixed spasm</td>
</tr>
<tr>
<td>Rapid progression</td>
</tr>
<tr>
<td>Spread to maximum disability early in the course</td>
</tr>
<tr>
<td>Dystonic movements inconsistent over time</td>
</tr>
<tr>
<td>No sensory trick</td>
</tr>
<tr>
<td>Selective disabilities</td>
</tr>
<tr>
<td>Abilities inconsistent with fixed spasms</td>
</tr>
<tr>
<td>Pain or tenderness to touch and exaggeration with passive movement</td>
</tr>
<tr>
<td>Lack of improvement after sleep</td>
</tr>
<tr>
<td>Attempted voluntary movement to command in the opposite direction of the dystonic posturing may activate antagonist muscles with little apparent action in agonist muscles</td>
</tr>
<tr>
<td>Paroxysmal dystonia (isolated or combined with persistent dystonia)</td>
</tr>
<tr>
<td>Other paroxysmal movements</td>
</tr>
<tr>
<td>Other psychogenic movement disorders</td>
</tr>
<tr>
<td>Other non-organic neurologic signs</td>
</tr>
<tr>
<td>Precipitants</td>
</tr>
<tr>
<td>Remissions, spontaneous or with placebo</td>
</tr>
<tr>
<td>Absence of family history</td>
</tr>
</tbody>
</table>

<sup>a</sup>Any or all of these features can also be seen present in organic dystonias. See text for details.
The concept of post-traumatic movement disorders warrants separate discussion. Of note, is the occurrence of movement disorders, particularly dystonia, accompanying the complex regional pain syndrome (CRPS), which is characterized by a combination of sensory, autonomic, and other motor disturbances following trauma to a limb. This is now divided into CRPS type I (clinical syndrome not limited to the distribution of a single peripheral nerve, previously referred to as reflex sympathetic dystrophy [RSD]) and CRPS type II after partial injury of a nerve or one of its branches, often referred to previously as causalgia. Motor manifestations described in these patients include dystonic posturing, weakness, tremor, and myoclonic jerks. Despite the attention given to these motor manifestations in recent times, the pathophysiologic mechanisms remain obscure.

Van Hilten and colleagues, among others, champion the concept of multifocal or generalized tonic dystonia of complex regional pain syndrome, which they feel has an unequivocal organic basis, is associated with a particular HLA-type predisposition (HLA-DR13), and responds to intrathecal baclofen. However, many of the features reported to be typical of this disorder are also characteristic of psychogenic dystonia, including precipitation by minor injury, rapid onset with fixed postures, unusual distributions, spontaneous remissions, atypical pain and tenderness, non-anatomic sensory changes, and weakness. Verdugo and Ochoa studied 58 patients, 47 had sustained a minor physical injury at work. Patients exhibited various combinations of dystonic spasms, coarse postural or action tremor, and irregular jerks. Patients underwent rigorous clinical and laboratory evaluation aimed at characterizing their neurologic disturbance. Only patients with CRPS I or RSD displayed abnormal movements, and all patients exhibited pseudoneurologic signs, suggesting that the abnormal movements were also non-organic in nature. Features of the abnormal movements experienced by patients, such as paroxysmal worsening of dystonic postures, and the clenched fist syndrome were characteristic of psychogenic abnormal movements. Video surveillance tapes were forwarded to the clinic for 4 patients, confirming a diagnosis of malingering. The authors conclude that the abnormal movements of CRPS I are of somatoform or malingering origin. In contrast to these findings, Birklein and colleagues reported that ‘irregular myoclonic jerks and dystonic muscle contractions’ were present in 33 of 122 CRPS I patients but also in 11 of 23 CRPS II cases. This remains a controversial area. As more definitive diagnostic tools become available for psychogenic dystonia, further studies of patients with unusual forms of dystonia following minor peripheral injury will be necessary. The study of Schrag and her colleagues sheds important light on this difficult group of patients. These authors reviewed 103 patients with fixed dystonia, 41 of whom were evaluated intensively. Fifteen (36%) had clinically definite psychogenic dystonia and in only 4 (10%) was there no suggestion of a psychogenic movement disorder. Twenty-six of the 41 patients had developed dystonia following some form of peripheral injury; of these, 23 had evidence for a psychogenic cause (5 documented, 3 clinically established, and 15 probable). Fifteen of these 26 cases had evidence of CRPS, 13 of whom were diagnosed as psychogenic dystonia (3 documented, and 10, probable). Forty-one percent (7/17) of those in whom general practice notes could be obtained and evaluated had evidence for a somatization disorder and in most of these the diagnosis was only evident after review of past records was possible, raising concerns about the accuracy of the past history provided by patients with neurologically unexplained symptoms.

A similar disorder has been termed post-traumatic cervical dystonia. Our groups at the Toronto Western Hospital Movement Disorders Unit and Comprehensive Pain Program have recently evaluated 16 patients with what we prefer to designate as post-traumatic painful torticollis. These patients developed a characteristic, exceedingly painful fixed head tilt and shoulder elevation after a motor vehicle accident or work-related accident. The onset of the abnormal posturing is very often within the first week after the accident. Additional abnormalities on physical examination were common, including non-dermatomal sensory loss, give-way limb weakness, psychogenic dystonia of the limb or jaw, and psychogenic tremor. Litigation or compensation was present in all 16 patients. Oral medications commonly used for dystonia and even botulinum toxin were generally ineffective or worsened pain, although 1 patient had excellent response to both active and placebo botulinum toxin injections. Sodium amytal interview resulted in improvement in posture, pain, or both, in all 13 patients undergoing this procedure, and marked improvement or normalization of sensory deficit occurred in 7 of the 13 patients. These patients met the accepted criteria for the diagnosis of peripheral trauma-induced dystonia. However, our clinical and psychological evaluations strongly support the importance of contributing psychological factors to the etiology of this condition. As outlined in the following section, we have argued that this is a disorder occurring in psychosocially vulnerable individuals following minor physical injuries.
PSYCHOPATHOLOGY

Patients with psychogenic dystonia are considered in the Diagnostic and Statistical Manual of Mental Disorders to suffer from conversion disorder, motor subtype. Conversion disorder falls into the category of somatoform disorders. Conversion theory holds that primary or secondary gain or both underlie symptom production. Primary gain refers to the conversion of psychological distress into physical symptoms. Secondary gain refers to external factors that may be influenced by the symptom development, such as the sympathy and attention of family members. Studies of patients with motor conversion disorder have revealed a number of trends. Comorbidity between motor conversion and both Axis I (clinical disorders) and Axis II (personality disorders) is significant. In fact, the majority of patients with motor conversion have at least one comorbid Axis I diagnosis, with rates of depression ranging from 26% to 71%, and anxiety disorder present in 7–38%. Personality disorders were diagnosed in 42–67% of patients, and included a variety of personality subtypes, with dependent and borderline personalities being most common.

In the study of post-traumatic painful torticollis from our center described above, psychological evaluations suggested that psychological conflicts and/or stress were being expressed via somatic channels in 11 of 12 tested patients. The onset of physical trauma in these patients, in the context of critical psychological factors, might result in ongoing contraction and guarding of the neck and shoulder musculature associated with pain and non-dermatomal sensory deficits, a process which is primarily unconscious. It was postulated that injury may trigger poorly defined central mechanisms in psychologically vulnerable individuals who are at risk of developing these features. Indeed, other psychogenic movement disorders may also result from the triggering of such processes in vulnerable individuals, leading to motor dysfunction. Further studies are required to establish the importance of this dynamic interplay. It is critical that these include similar assessments in patients with established organic movement disorders.

NEUROIMAGING

There have been no neuroimaging studies evaluating psychogenic dystonia. One major stumbling block is the non-specific but critical confounding effect of the ongoing motor activity on widespread sensory and motor brain regions, particularly since the vast majority of patients with psychogenic dystonia maintain the abnormal postures at rest, and even in the lighter stages of sleep. The work of Eidelberg and colleagues in their studies using [18F]-fluorodeoxyglucose positron emission tomography (FDG PET) in patients with idiopathic torsion dystonia and essential blepharospasm might suggest novel approaches to the study of psychogenic dystonia. Studying clinically affected DYTI carriers in a sleep state, when involuntary movements were suppressed by sleep, allowed observation of the primary functional abnormality in brain metabolism in these patients without the secondary effects of movement (this abnormal neural network was similar to that found in asymptomatic DYTI carriers). FDG PET in awake and sleeping patients with essential blepharospasm also allowed the distinction to be made between the functional substrate of the disorder and the brain activity resulting from the clinical manifestations. Such a technique could be applied to patients with psychogenic dystonia. It will be important to compare these patients with the organic counterparts as well as normal controls feigning the same type of movements.

Interesting studies in patients with psychogenic paralysis may provide further insights or ideas of how to pursue these issues in psychogenic dystonia. For example, Marshall and colleagues measured changes in regional cerebral blood flow in a woman with longstanding left-sided paralysis due to motor conversion disorder. When the patient moved her right leg the areas activated included the dorsolateral prefrontal cortex bilaterally, and left lateral premotor areas, left primary sensorimotor cortex, bilateral secondary somatosensory areas (inferior parietal cortex), and the vermis and cerebellar hemispheres bilaterally. Preparation to move the right leg activated a subset of these areas, including the dorsolateral prefrontal cortex bilaterally, right lateral premotor and bilateral inferior parietal cortex, and the vermis and cerebellar hemispheres, but not the left primary sensorimotor cortex. Preparation to move the (paralyzed) left leg activated the left lateral premotor cortex and the cerebellar hemispheres bilaterally, indicating the patient’s readiness to move the paralyzed leg. Attempting to move the paralyzed leg led to activation of movement-related areas, including the left dorsolateral prefrontal cortex and the cerebellar hemispheres bilaterally, but no activation of the right premotor areas or of right primary sensorimotor cortex was seen. Instead, the right anterior cingulate and orbitofrontal cortices were significantly activated during this condition (when compared with preparing to move the left leg). The authors proposed that these areas actively inhibited movement of the left leg despite...
dorsolateral prefrontal cortex activation and downstream activation of the cerebellum. They proposed that the orbitofrontal cortex may be the distal source of unconscious inhibition while the anterior cingulate, which mediates emotion and action, is the proximal site that disconnects premotor/prefrontal areas from primary motor cortex. The authors speculated that in the absence of functional or structural pathology, it is a disturbance of the will to move that triggers the hemi-paralysis via pathologic activation of orbitofrontal and cingulate cortex. Supporting suggestions that hypnosis and conversion disorders are pathogenetically linked, the same researchers found that hypnotically induced paralysis of the left leg activated similar brain areas to those of motor conversion disorder.32

Other clinicians have found reversible alterations in regional cerebral blood flow in the thalamus and basal ganglia contralateral to hysterical ‘sensorimotor’ loss, with lower activation in the contralateral caudate nucleus predicting poorer recovery at follow-up.33 Functional magnetic resonance imaging (FMRI) has also been used to evaluate patients with hysterical sensory loss and functional pain syndromes.34 Similar studies in psychogenic dystonia are awaited with interest; however, as mentioned, there are important confounding factors, particularly the effects of the ongoing persistent muscle activity, which will need to be addressed if these are to provide useful pathophysiological insights.

**NEUROPHYSIOLOGIC STUDIES**

Electrophysiologic studies are extremely useful in defining the psychogenic nature of some movement disorders, most notably myoclonus and tremor.35 Unfortunately, to date, the utility of neurophysiologic assessment in psychogenic dystonia has not been established. Comparison of electromyographic (EMG) activity in the sternocleidomastoid and splenius capitis muscles of patients with idiopathic torticollis with that of controls matching the head posture or imitating tremulous torticollis has provided information regarding the pattern of rhythmic drive to the muscles of the neck which could be useful in differentiating organic from psychogenic torticollis.36 Control subjects showed a significant peak in the autospectrum of the splenius capitis EMG at 10–12 Hz, which was absent in all patients with organic torticollis. Patients with torticollis had evidence of a 4–7 Hz drive to the splenius capitis and sternocleidomastoid that was absent in coherence spectra from controls. The activity in the sternocleidomastoid and splenius capitis was in phase in patients but not in controls. These EMG features might prove useful in differentiating organic from psychogenic dystonia, although the extent to which the findings in controls can be applied to patients with psychogenic dystonia is not known.

A variety of electrophysiologic features have been defined in patients with organic forms of dystonia. However, it is unclear whether many of the electrophysiologic features described in dystonia are a primary feature of the disorder or simply secondary to the abnormal postures, in which case they would be of little help in differentiating psychogenic from non-psychogenic dystonias. For example, abnormalities of recurrent spinal inhibition are widely described in patients with dystonia.31 However, similar abnormalities of recurrent spinal inhibition are not known.

There is a great need for further electrophysiologic and imaging studies in psychogenic dystonia. However, considerable care will have to be taken to address the important confounding secondary or compensatory changes that occur as a consequence of the abnormal movements.
TREATMENT AND PROGNOSIS

Patients with psychogenic dystonia can experience profound disability due to their condition, making proper diagnosis and treatment essential. Patients with lower limb symptoms may become wheelchair-bound. Psychogenic dystonia patients may reach the point of requiring assistance for self-care tasks, lose their ability to work, and be unable to participate in activities they formally enjoyed.6

Studies of patients with psychogenic movement disorders in general, including psychogenic dystonia, show that prognosis is better in patients with a shorter duration of symptoms prior to diagnosis. In one study of 30 patients admitted to hospital with motor conversion symptoms of less than 3 months’ duration prior to diagnosis and treatment, 63% of patients had complete remission of their symptoms, 27% were improved, and only 10% were unchanged or worse after 2–5 years. The majority of patients were symptom-free within 6 months of receiving the diagnosis of conversion.40

In studies where the majority of the cases have had a long duration between initial presentation and diagnosis, remission rates have not been nearly as favorable. Rates of complete resolution of symptoms range from 10% to 28%, with the average length of time between presentation and diagnosis of 18 months to 2 years.9,27,28 However, these numbers may not represent the prognosis in unselected psychogenic dystonia since they come from movement disorders clinics, with a clear referral bias toward more severe and long-lasting cases. In collaboration with our group, Feinstein et al found a significant correlation between the mode of onset and the course of symptoms, with a more sudden onset predicting a better outcome, as well as a significant correlation between the extent of psychiatric comorbidity and the course of symptoms.27 Crimlisk and colleagues found that a new psychiatric diagnosis coinciding with the onset of symptoms prior to diagnosis and treatment, 63% of patients had complete remission of their symptoms, 27% were improved, and only 10% were unchanged or worse after 2–5 years. The majority of patients were symptom-free within 6 months of receiving the diagnosis of conversion.40

In studies where the majority of the cases have had a long duration between initial presentation and diagnosis, remission rates have not been nearly as favorable. Rates of complete resolution of symptoms range from 10% to 28%, with the average length of time between presentation and diagnosis of 18 months to 2 years.9,27,28 However, these numbers may not represent the prognosis in unselected psychogenic dystonia since they come from movement disorders clinics, with a clear referral bias toward more severe and long-lasting cases. In collaboration with our group, Feinstein et al found a significant correlation between the mode of onset and the course of symptoms, with a more sudden onset predicting a better outcome, as well as a significant correlation between the extent of psychiatric comorbidity and the course of symptoms.27 Crimlisk and colleagues found that a new psychiatric diagnosis coinciding with the onset of symptoms prior to diagnosis and treatment, 63% of patients had complete remission of their symptoms, 27% were improved, and only 10% were unchanged or worse after 2–5 years. The majority of patients were symptom-free within 6 months of receiving the diagnosis of conversion.40

In dealing with these patients, appropriate investigation should be undertaken to exclude organic dystonia and reassure the patient and clinician that no organic basis for the symptoms has been overlooked. This should be completed before the diagnosis of psychogenic dystonia is raised with the patient. Fahn and Williams recommended that patients suspected of having psychogenic dystonia be admitted to hospital.5,9 This is due to the reluctance of most patients to accept a psychological explanation for their symptoms, and concern regarding proper follow-up and treatment once this diagnosis is made. It will also expedite the completion of any necessary investigation and allow more intensive observation and evaluation. Certainly, we would agree that this is necessary for complex cases where the diagnosis is uncertain or for the more entrenched and long-standing symptoms, especially when profound disability is present. On the other hand, this approach is not mandatory in all patients and the benefit of such intensive care to long-term outcome has not been proven. Placebo and suggestion can be used to exacerbate movements or relieve them, and may provide further diagnostic information. Utilization of placebo is controversial, and there are legal and ethical concerns. The deception that it implies can endanger the physician–patient relationship. Furthermore, the response to placebo is typically not lasting, and further treatment will be necessary. Psychiatric consultation should be obtained to identify coexisting psychopathology or psychosocial issues which can be treated accordingly. The collaboration between the neurologist and the psychiatrist is of great importance. It would be counterproductive and detrimental to the patient if the psychiatrist expresses doubt regarding the psychological basis of the disorder and insists on further investigation for an organic etiology. It is also important, as emphasized earlier in the chapter, that underlying psychiatric disturbances in a patient with dystonia not be accepted as causative of the movement disorder, especially when the clinical features are compatible with idiopathic or symptomatic forms of dystonia.

Cases of unequivocal malingering and rare examples of Munchausen syndrome are dealt with quite differently than those with conversion disorder. Individuals with the former two conditions are consciously and purposefully causing their symptoms for financial or psychological gain. We will not discuss these further.

In patients with conversion disorder, the diagnosis of psychogenic dystonia should be presented in an assertive but supportive fashion only after the diagnosis is certain and planned investigations are complete. The absence of a severe neurologic disorder should be stated clearly. This should be emphasized in a very positive light, underscoring the potential for recovery in view of the absence of an underlying ‘brain disease’. The unconscious nature of symptom production should be explained (i.e. emphasizing that it is not believed that the patient is feigning or purposefully causing the symptoms), as well as the ability of psychological conflicts to express themselves via somatic channels. Preferably, both neurologist and psychiatrist should participate in this exercise. Providing analogies of physical symptoms commonly accepted (correctly or not) as caused by stress by the lay public such as high blood pressure, duodenal ulcer, chest or abdominal pains, dermatitis, etc. helps the
patient and family to understand the potential for psychological factors to induce dystonia. We often emphasize the interactions or ‘connections’ of the large parts of the brain involved in emotional or psychological function with those that control movement and posture. Treatment employing psychotherapy, physical therapy, and psychopharmacologic therapy may be necessary and, when appropriate, should be started in hospital. Intensive follow-up is required for the best outcome, although considerable research is required to evaluate the impact of various possible treatment strategies. Outcomes are generally poor when patients are simply given the diagnosis and returned to their referring physician for ongoing management or it is left to the referring physician to discuss the diagnosis and arrange further care.

CONCLUSION

Psychogenic dystonia is a rare cause of dystonia, but does occur and often results in profound disability. It is difficult to diagnose with certainty, and this should only be undertaken by a neurologist with considerable experience with organic dystonias. A great deal of controversy surrounds the primary role of psychological factors in the pathogenesis of dystonia following minor injury. The pathophysiology of psychogenic dystonia is poorly understood, but may improve with novel neuroimaging techniques or the development of new electrophysiologic strategies. Prompt diagnosis and treatment is necessary, given the poor prognosis of conversion disorders when considerable delays occur between symptom onset and diagnosis. There is a major need for research evaluating various treatment options, given the overall poor prognosis experienced by these patients.

REFERENCES

INTRODUCTION

The last decade has seen an increase in the treatment options for many forms of dystonia, primarily due to the dramatic expansion in the use of botulinum toxin (BTX) and the more recent application of deep brain stimulation to both childhood and adult dystonia. During this period, despite the discovery of the DYT1 gene, there have been few new developments in the pharmacologic treatment of dystonia. Nonetheless, there still is an important role for drug therapy of both idiopathic and some symptomatic forms of dystonia:

- Patients with dopa-responsive dystonia (DRD) have dramatic, sustained improvement taking small doses of levodopa. Unless an alternative diagnosis is certain (e.g. a gene for an alternative form of dystonia has been found in the family), a trial of levodopa as initial therapy should be strongly considered. This applies primarily to childhood-onset dystonia, but patients with adult-onset dystonia and a history of a relative with childhood-onset dystonia might also be candidates for a trial of levodopa.

- Many children with dystonia have disabling symptoms in multiple regions of the body, so that the use of BTX injections as sole therapy is impractical. Despite the reassuring safety record of BTX to date, the consequences of chronic BTX injections over multiple decades are unknown. It is, therefore, preferable to treat children with medication when possible.

- Most patients with adult-onset dystonia have symptoms primarily in one region of the body (usually involving neck, upper face, vocal cords, upper extremity, or oromandibular muscles). Some patients, however, require treatment of muscles that are not limited to a single segment and it may not be practical to inject BTX into a sufficient number of contracting muscles. These patients may be candidates for medication trials.

- Some patients with focal or segmental dystonia will fail to improve significantly after BTX treatment or develop resistance to the injections. Until there is more data about the role of deep brain stimulation in focal, adult-onset dystonia, these patients may benefit from medications.

I will discuss the most common medications used to treat dystonia, considering the evidence for efficacy, indications, and adverse effects. In uncontrolled studies, small response rates may suggest placebo effect. However, it is well to keep in mind that even well-designed prospective, placebo-controlled trials may fail to detect significant benefit that occurs in only a small percentage of patients.

DOPAMINERGIC AGENTS

Patients with Segawa variant dystonia or DRD usually develop symptoms in the lower extremities before puberty and may have parkinsonism, corticospinal tract signs, improvement after sleep, and a family history of levodopa-responsive dystonia. Patients with DRD improve dramatically with small doses of levodopa – ranging from 50 mg/day to 900 mg/day of levodopa with decarboxylase inhibitor (mean = 250 mg/day). It is necessary to initiate therapy with very small doses of levodopa (usually 50 mg/day) because higher doses may produce unpleasant dyskinesias. Supplemental carbidopa may be necessary at these low doses to prevent nausea. Symptoms in these patients may also improve with dopamine agonists or anticholinergic medications. If there is any chance that a patient has DRD, a trial of Sinemet (carbidopa + levodopa) should be performed.

The results of controlled, oral studies of dopaminergic agents in dystonia have been contradictory. Several small controlled studies found benefit from bromocriptine
or lisuride.4–8 Other studies failed to find such benefit from bromocriptine, amantadine, or levodopa.4–8 An early review of studies up to 1985 concluded that improvement from dopaminergic agents was rarely dramatic, and that these agents worsened symptoms in almost 20% of patients.14 Later open-label reports came to similar conclusions.15,16 Despite these disappointing results, an occasional patient with non-DRD does seem to improve, suggesting more than a placebo response.17

Most patients with dystonia tolerate dopaminergic agents well. Nausea, orthostatic hypotension, confusion or hallucinations and dopa dyskinesias have been reported in patients with dystonia, but are uncommon. However, a substantial minority will experience worsening of symptoms or the development of superimposed levodopa dyskinesias.

**ANTICHOLINERGICS**

A prospective, placebo-controlled, study documented the efficacy of high-dose trihexyphenidyl in alleviating the symptoms of dystonia in children and young adults.18 Thirty-one childhood-onset patients were studied, with a mean age at time of treatment of 18.6 years: 67% of patients treated with trihexyphenidyl improved, which was significantly better than those treated with placebo; 68% continued to benefit from trihexyphenidyl after a mean 2.4 years at a mean dose of 40 mg/day. There has not been another prospective controlled study in children, although uncontrolled reports have found similar benefit in children.12,19,20 One retrospective study found only modest benefit in patients with DYT1 dystonia, but the age at therapy was not specified.21 Several case reports and small series have suggested that anticholinergics may be effective for children and young adults with dystonia after cerebral infarct,22 cerebral hemorrhage,23 delayed-onset dystonia after birth injury,24 and other causes.25

It has been more difficult to determine the effectiveness of oral anticholinergic agents in treating adults with focal dystonia. There have been several small prospective studies of the acute administration of anticholinergic agents (usually by the intravenous or intramuscular route) in adult-onset dystonia.4,13,26–28 These older studies had varying degrees of control and blinding and concluded that acute administration of anticholinergics is effective in dystonia and predicts long-term improvement with oral anticholinergic agents. However, a somewhat larger study found no statistically significant benefit and attributed the modest benefit to sedation.29 None of three published prospective studies of oral anticholinergics in adult-onset dystonia meet modern criteria for well-designed studies.12,30,31 One open-label study of 38 patients using blinded ratings found benefit in 45% of patients with a mean dose of 23 mg/day of trihexyphenidyl.31 Anticholinergics were not well tolerated, and many patients stopped medication due to forgetfulness, constipation, dry mouth, blurred vision, etc.

In addition to the studies cited above, there are open-label reports of the use of anticholinergics in adults with dystonia, some finding benefit15,19,32–34 and others finding minimal if any benefit.16,29,35

In both children and adults, the dose of anticholinergic medications must be increased gradually if side effects are to be avoided. Benefit may not appear for many weeks on a constant dose, and so lengthy trials are more likely to be productive.18 Most patients require high doses of anticholinergic agents before improvement is seen. The effective dose varies from patient to patient and from agent to agent. For example, the published effective doses of trihexyphenidyl vary from 5 mg/day to 120 mg/day,15 and of ethopropazine from 50 mg/day to 800 mg/day.15 Many anticholinergics have been used to treat dystonia, including trihexyphenidyl, benztropine, biperiden, ethopropazine, atropine, procyclidine, orphenadrine, scopolamine, and trans-derm scopolamine. Side effects may vary from agent to agent, so that switching anticholinergic medications is sometimes helpful. Peripheral side effects such as blurred vision, constipation, dry mouth, and urinary retention can usually be treated with pilocarpine eye drops for blurred vision and with pyridostigmine for the other side effects. Central nervous system side effects such as short-term memory loss, confusion, or psychosis are frequently dose-limiting, especially in adults. Other central side effects occasionally occur, such as restlessness, chorea, or exacerbation of a pre-existing tic disorder.19 Abrupt withdrawal of anticholinergics may not only precipitate cholinergic crisis but may also cause dramatic increase in dystonia.36

**BACLOFEN**

Baclofen is a derivative of γ-aminobutyric acid (GABA) that reduces spinal cord interneuron and motor neuron excitability, possibly via activation of the presynaptic GABA_{B} receptor by the L isomer.37 There have been no controlled studies of baclofen in the treatment of dystonia, but in retrospective studies at the Movement Disorder Center at Columbia Medical Center, we found baclofen to be of marked benefit in a significant minority of children and of some benefit in a small minority of adults with dystonia.15,38–40 Baclofen was the medication most often used in one study of patients with DYT1 dystonia, but age at therapy was not specified.21
In other small series, there was no significant benefit from baclofen. There have been several reports of improvement in dystonia in a handful of patients with various focal dystonias using a combination of baclofen and valproate.

Side effects are a major limiting factor in treating adults with baclofen. Even with gradual increase in dosage, lethargy, upset stomach, dizziness, ‘floppiness’, dry mouth, or urinary urgency or hesitation prevent treatment with high doses of baclofen in many patients. Confusion, hallucinosis, and paranoia have been reported, but are rare. Rapid decrease in the dose of baclofen may precipitate psychosis or seizures, so all patients should be warned not to discontinue baclofen abruptly. Baclofen is better tolerated in children, although the same kinds of side effects can be seen.

**BENZODIAZEPINES**

Benzodiazepines are frequently used in the treatment of dystonia, but documentation of benefit in well-designed controlled studies is lacking. There have been many uncontrolled reports of benefit from benzodiazepines, including clonazepam, diazepam, and others. Benzodiazepines were the medications most often successful in one series of patients with symptomatic hemidystonia. Sedation and ataxia are the limiting side effects for most patients taking benzodiazepines. Patients with dystonia can sometimes tolerate very large doses of benzodiazepines if the doses are increased gradually. Some patients taking high doses of clonazepam become irritable. Nocturnal drooling and depression are possible side effects of benzodiazepines, but seem to be rare. There is always concern that patients taking benzodiazepines may develop withdrawal on stopping the medication, or develop tachyphylaxis. Patients with dystonia do get withdrawal symptoms if benzodiazepine doses are lowered rapidly, and it may be difficult to determine if the resulting worsening of dystonia represents evidence that the medication produced unsuspected benefit. We have rarely seen tachyphylaxis in patients with dystonia.

**ANTIDOPAMINERGIC AGENTS**

Paradoxically, occasional patients with dystonia seem to improve with a variety of antidopaminergic agents. Some controlled studies with pimozide and the investigational dopamine depleter/dopamine receptor blocker tetrabenazine found benefit. Other controlled studies found no benefit. Open-label studies with pimozide, haloperidol, α-methylparatyrosine, or tetrabenazine have also produced mixed results: some studies reported benefit, whereas other studies found improvement in only 9–11% of patients. Some patients seemed to improve with the combination of tetrabenazine and lithium. Patients with severe dystonia, or acute exacerbation of dystonia (‘dystonic storm’) sometimes improve with the combination of a dopamine receptor blocker, a dopamine depleter, and an anticholinergic agent. In the case of tardive dystonia, dopamine depleters such as reserpine and tetrabenazine are especially useful.

With the exception of reserpine, tetrabenazine and the atypical neuroleptic clozapine, dopamine receptor blockers can produce tardive symptoms (akathisia, dyskinesias, or even dystonia) in patients with dystonia, and these may become more disabling than the original symptoms. At this time, clozapine is the only atypical neuroleptic that does not produce tardive syndromes, although there are very few reports of tardive syndromes from the atypical neuroleptic quetiapine. Clozapine and quetiapine have both been
reported to help some patients with tardive dystonia affecting various parts of the body. Clozapine was effective in some patients with idiopathic dystonia but not in others.71 One single-blinded, uncontrolled study found clozapine to benefit the jerky movements in spasmodic torticollis but not the head deviation.72 In addition to the risk of tardive syndromes, patients with dystonia often tolerate antidopaminergic agents poorly. Sedation, apathy, nausea, orthostatic hypotension, insomnia, acute dystonic reactions, acute akathisia, worsening of dystonic symptoms, and confusion have all been seen with these agents, but usually can be reversed with reduction in dose or discontinuation of the medication. Depression, especially with dopamine depleters, is uncommon, but can be severe and can be life threatening if not recognized and treated, usually with reduction in dose. Drug-induced parkinsonism is often the limiting factor in treating patients who seem to benefit from dopamine depleters. The parkinsonism is reversible and dose dependent and can be controlled with reduction in dose. Unfortunately, dystonia does not improve in some patients until parkinsonism appears. In these patients, parkinson symptoms may be reduced by the addition of anticholinergic agents, amantadine, or levodopa. This is not always effective, however, and addition of dopaminergic agents may also reverse improvement in dystonic symptoms induced by the antidopaminergic treatment.

CARBAMAZEPINE

Carbamazepine occasionally produces dystonia as a toxic effect in patients treated for seizures.73 Paradoxically, it has been reported to treat dystonia in some uncontrolled series.15,74,75 Some carbamazepine successes may have been patients with DRD, since these patients improve with carbamazepine, although not to the same degree as with levodopa.3 However, some patients who improved with carbamazepine did not have DRD, as they did not improve with levodopa.74,75 Patients with paroxysmal kinesigenic dystonia improve dramatically with carbamazepine, phenytoin, and other anticonvulsants.76

OTHER AGENTS

Many other medications have been used to treat dystonia in isolated cases. Tricyclic antidepressants,15,47,49 dantrolene,47 propranolol,31 phenytoin,49 clonidine,15,26 monoamine oxidase (MAO) inhibitors,77 barbiturates,77 and t-tryptophan78 have generally not been noted to produce improvement in the small number of cases tried. Sporadic reports of improvement with amphetamines have not been vigorously pursued. Tetrahydrobiopterin has been reported to benefit some patients with dystonia,80 but most of these patients probably had DRD. Double-blind studies of the GABAergic agent γ-vinyl GABA81 and the muscle relaxant tizanidine82 did not document benefit in dystonia. A subsequent open trial of tizanidine (with an initial placebo wash-in) in 9 patients with cranial dystonia found that 22% (2/9) improved at tolerated doses, and benefit was transient in both of these.83 Antihistamines have occasionally been reported to produce benefit, and it has been suggested that the effect may not be entirely due to their anticholinergic properties.84,85 Cyproheptadine, which has serotonin antagonist properties, has been reported to help dystonia in two reports by the same group.86,87 5-Hydroxytryptophan, a serotonin precursor, was reported to benefit some patients with torticollis but not patients with Meige syndrome.77 Individual reports claimed benefit from salmon calcitonin and cannabidiol.90 Lasting benefit using lithium was reported in 26% (9/34) of patients with torticollis and cranial dystonia, but only 4 of these improved on lithium alone.83 Mexiletine, an oral antiarrhythmic related to lidocaine, was found to be of benefit in uncontrolled studies in small numbers of patients with torticollis, blepharospasm, and generalized dystonia.91–93 Riluzole was described to benefit some patients with torticollis in an uncontrolled study with blinded video ratings.94 Despite some anecdotal reports of benefit in focal and generalized dystonia with levetiracetam,95,96 a prospective, uncontrolled study in 10 patients found no benefit in any of the 7 patients that tolerated the planned dose target of 1000 mg twice a day.97

SUMMARY

Treating dystonia requires patience and persistence on the part of the patient, family, and physician. Medications are often successful in children and adolescents and a large minority of patients improve dramatically. Unless surgery becomes a first-line treatment for dystonia in children, medications will remain the mainstay of therapy. A L-dopa trial is often the first maneuver. Anticholinergics remain the medication most likely to produce benefit in most children, but baclofen and benzodiazepines remain reasonable options. Treatment with the other medications listed above may be appropriate where surgery is inappropriate or ineffective. While dopamine receptor blocking agents may help a small percentage of patients, the risk of tardive syndromes makes the use of these agents undesirable except for the most severely affected patients. Medications are
much less effective in adults, and many adults can benefit from botulinum toxin or surgical procedures. Medications remain an option for selected adults, as outlined above. With the exception of dopaminergic agents, which are much less likely to benefit adults, medication trials in adults proceed in the same order as trials in children.

REFERENCES

188 CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA

INTRODUCTION

Dystonia is a neurologic disorder characterized by sustained, repetitive, and patterned muscle contractions that produce twisting and repetitive movements or abnormal postures. Dystonia can be generalized and affect many regions of the body, including the trunk and legs, or it can be relatively focal or segmental. Focal dystonia affects a single body part and includes cervical dystonia (CD; also known as spasmodic torticollis), blepharospasm (bilateral, involuntary, synchronous, forceful eye closure), oromandibular dystonia (OMD; forceful involuntary jaw opening or closing), laryngeal dystonia (LD; spasmodic dysphonia – strained or breathy voice), and limb dystonias (task-specific focal dystonia such as writer’s cramp or other occupational cramps). Generalized dystonia is usually treated with orally administered medications, intrathecal baclofen infusions, or surgery such as ablation or high-frequency stimulation of the globus pallidus or thalamus. Because of its local action, restricted to or near the site of intramuscular injection, and thus limiting side effects, botulinum toxin (BTX) has become the predominant mode of therapy for focal and segmental dystonias. The use of BTX in different forms of dystonias is covered in the respective chapters and, therefore, we concentrate here on the overlapping BTX-related issues common to all the dystonic disorders.

HISTORY

Justinus Kerner first described the clinical symptoms of food-borne botulism between 1817 and 1822 and also suggested a possible therapeutic use of BTX, which he called ‘sausage poison’. The symptoms associated with BTX poisoning can be categorized as generalized (fatigue, dizziness), oculomotor (double and blurred vision), oral (dysphagia, dry mouth, dysarthria, sore throat), gastrointestinal (GI) (constipation, nausea, vomiting, abdominal cramps, diarrhea), and somatic (bulbar, arm, leg, and diaphragmatic and chest muscle weakness, and paresthesias). Botulism can be incurred not from only GI intake but also through the skin. This was initially seen after traumatic or surgical wounds, described in 1943, and after drug abuse in the mid-1980s. In 1895, Emile Van Ermengem first isolated the bacterium Clostridium botulinum; in 1944, Edward Schantz cultured C. botulinum and isolated the toxin; and in 1949, Burgen et al discovered that BTX blocks neuromuscular transmission. The first medical use for botulinum toxin was conceived and implemented by Alan Scott in 1973 for strabismus.

BTX consists of a naturally occurring group of seven peptides, produced by C. botulinum (CB). These are immunologically distinct neurotoxin serotypes produced by different strains of the bacterium. In addition, this bacterium also produces tetanus toxin, which acts in a similar manner.

Botulinum toxin type A (BTX-A) is the serotype used most extensively in clinical practice. A formulation of BTX-A approved for clinical use in the USA in December 1989, Botox (Allergan), was based largely on the results of two double-blind, placebo-controlled studies. Many different botulinum toxins are now available on the market in one or more countries (Table 18.1). Four of them contain BTX-A (Botox, Dysport, Xeomin, and CBTXA), as well as a new preparation, free of complexing proteins (NT 201), and the other contains BTX type B (BTX-B; Myobloc/NeuroBloc).

Initially approved under the Orphan Drug Act, for the treatment of blepharospasm and hemifacial spasm (HFS) and strabismus, Botox was approved in December 2000 for the treatment of CD. At the same time, BTX-B (Myobloc in the USA, NeuroBloc in Europe; Elan...
### Table 18.1 Commercially available formulations of botulinum toxin and some characteristics

<table>
<thead>
<tr>
<th></th>
<th>Botox</th>
<th>Dysport</th>
<th>Xeomin</th>
<th>Chinese type A botulinum toxin (CBTX-A)</th>
<th>Neuronox</th>
<th>Myobloc/NeuroBloc</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Allergan, Inc., Irvine, CA, USA</td>
<td>Ipsen Ltd, Slough, Berks, UK</td>
<td>Merz Pharmaceuticals, Frankfurt, Germany</td>
<td>Lanzhou Institute of Biological Products, Lanzhou, China</td>
<td>CJ Corp/Medy-Tox, Inc., South Korea</td>
<td>Elan plc, Dublin, Ireland</td>
</tr>
<tr>
<td><strong>BTX serotype</strong></td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>B</td>
</tr>
<tr>
<td><strong>Strain</strong></td>
<td>Hall A</td>
<td>Ipsen strain</td>
<td>Hall A</td>
<td>A</td>
<td>A</td>
<td>Bean B</td>
</tr>
<tr>
<td><strong>Site of SNARE hydrolysis</strong></td>
<td>SNAP-25</td>
<td>SNAP-25</td>
<td>SNAP-25</td>
<td>SNAP-25</td>
<td>SNAP-25β</td>
<td>VAMP</td>
</tr>
<tr>
<td><strong>Conversion factor (from Botox)</strong></td>
<td>1a</td>
<td>3a</td>
<td>1a</td>
<td>1.08c</td>
<td>1a</td>
<td>40a</td>
</tr>
<tr>
<td><strong>Reconstituted pH</strong></td>
<td>Lyophilized</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
<td>Lyophilized</td>
<td>Solubilized</td>
</tr>
<tr>
<td><strong>Specific biological potency, mouse units/ng BNT</strong></td>
<td>7.4/60</td>
<td>7.4/100</td>
<td>7.4/167</td>
<td>6.0/?</td>
<td>6.8/5</td>
<td>5/5</td>
</tr>
<tr>
<td><strong>Other constituents (per vial)</strong></td>
<td>HAS 500 μg</td>
<td>HSA 125 μg</td>
<td>HSA 1 mg</td>
<td>Gelatin 5mg</td>
<td>HSA 500 μg</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>NaCl 900 μg</td>
<td>Lactose 2500 μg</td>
<td>Sucrose 5 mg</td>
<td>Dextran 25 mg</td>
<td>NaCl 900 μg</td>
<td>?</td>
</tr>
<tr>
<td><strong>Stability (months)</strong></td>
<td>24</td>
<td>15</td>
<td>36</td>
<td>?</td>
<td>?</td>
<td>24</td>
</tr>
<tr>
<td><strong>Product-specific units/vial</strong></td>
<td>100</td>
<td>500</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>1.0/2.5/10.0 x 10^3</td>
</tr>
</tbody>
</table>

BTN = botulinum neurotoxin; HSA = human serum albumin.

*a From Dressler.*

*b From manufacturer PDF.

*c From Tang and Wan.*

*d From Tang and Wan.*
Pharmaceuticals) was approved for treatment of CD. Botulinum toxins are now used for a large number of disorders of hyperactive muscles or glands, although official approval is for a much smaller number of indications.

In the USA, both Botox and Myobloc are approved for cervical dystonia. In addition, Botox has been approved in the USA, for axillary hyperhidrosis and moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity (frown lines) in adult patients less than 65 years of age.

**BOTULINUM TOXIN – BASIC SCIENCE**

**Preparation of botulinum toxin**

Current preparations of BTX are harvested and purified from the medium of cultured CB, as opposed to in-vitro synthesis. BTX-A is the serotype used most extensively in clinical practice. The material used from 1989 until 1998 (specifically for Botox) was a single batch prepared from the Hall strain of CB and consisted of a protein complex containing the neurotoxin as well as non-neurotoxic proteins. A new batch of Botox, used since 1998, has higher neurotoxic activity per mg of protein and, therefore, seems to be less antigenic (see below). While Botox is a freeze-dried preparation, Myobloc is marketed in a solubilized form.

**Chemistry**

Several excellent reviews of the pharmacology of BTX have been published and the reader is referred to these publications for additional information. The botulinum neurotoxins act enzymatically at the neuromuscular junction to cleave a number of nerve terminal proteins critical to normal neurotransmitter release. Three proteins form the so-called SNARE complex: vesicle-associated membrane protein (VAMP), syntaxin, and SNAP-25 (synaptosomal protein with a molecular weight of 25 kDa). VAMP, also known as synaptobrevin, is attached to the membrane of transmitter-containing vesicles. Syntaxin and SNAP-25 are located on the inner plasma membrane of the nerve terminal. Soluble NSF (N-ethylmaleimide sensitive factor) attachment protein binds tightly to this preformed complex, which permits the association of NSF, from which is derived the term SNARE (soluble N-ethylmaleimide sensitive factor attachment protein receptor). The SNARE complex serves an essential role in synaptic transmission by bringing the synaptic vesicle membrane into close proximity to the plasma membrane to allow exocytosis of acetylcholine (ACh) or other transmitters into the synaptic cleft. This complex forms a multimeric array around the vesicle attachment site, although the exact stoichiometry of this is not known at the moment.

The BTX molecule is synthesized as a single chain and then cleaved to form a two-chain molecule with a disulfide bond joining a heavy chain and a light chain. The proposed mechanism of action involves three steps (Figure 18.1).

First, the toxin binds to a membrane receptor via the heavy chain. This imparts specificity to the site of action of BTX, as BTX introduced intracellularly can impair exocytosis in any cell. The nature of this receptor is complicated and has been the subject of years of speculation and inquiry. Current evidence suggests that the receptors are composed of gangliosides and proteins that cooperate to form high-affinity toxin-binding sites. Gangliosides seem to constitute relatively low-affinity toxin-binding sites that serve to capture *Clostridium* neurotoxins to facilitate interactions with cell surface receptor proteins. Gangliosides are ubiquitous glycosphingolipids in the outer leaflet of plasma membranes. They are classified according to the number and position of sialic acids present. Polysialogangliosides, which are present almost exclusively in neurons and neuroendocrine cells, bind to *Clostridium* neurotoxins with the greatest affinity. The protein components have recently been identified. SV2 and synaptotagmin (specifically synaptotagmin I and II), also known as Syt I and Syt II, are two proteins that span the membrane of synaptic vesicles and have domains that lie within the lumen of the vesicle. These luminal domains are exposed during cycles of exo-endocytosis. BTX-A binds to the intraluminal domain of SV2, which acts as a high-affinity binding component of the BTX-A receptor complex. SV2 is involved in regulating the presynaptic interactions with calcium that drive vesicular exocytosis. BTX-B binds to synaptotagmins I and II. This interaction is stoichiometric, highly specific, facilitated by gangliosides, and is mediated by a region of Syt that is transiently exposed outside of cells during exocytosis. Cholinergic neurons at the neuromuscular junction express Syt II and are the major physiologic target of BTX-B. Using motor neurons that innervate the diaphragm, binding and uptake of BTX-B is activity-dependent and can be blocked by synaptotagmin fragments in conjunction with gangliosides at the neuromuscular junction. Synaptotagmin I (Syt I) is a less effective receptor, but at high local ganglioside concentrations, Syt I may also mediate entry of BTX-B into neurons that lack Syt II. Therefore, the sensitivity of a particular neuron terminal to BTX-B might depend on the local levels of gangliosides and whether it expresses Syt I or Syt II. Exposure of these receptors at the surface of nerve terminals also increases when a synapse...
releases more ACh (i.e. actively exocytosing), thus giving the toxins an additional advantage of preferably attacking active nerve terminals. The identification of two structurally unrelated receptors for BTX-A and BTX-B sheds new light on a remarkable evolutionary adaptation. Although the toxins originated from a common ancestral precursor protein, both the A and the B chains have evolved to interact with structurally very different proteins. Syt-II also acts as receptor for BTX-G.33–35

It is important to remember that even if cholinergic receptors are required for BTX entry into an intact neuron, that does not mean that there is specificity for inhibition of ACh release. First, there are a variety of co-transmitters with ACh in ‘cholinergic’ neurons36 and vesicular release of those co-transmitters is impaired as much as ACh, once the toxin is in the cell.

Secondly, the heavy and light chains are internalized (endocytosis). As the pH inside the endocytosome decreases, the disulfide bond that joins the heavy and light chain is enzymatically cleaved and the light chain then dissociates and is exocytosed into the cytoplasm of the presynaptic terminal.

The third step is proteolysis. Once the light chain is cleaved free, it is able to act as a zinc endopeptidase that lysys its target protein, thus preventing proper docking of the presynaptic ACh vesicle with the presynaptic membrane, and blocking the release of the neurotransmitter into the neuromuscular junction. Toxin serotypes A, C, and E hydrolyze SNAP-25, whereas serotypes B, D, F, and G cleave VAMP. BTX type C additionally cleaves syntaxin.37 Besides lysing and inactivating the cleaved protein, the product of this hydrolysis is a truncated peptide. It has been shown that these
truncated peptides can further interfere with normal organelle trafficking at the synaptic ending and the longer these abnormal truncated peptides persist, the longer the physiologic dysfunction. The different toxins create different and differentially acting truncated peptides. In addition, the protease activity associated with the different serotypes persists for different lengths of time. Although the actual duration of the effect of different BTX serotypes varies in different species and preparations, the rank ordering does not. In an interesting biochemical study performed in rat cerebellar neurons (since these experiments are not practical at motor nerve endings), the authors quantified the half-life of the effect of each toxin, the speed of replenishment of their substrates, and the degradation of the cleaved products. The half-lives of inhibition for BTX-A, BTX-C, BTX-B, BTX-F, and BTX-E were approximately 31, 25, 10, 2, and 0.8 days, respectively. This is equivalent to the neuromuscular paralysis times found in mice, and the recovery of neurotransmitter release coincided with the reappearance of the intact SNAREs. A limiting factor for the short in-vivo duration of action of BTX-F and BTX-E is the replenishment of synaptobrevin or SNAP-25, whereas the longer action of BTX-A, BTX-B, or BTX-C results from the persistence of protease activity. Hydrolysis of the intracellular docking proteins causes a functional denervation at the neuromuscular junction. When BTX-A was injected into human extensor digitorum brevis (EDB), all EDB motor action potentials decreased within 48 hours, with peak decline at day 21, whereas atrophy peaked at day 42. With time (>28 days in rats) there is associated sprouting however, a second, distinct phase of the recovery process followed, with a return of vesicle turnover to the original terminals, accompanied by an elimination of the by then superfluous sprouts. It is not clear what happens with multiple injection cycles over long periods of time, but after true denervation (e.g. after peripheral nerve transaction) there is a limited period of time in which reinnervation remains possible. It is not known if this happens with chronic BTX therapy.

**How does botulinum toxin work in dystonia?**

Although it seems that the mechanism of BTX action is via denervation of motor endplates, other potential mechanisms of action have been proposed. For example, one of the most striking and important features of BTX treatment is its ability to decrease associated sensory symptoms. The potential analgesic effect of BTX was first suggested by the observation that a higher-than-expected percentage of patients with CD experienced decreased pain and burning than could be attributed to an observable decrease in the intensity and severity of dystonic movements. BTX is extremely potent in inhibition of release, and possibly enzymatic hydrolysis of, substance P, which may be important in myopathic pain. As a result, BTX is now being intensely studied as a potential analgesic. Using a randomized, double-blind, paired study design, Sycha et al compared the effects of 100 mouse units of BTX vs pure saline and found no direct effect on acute, non-inflammatory pain and failed to observe any anti-inflammatory effects of BTX. The strong placebo effect should always be considered when designing and interpreting studies of BTX treatment of pain disorders. Studies examining the effect of BTX on sensory (primarily pain) thresholds have generally not found an effect, although they may show alterations in secondary effector-mediated responses such as neurogenic flare. It is likely that sensory processes are involved at some point, as there is evidence that BTX treatment can result in changes in the central nervous system (CNS). Blood et al used diffusion tensor imaging to examine six patients with primary focal dystonias. They found that all patients exhibited an abnormal white matter hemispheric asymmetry in a focal region between the pallidum and the thalamus. This asymmetry was absent 4 weeks after the same patients were treated with intramuscular botulinum toxin injections. Secondary alteration of central sensorimotor physiology and an additional primary effect on muscle spindle function may be critical in the long-term efficacy of BTX in dystonia. One study demonstrated differential suppression of the tonic vibration reflex (TVR) by BTX-A treatment. Specifically, 10 patients with writer’s cramp were evaluated electrophysiologically before and 3 weeks after treatment. The ratio between pre- and postinjection values of maximal M-wave (M-max), maximal voluntary contraction (MVC), and TVR were measured in the injected wrist muscles. In all the subjects, BTX-A injection reduced the TVR more than the M-max and MVC. Long-term evaluation of 2 patients disclosed that, after 7 months, when some clinical benefits persisted, M-max and MVC had fully recovered, whereas the TVR was still depressed. The authors suggest that ‘this special sensitivity of the TVR to suppression by BTX-A injection could be mediated by the chemodenervation of intrafusal muscle fibers, leading to a reduction in spindle inflow to the central nervous system during vibration’. This alteration in spindle afferent activity might form the basis for the treatment of dystonia with muscle afferent block as well as providing a mechanism for BTX to alter sensory input to the CNS.
Dose equivalence and comparative actions of BTX preparations

Dose equivalence between formulations of BTX, even of the same serotype, remains problematic. All BTX preparations are standardized to the same type of bioassay, but the units are not therapeutically equivalent, although the reason is not clear. The two initial manufacturers of BTX-A use somewhat different bioassay methodologies, including different dilution media, which differentially activate the enzyme. The activity of the preparations has been expressed as mouse units, where 1 unit (U) is the median lethal intraperitoneal dose in mice. This assay measures the potency of the toxin–protein complex to traverse the journey from peritoneum to site of lethality (probably the respiratory and laryngeal musculature); thus, factors protective in the systemic milieu that increase potency in this assay, such as the non-neurotoxic proteins that are part of the BTX complex, may be irrelevant in the milieu of the muscle itself. In one direct comparison study using the same mouse lethality assay system, Botox was 2.86 times as potent as Dysport, which is close to other estimates of Dysport:Botox ratio. In another study of CD, Dysport at 3:1 was a little more effective than Botox, with a few more side effects, suggesting an equivalency ratio less than 3:1, whereas a study on writer’s cramp found that 1 unit of Botox was roughly equivalent to about 3.5 units of Dysport. A bioassay that assesses local effects of regional denervation in muscle may be an appropriate method to assess relative potency of BTX, but in-vitro assays have been also proposed. It has been suggested that each BTX product can be considered as a unique drug and the idea of standard assay can be abandoned.

Calculating equivalent doses of BTX-A and BTX-B is even more uncertain. Sloop et al compared the dose–response (DR) curves, maximal paralysis, and post-exercise M-wave facilitation of BTX-A and BTX-B by injecting in EDB. They demonstrated that human muscle paralysis resulting from BTX-B injection is not as complete or long-lasting as that resulting from BTX-A. Whether M-wave amplitude is a reliable measure of clinical response and whether the doses of BTX-A and BTX-B, with B/A ratio of about 45:1, are comparable is, however, debatable. There is some evidence in patients who receive BTX for cosmesis that BTX-B has a quicker onset of action and BTX-A has longer benefit for glabellar wrinkles, but this has not been confirmed by well-designed, controlled studies. One controlled, but not blinded, study of 30 consecutive patients treated with BTX-B, of which 5 patients also received BTX-A, suggested that BTX-B may have more autonomic side effects than BTX-A, an observation consistent with descriptions of clinical botulism. In patients with CD, side effects consisted of dryness of mouth (total 21/24, duration 4.4 ± 2.0 SD weeks, 10 severe, 7 moderate, 4 mild), accommodation difficulties (7), conjunctival irritation (5), reduced sweating (4), swallowing difficulties (3), heartburn (3), constipation (3), bladder voiding difficulties (2), head instability (1), dryness of nasal mucosa (1), and thrush (1). In 6 patients with focal hyperhidrosis, side effects consisted of accommodation difficulties (4), dryness of mouth (2), and conjunctival irritation (1). The authors concluded that autonomic side effects occur far more often after BTX-B than after BTX-A, suggesting systemic spread of BTX-B. There is a report on three individual patients who received BTX-B and who subsequently developed parasympathetic dysfunction of the visual system after injections of BTX-B at remote sites. In a prospective study, however, using both quantitative physiologic measurements as well as questionnaires, patients with CD were randomized to receive either BTX-A or BTX-B in a double-blind manner. Efficacy and physiologic questionnaire measures of autonomic function were assessed at baseline and 2 weeks after injection. Patients treated with BTX-B had significantly less saliva production and greater severity of constipation than those treated with BTX-A, but did not differ in other tests of autonomic functions.

In a study by the Dystonia Study Group, subjects with CD who had a previous response from BTX-A were randomly assigned to BTX-A or BTX-B at 1:40 U dose ratio, and evaluated in a blinded fashion at baseline, 4 weeks, 8 weeks, and 2-week intervals thereafter until loss of 80% of clinical effect or completion of 20 weeks of observation. Of a total of 139 subjects (BTX-A, n = 74; BTX-B, n = 65), dysphagia and dry mouth were significantly more frequent with BTX-B (dysphagia, BTX-A 19% vs BTX-B 48%; dry mouth, BTX-A 41% vs BTX-B 80%). This finding of increased autonomic nervous system (ANS) adverse effects, may be partially a factor of initial exposure, since in a multiple injection study: ‘Dry mouth frequency decreased with each session despite increasing doses whereas flu-like syndrome and weakness increased’.

THERAPEUTIC TRIALS

Blepharospasm and hemifacial spasm

Blepharospasm is a focal cranial dystonia characterized by sustained, involuntary spasms of the orbicularis oculi muscle, resulting in eyelid closure. HFS is another disorder associated with, usually unilateral, eyelid spasms with additional involvement of other facial
nerve innervated muscles. HFS, however, is not a dystonia but rather a peripherally induced movement disorder due to hyperexcitability of the facial nerve (usually due to compression of the facial nerve by a vascular loop).

BTX injections in the orbicularis oculi have become the primary therapeutic modality for both blepharospasm and HFS. In the first published double-blind placebo-controlled trial of BTX-A, all 12 patients with blepharospasm improved by 72% in the severity score and by 61% in the self-assessment score. There have been several open trials since. In a long-term follow-up of 90 treated patients there was moderate or marked improvement in 94% with 12.4 weeks duration of maximum, but longer duration of any effect. In all, 41% of patients reported some adverse effects (ptosis, blurred vision, diplopia, tearing); in all but 2% of affected patients, the side effects generally spontaneously resolved within 2 weeks. In another report of long-term clinical experience with BTX-A for blepharospasm, of 178 cases followed between 1980 and 2001, 10 were lost to follow-up; of the remaining patients, 93% reported improvement after treatments. The mean duration of improvement was 3.6 months. Twelve patients (76%) who underwent more than 14 treatments maintained stable relief. Three patients (1.7%) had a total remission of spasms. Side effects were exclusively local. In yet another 10-year experience, it was shown that over the long term, there is neither loss of efficacy nor increased dose requirement and the frequency of complications tends to decline with repeat injections. More recently, NT 201 has been studied in 300 patients with blepharospasm, 256 of whom completed the study, and found no difference in efficacy or adverse effects between NT 201 and Botox. The adjusted mean change in the Jankovic Rating Scale was −2.90 for the NT 201 and −2.67 for the Botox group; the frequency of ptosis, the most common adverse effect, was 6.08% and 4.52%, respectively.

A 2005 Cochrane Database Review concluded that:

There are no high quality, randomised, controlled efficacy data to support the use of BTX for blepharospasm. Despite this, other studies suggest that BTX is highly effective and safe for treating blepharospasm and support its use. The effect size (90% of patients benefit) seen in open studies makes it very difficult and probably unethical to perform new placebo-controlled trials of efficacy of BTX for blepharospasm.

An open trial with BTX-B in patients non-responsive to BTX-A (that were AB positive) found generally disappointing results in patients with blepharospasm and HFS.

There is an ongoing debate surrounding the optimal injection sites. The orbicularis oculi consists of three portions:

- an orbital portion, surrounding the orbital margin, including the brow
- a palpebral (tarsal or septal) portion consisting of thin bundles of fibers that concentrically cross the eyelids in front of the orbital septum
- at the lid margin (pretarsal portion of the orbicularis oculi), a small group of fine muscle fibers known as the ciliary (or Riolan’s) muscle.

Price et al compared four different treatment site applications in a prospective trial of 92 patients with blepharospasm and HFS. Patients were assigned randomly to one of four different treatment groups: standard (medial and lateral aspects of upper eyelid, and lateral and central portion of lower eyelid), brow (medial and lateral aspects of upper eyebrow and lateral and central portion of lower eyelid), inner orbital (medial to the lateral orbital margin), or outer orbital (just lateral to the lateral orbital margin). In the patients with blepharospasm, those assigned to the standard group had a significantly longer duration of effect than for those in the other groups, whereas of the patients with HFS, those in the outer orbital group had significantly shorter duration of effect than those in the other groups. The inner orbital treatment produced significantly more episodes of ptosis (13% of treatments). However, the standard treatment produced the most epiphora and ocular irritation (18% of treatments). Thus, the standard treatment produces the longest duration of effect in the blepharospasm group but with the most transient ocular irritation and epiphora. In the HFS group, the brow treatment had an equally long duration of effect as that of the standard treatment, with fewer side effects. It is not clear from the methods section exactly where in the eyelids the injections were made: i.e. relative to the inferior margin of the upper eyelid. Another controlled study showed that an injection in the most inferior aspect (pretarsal) rather than septal portions of the orbicularis oculi is associated with significantly less ptosis. In 10 patients with blepharospasm treated unsuccessfully with bilateral periorbital injections, injecting BTX into the pretarsal region of the orbicularis oculi proved to be highly efficacious; in addition, 26/30 of the patients with hemifacial spasm preferred these ciliary injections. Other studies have confirmed the superior efficacy of pretarsal injection in patients with blepharospasm.
Oromandibular dystonia (see Chapter 9)

Oromandibular dystonia consists of involuntary spasms of masticatory, lingual, and pharyngeal muscles, resulting in jaw closing dystonia (JCD), jaw opening dystonia (JOD), jaw deviation dystonia (JDD), or a combination of these abnormal movements, and its management represents a formidable challenge. For JCD, the masseters, temporalis, or internal pterygoids may be injected; for JOD, the submentalis complex or external pterygoids, and for JDD, various combinations may be needed. We have reviewed the use of BTX in these conditions at greater length recently.87 Tan and Jankovic88 reported their long-term experience with BTX for OMD in 162 patients over a period of 10 years (mean follow-up period = 4.4 years). More than half the patients had JCD. BTX treatments were administered into the masseter muscles, submentalis complex, or both. The mean doses (± SD) of BTX (per side) were 54 ± 15 U for the masseters and 29 ± 17 U for the submentalis complex. The mean total duration of response was 16 ± 7 weeks. The mean global effect of BTX was 3.1 (range 0–4, where 4 equals the complete abolition of the dystonia). A score >3, was seen in 80% of the JCD patients, but in only 40% of the JOD, 33% of the JDD and 52% of the mixed dystonia patients. Adverse effects were reported in at least one visit in 31.5% of patients with BTX and complications such as dysphagia and dysarthria were reported in 11% of all treatment visits. Using a broader range of muscles and electromyographic (EMG) localization, Brin et al89 also found that patients with JOD and JDD may not respond as well as those with JCD.

Bruxism is a diurnal or nocturnal jaw activity manifested by clenching, grinding, bracing, and gnashing of the teeth. Possibly a manifestation of dystonia, bruxism is a common occurrence in otherwise normal individuals. However, it does seem to appear more frequently in patients with dystonia and was present in 79% of 79 patients with cranial-CD.90 In an open trial of 18 subjects in patients with dystonia and was present in 79% of 79 patients with severe bruxism, BTX-A injections of the masseter muscles (mean dose 62 U per side, range 25–100 U) were an effective treatment.91 The mean peak effect on a scale of 0–4 (4 is equal to total abolishment of grinding) was 3.4; mean total duration of response was 19 weeks. Only one subject reported dysphagia.

Laryngeal dystonia (spasmodic dysphonia) (see Chapter 11)

Laryngeal dystonia may produce strained or breathy voice, referred to as spasmodic dysphonia (SD), which has been categorized primarily into adductor spasmodic dysphonia (strain-strangled voice interrupted by voiceless pauses), which accounts for the vast majority of cases of LD, and abductor spasmodic dysphonia (whispering, breathy voice). Prior to the introduction of BTX, treatment consisted of speech therapy or unilateral nerve resections, neither of which was completely satisfactory. The use of BTX in SD has been reviewed elsewhere.92,93 In contrast to the adductor form of SD, which is easily managed with BTX, the abductor form of SD is more difficult to treat. Blitzer et al94 performed a retrospective analysis of a 12-year experience in which more than 900 patients with SD were treated with BTX. While the adductor patients, injected into the thyroarytenoid muscle, had an average benefit of 90% of normal function (lasting an average of 15 weeks), the abductor patients, usually injected into the posterior cricoarytenoid muscle, had an average benefit of 67% of normal function (lasting an average of 11 weeks). Adverse effects included mild breathiness and coughing on fluids in the adductor patients, and mild stridor in a few of the abductor patients.

The primary controversy involving the use of BTX in SD involves technique. The main approaches now used are percutaneous injection through the cricothyroid membrane under EMG guidance, either unilaterally or bilaterally, or transorally under visual laryngoscopic control. The main side effect is prolonged breathy hypophonia, which is seen more with large bilateral injections. Langeveld et al95 compared unilateral (5 U in the left thyroarytenoid muscle) and bilateral (2.5 U in both sides) percutaneous BTX-A injections in a prospective, crossover study in 27 patients with adductor spasmodic dysphonia. Voice quality, duration of effect, and side effects were assessed. There was no difference between the procedures in duration of voice improvement or in the occurrence of breathy dysphonia. Although more patients preferred the bilateral injection, this approach was associated with more and longer-lasting side effects, particularly dysphagia. A large Australian clinical experience has also been reported;96 a consecutive series of 169 patients with SD were studied prospectively, of whom 144 were treated with BTX injections between 1983 and 1999. Adductor SD (89.4%) was more frequent than abductor SD (1.8%) or mixed SD (4.7%). The median treatment outcome score was excellent in 63.2%, very good in 18.5%, satisfactory in 14.7% and unsatisfactory in 3.5% of patients. Poorer treatment outcome was associated with abductor SD (odds ratio [OR] = 4.69, confidence interval [CI] = 1.23–17.92 and age >63 years old (OR = 2.83, CI = 0.95–8.42). Mild post-injection paralytic dysphonia was associated with longer-lasting treatment and superior treatment outcome rating. The authors hypothesize that mild post-injection paralytic dysphonia may be a marker for more effective and
last ing treatment in adductor SD. BTX-B has been reported in cases to also be effective for SD.97

Warrick et al98 examined the efficacy of BTX-A for the closely related entity of voice tremor using either a bilateral 2.5 U or a unilateral 15 U EMG-guided injection, followed by the other injection type 16–18 weeks later. A minority of patients demonstrated objective reduction of tremor; however, 8 of 10 patients wished to be reinjected at the conclusion of the study. A reduction in vocal effort appeared to be coincident with reduction in laryngeal airway resistance after BTX injection.

In another study unilateral and bilateral injections were compared.99 Sixteen patients received unilateral injections (72 injections total) and 33 patients bilateral injections (133 injections total). Individual assignments to injection type were based on treatment previously received and dose was adjusted according to the patient’s previous treatment response rather than on any kind of randomized basis. Compared to patients receiving bilateral injections, those patients receiving unilateral injections more frequently noted a statistically significant benefit of ≥3 months, side effects of ≤2 weeks duration, as well as simultaneous 3-month benefit. Injection type had no effect on optimal BTX dosing with repeat injections. These authors concluded that unilateral injections provided a more optimal and consistent efficacy/side-effect profile.

Treatment with BTX for SD results in improved quality of life. In 5 patients with OMD and 18 with SD, BTX-A injections were effective on the basis of quality-of-life criteria.100 The mean total benefit score on the Glasgow Benefit Inventory, which was used to quantify the health benefit of treatment, was +38.04 (possible range = −100 to +100). Also in a study of 27 consecutive new patients presenting with SD, voice-related quality of life (V-RQOL) was low and botulinum toxin injections improved it significantly for each injection cycle studied.101

Cervical dystonia (see Chapter 8)

Cervical dystonia is the most common form of focal dystonia seen in movement disorders clinics. It consists of jerky or sustained, but nearly always patterned (same muscles involved), movements of the head and neck. The goal of treatment of CD is not only to treat the abnormal postures and associated neck pain but also to prevent secondary complications such as contractions, cervical radiculopathy, and myelopathy.102 This topic has been reviewed in recent articles.103–105

Muscle selection

Several muscles are involved in neck movement, particularly the sternocleidomastoid (SCM), splenius capitus, scalenus complex, levator scapulae, and semispinalis capitis. One of the challenges in BTX treatment of CD has been to determine which muscles to inject. This difficulty is compounded by the fact that multiple muscle combinations can produce the same movements, the particular pattern of abnormal muscle activity is highly individualized, and that antagonist muscles may contract more intensely and may be more hypertrophic than the agonist muscles. Only the latter group of muscles should be targeted for BTX injection. Although some investigators have suggested that after injection of BTX, the pattern of muscle activity may change,106 this is quite rare in our experience. Some investigators have also shown that although there are no further changes in the EMG activity of the injected SCM subsequent to the first dose of BTX-A, there may be a progressive change in the contralateral (i.e. antagonist) muscle.107

Selection of methods used to target and inject muscles remains controversial: i.e. it should be determined solely by clinical inspection or with the addition of EMG analysis. Even the specifics of ‘EMG guidance’ can vary. EMG can be used to confirm localization of the needle to a muscle or confirm and possibly quantify the occurrence of specific muscular activity during ongoing dystonic movements.108–111 In comparison to an EMG mapping study, the clinical predictions of individual muscle involvement by four movement disorder specialists were only 59% sensitive and 75% specific. Muscle hypertrophy, shoulder elevation, and dominant head vector did not bolster clinical accuracy.112 One study showed that patients did better with EMG-guided than strictly clinically guided injections.113 The difference in the overall magnitude of this effect was, however, small and there was no difference between groups in the number of patients returning for booster injections. Although patients with retrocollis, head tilt, and shoulder elevation in particular demonstrated additional benefit with EMG-guided Botox injection, the patients that did not have EMG assistance got higher doses of Botox, suggesting more severe disease. In the Dystonia Study Group Botulinum Toxin A vs B in cervical dystonia trial, there was no benefit shown for patients that received EMG guidance, although the study was not designed to answer this question.114 We reserve EMG for non-responding patients or those in whom proper identification of the target muscle by palpation is difficult. This issue is discussed at length in a position paper by one of the authors (JJ).115 Frequency of individual muscle involvement and typical BTX doses in CD are given in the Table 18.2.

Other localization techniques may become useful in the future and may include anatomically based methods such as ultrasonography.108 An excellent mode of visualizing exactly which muscles were being injected was
described in a paper using BTX to denervate the scalene muscles in apparent neurogenic thoracic outlet syndrome. The muscles were first localized with EMG, then BTX-A was co-administered with radiopaque dye under fluoroscopy. The degree of confirmation with this technique is far greater than with EMG, but as yet there are no proponents for widespread use of this technique. Computed tomography (CT) has also been used.

### Efficacy

The efficacy of BTX in CD has been demonstrated in both controlled and open-label trials and in an evidence-based medicine criteria analysis. In one double-blind placebo-controlled trial, 61% of patients injected with BTX-A improved; 74% of patients subsequently improved during a later open phase at a higher dose of Botox. In general, improvement rates run from as low as 65%, but no complete improvement, to as high as 92%, and near-complete improvement in 83%, with further improvement after repeated treatments being seen up to 5 years. A recent large-scale retrospective analysis (616 patients) with BTX-A showed sustained significant benefit, as measured by a disease severity score, independent of the type of CD. Pronounced individual differences were found in response to this treatment, even in patients with similar initial clinical scores and doses of BTX-A. Whereas secondary non-response was seen in about 5% of patients, antibody tests revealed neutralizing serum antibodies in only 2%. Lew et al have reviewed the prior studies with BTX-B, which taken together, showed about a 25% reduction in the TWSTRS (Toronto Western Spasmodic Torticollis Rating Scale) score and duration of action of 12–16 weeks. The two pivotal studies, one using BTX-A (Botox) and the other BTX-B (Myobloc), that led to the approval of BTX by the Food and Drug Administration (FDA) in CD, have not been published, but have been recently reviewed.

CD may also cause pain outside the neck per se. BTX-A safely improved headache associated with craniovascular dystonia when administered for the primary condition of craniovascular dystonia, measured with headache diaries, Headache Impact Test (HIT-6), and Migraine Disability Assessment Scale (MIDAS).

### Complications

The most common complication of BTX for CD is pharyngeal weakness manifested by dysphagia. Although usually mild and rarely disabling, it may require a change to a soft diet to prevent aspiration. In one study, 33% of patients receiving their first dose of BTX experienced dysphagia and a greater number displayed radiographic swallowing abnormalities. Dysphagia has

### Table 18.2 Cervical muscles frequently injected with botulinum toxin (BTX): functions, relative involvement in cervical dystonia, and typical botulinum toxin doses

<table>
<thead>
<tr>
<th>Muscle</th>
<th>Action</th>
<th>BTX (U)a</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sternocleidomastoid</td>
<td>Contralateral rotation; anterior flexion</td>
<td>40–70</td>
</tr>
<tr>
<td>Trapezius</td>
<td>Elevation of scapula and shoulder, extension of neck</td>
<td>25–100</td>
</tr>
<tr>
<td>Splenius capitis</td>
<td>Ipsilateral rotation; extension of neck</td>
<td>60–100</td>
</tr>
<tr>
<td>Levator scapulae</td>
<td>Elevate scapulae and shoulder</td>
<td>25–60</td>
</tr>
<tr>
<td>Scalene complex</td>
<td>Ipsilateral turn with neck flexion (anterocollis)</td>
<td>15–50</td>
</tr>
<tr>
<td>Deep post-vertebrae:</td>
<td>Ipsilateral tilt, neck extension</td>
<td></td>
</tr>
<tr>
<td>Longissimus capitis</td>
<td></td>
<td>55–90</td>
</tr>
<tr>
<td>Semispinalis capitis</td>
<td></td>
<td>30–60</td>
</tr>
<tr>
<td>Hyoid muscles</td>
<td>Head flexion (anterocollis)</td>
<td>10–30</td>
</tr>
</tbody>
</table>

*From Dressler.*

Movements refer to the neck; maximal involvement = 1.

aBotox units.
been reported to occur on average 9.7 days after injection and last on average 3.5 weeks. Dysphagia most commonly occurs with bilateral injections of the SCM or scalenus muscles, presumably because of local spread of the toxin from these muscles to posterior pharyngeal muscles. This complication may occur less frequently if the biologic activity of the toxin is contained within the target muscle by using multiple small injections rather than a single large bolus. Neck weakness is the second most common local complication following BTX treatment of CD. In addition, BTX-B has a relatively high incidence of injection site pain and dry mouth. It is not clear whether the dry mouth noted with BTX-B was present but interpreted as dysphagia in a subset of the patients in the earlier trials with BTX-A.

Although BTX has been considered the treatment of choice for CD, it has been formally compared to medical therapy in only one study. Brans et al. compared the effectiveness of BTX-A with that of trihexyphenidyl in a prospective, randomized, double-blind design. Sixty-six consecutive patients with idiopathic CD were randomized to treatment with trihexyphenidyl tablets plus placebo injection or placebo tablets plus BTX-A injections. Dysport or saline was injected under EMG guidance at study entry and again after 8 weeks. Patients were assessed for efficacy at baseline and after 12 weeks by different clinical rating scales. Sixty-four patients completed the study, 32 in each group. Mean dose of BTX-A was 292 U (first session) and 262 U (second session). Mean dose of trihexyphenidyl was 16.2 mg. The changes on the Disability section of the TWSTRS (TWSTRS-Disability) (primary outcome), Tsui Scale, and the General Health Perception Subscale were significantly improved in favor of BTX-A. Furthermore, adverse effects were significantly less frequent in the BTX-A group.

**Dosing**

Several studies have attempted to determine optimum dosing in patients with CD. Poewe et al. performed a prospective multicenter placebo-controlled double-blind dose ranging study in a homogeneous group of previously untreated patients with rotational torticollis to obtain objective data on DR relations. Seventy-five patients were randomly assigned to receive treatment with placebo or total doses of 250, 500, and 1000 Dysport U divided among three splenius capitis and the contralateral SCM. Seventy-nine percent reported subjective improvement at one or more follow-up visits. Decreases in the modified Tsui scale score were significant at week 4 for the 500 and 1000 U groups vs placebo. There was a positive relation between dose injected and the duration of clinical benefit. Ninety-four percent of patients treated with placebo and about 50% of patients receiving 200 and 500 U requested reinjection by 8 weeks, whereas only 39% of those having received 1000 U asked for a second treatment by this time. A dose relation was also established for the number of adverse events overall and for the incidence of neck muscle weakness and voice changes. They concluded that although magnitude and duration of improvement was greatest after injections of 1000 U of Dysport, it was at the cost of significantly more adverse events. They suggested a starting dose of 500 U Dysport, with upward titration if clinically necessary.

Another double-blind, randomized study, involving 31 patients with CD (patients had received at least two previous Dysport injections), examined low-dose therapy. The patients received either a mean total target dose of 547 ± 113 mouse units (MU) at a concentration of 500 MU Dysport/ml or a 4-times-diluted preparation of 130 ± 32 MU at a concentration of 125 MU Dysport/ml. TWSTRS and self-rating before and after injection revealed comparable clinical improvement in both groups; however, 3 patients in the low-dose group received reinjections due to insufficient effects from the previous injection. These findings again suggest that low-dose treatment of CD with Dysport may be clinically effective during maintenance therapy, at least for a limited period of time. The authors suggest that the low-dose Dysport effects may have been potentiated by the long-lasting effects of previous Dysport treatments at conventional doses.

**Resistance and other clinical factors**

Several factors can influence failure to respond to BTX. Primary non-response results from contractures (long-standing disease), insufficient dosage of BTX, injection of the incorrect muscles, or some other technical factor (e.g. failure to properly prepare the BTX). In CD, about half of these patients will subsequently benefit from BTX injections. More recently, in a long-term study (median 5.5 years, range 1.5–10 years) in 78 patients with idiopathic CD, treatment with BTX-A was assessed using patient and treating neurologist scores as well as ‘Global Burden of Disease’, as expressed on Visual Analog Scales (VAS, 0–10). By combining these outcome measures, 67% of the patients were characterized as having a good effect, and 33% an unsatisfactory effect. This outcome (good or unsatisfactory effect) was independent of the severity of head deviation or complexity pattern of CD prior to treatment, the delay from onset to start of BTX treatment, or the number of treatments. The complexity pattern remained stable during treatment in 64% of the patients, became
less complex in 19%, whereas 17% of the patients developed more complex patterns.

EMG may be required to properly localize the muscles primarily responsible for the dystonic posture in the patients that do not respond well. However, even after these factors are considered, some patients will still fail to benefit. This is believed to result from the involvement of inaccessible deep neck musculature, but no studies have specifically analyzed these patients.

Cervical dystonia is due to a number of different etiologies, including genetic predisposition, local trauma, and certain drugs, which may affect the responsiveness to BTX. In one study, the response of patients with tardive CD was similar to that of idiopathic CD, although the tardive patients required higher BTX-A doses by about 30%, partly because of greater pain, larger muscles, and more complicated movements. Acute-onset CD (occurring within 4 weeks of trauma) is characterized by markedly reduced cervical mobility, prominent shoulder elevation with trapezius hypertrophy, isometric contraction of the affected muscles without involuntary movements, lack of effect of sensory tricks, or activation maneuvers. Although patients with post-traumatic CD do not generally respond to BTX injections as well as patients with idiopathic dystonia, this is usually the most effective treatment, particularly for pain relief. By contrast, delayed-onset CD (between 3 months and 1 year after trauma) is clinically indistinguishable from non-traumatic idiopathic CD with respect to response to BTX.

In a multicenter study of 100 patients with cervical dystonia, we examined the immunogenicity of BTX-B and correlated the clinical response with the presence of blocking antibodies using a novel mouse protection assay. A third of the patients who were negative for BTX-B antibodies at baseline became positive for BTX-B antibodies at last visit. Thus, the high antigenicity of BTX-B limits its long-term efficacy.

**Writer’s cramp and other limb dystonias and tremors (see Chapter 10)**

Most limb dystonias consist of position- or task-specific dystonias such as writer’s and musician’s cramp, but also include foot dystonias. The latter is typically present in children with generalized dystonia, such as DYT1 dystonia, or adults with Parkinson’s disease. Prior to BTX, treatment with systemic agents or local surgery rarely provided satisfactory results.

**Muscle selection**

Large groups of muscles can be localized clinically. Although writer’s cramp and other hand and distal arm dystonias can affect both flexor and extensor muscles, success can usually be achieved by injecting the forearm flexor compartment exclusively, with little significant morbidity, whereas wrist drop after injection of extensors is not uncommon. When more precise determination of muscles is needed, especially if there are relatively high risks of clinically significant morbidity, EMG guidance is needed for correct localization of desired limb muscles. In one study, the accuracy of muscle localization in 38 muscles in patients with focal hand dystonia without EMG guidance was examined. Only 37% of needle placement attempts reached the target muscles or muscle fascicles.

**Clinical efficacy**

Jankovic and Schwartz injected forearm muscles with BTX-A in 130 treatment sessions for writer’s cramp without EMG guidance. Average peak response was 2.3 (0 = none to 4 = maximum), average latency to onset was 5.6 days, and average duration of response was 9.2 weeks. Temporary hand weakness occurred in 54% of all patients. However, the frequency of adverse effects has dramatically increased since the initial report, as a result of using lower doses in specific, targeted muscles most involved in the production of the abnormal movement or posture. In an open-label prospective analysis, Pullman et al injected BTX-A into selected upper and lower limb muscles under EMG guidance in 187 patients with limb disorders, including 136 with dystonia, during an 8-year period. Average BTX efficacy (calculated as an arithmetic combination of changes in the three clinical ratings before and after administration of BTX) was 65% overall and 83.5% for focal hand dystonia. BTX-A injections relieved pain, independent of motor function, in 82.7% of patients with painful muscle spasms. The only notable adverse effect of BTX injection in limbs was transient weakness in injected or neighboring muscles. Over a 5-year period, Ross et al treated 40 patients with hand dystonias with BTX-A using either standard EMG recording of voluntary potentials or muscle twitch stimulation guide injection. Moderate to complete improvement in dystonia occurred in 28 patients (70%) after the first injection and in 34 patients (85%) after the second. Of note, weakness of uninjected muscles, immediately adjacent to those injected, was found in 23/40 patients (63%). Spread to, and weakness of, adjacent uninjected muscles was a major factor contributing to suboptimal outcome in 6/39 (15%) such patients. A randomized, placebo-controlled trial of BTX-A for writer’s cramp has also been performed. Forty participants were randomized to treatment with either BTX-A or
placebo injections in two sessions; the trial duration was 12 weeks. The primary outcome measure was the patient’s decision to continue the particular treatment. In addition, clinical rating scales of impairment and disability were used as secondary outcome measures. Assessments were made at baseline and 2 months (secondary outcomes) and 3 months (primary outcome), but patients were followed for a total of 1 year. Fourteen of 20 patients (70%) receiving BTX-A vs 6 of 19 patients (31.6%) in the placebo group ($p = 0.03$) chose to continue treatment. The changes on most of the clinical rating scales were also significantly in favor of BTX-A. Side effects reported were hand weakness, which was mostly mild and always transient, and pain at the injection site. After 1 year, 20 of 39 patients were still under treatment with perceived benefit.

The observation that some patients treated for focal dystonia with BTX noted improvement in their tremor led to studies examining the effects of BTX specifically on tremor. In a placebo-controlled study,143 25 patients with hand tremor of 2+ (moderate) to 4+ (severe) on the tremor severity rating scale were randomized to receive either 50 U of BTX or placebo injections into the wrist flexors and extensors of the dominant limb. If patients failed to respond to the initial injection, they were eligible to receive another injection of 100 U 4 weeks later. Rest, postural, and kinetic tremors were evaluated at 2–4-week intervals over a 16-week study period, using tremor severity rating scales, accelerometry, and assessments of improvement and disability. Four weeks after injection, 75% of BTX-treated patients vs 27% of placebo-treated patients ($p < 0.05$) reported mild to moderate improvement (peak effect rating $>2$) and this effect was maintained for the duration of the study. There were no significant improvements in functional rating scales, although trends were observed for some items. Postural accelerometry measurements showed a greater than 30% reduction in amplitude in 9 of 12 BTX-treated subjects and in 1 of 9 placebo-treated subjects ($p < 0.05$). Although all patients treated with BTX reported some degree of finger weakness, no severe, irreversible, or unexpected adverse events occurred. This and other studies144 have demonstrated that chemodenervation with BTX may significantly ameliorate essential tremor in patients who fail to improve with conventional pharmacologic therapy. As a result of long-term experience with hundreds of patients treated with BTX for various tremors, we have modified our protocol and have markedly decreased the dosage in the forearm extensor muscles (to $< 15$ U) with little or no finger extensor weakness.

Although BTX is clearly a useful treatment in some patients with hand tremor, it has been found particularly effective in patients with head tremor.145

### Resistance to Botulinum Toxin – Antibody Development

Secondary failure to respond to BTX usually indicates the development of immunoresistance due to neutralizing antibodies. Antibody development relates to the inverse of the specific biologic activity, and this has been determined for the different preparations of BTX.146 For Botox, the specific biologic activity is 60 MU-EV/ng neurotoxin, for Dysport 100 MU-EV/ng neurotoxin, and for Myobloc/NeuroBloc 5 MU-EV/ng neurotoxin. For Myobloc/NeuroBloc this has been calculated by these authors to translate into an antibody-induced therapy failure rate of 44% in patients treated for cervical dystonia, whereas for BTX-A preparations this figure is approximately 5%. Although neutralizing antibodies have been thought to develop in less than 10% of treated patients,147 more recent studies of BTX-A and BTX-B in patients treated for CD suggest a frequency as high as 18%, according to yet unpublished data.119

We analyzed longitudinal follow-up data on 45 patients (32 women; mean age, 68.8 years) currently followed in the Baylor College of Medicine Movement Disorders Clinic, who have received BTX treatments continuously for at least 12 years (mean $15.8 \pm 1.5$ years).148 Antibody (Ab) testing was carried out in 22 patients due to non-responsiveness; blocking Abs were confirmed by the mouse protection assay in 4 of 22 (18%) patients. Of the Ab-negative patients, 16 resumed responsiveness after dose adjustments and 2 persisted as non-respondents.

The development of neutralizing antibodies is a serious problem because it essentially eliminates future response to that type of BTX, but the patient may respond to an alternative serotype of BTX.126 However, the high antigenicity of BTX-B limits its long-term efficacy.138 Four of nine patients (44%) with cervical dystonia receiving BT-B (NeuroBloc/Myobloc, Elan Pharmaceuticals) experienced complete therapy failure with BT-B-AB titers in excess of 10 mU/ml on the mouse diaphragm assay.149 This pilot result was confirmed in a multicenter study of 100 patients with cervical dystonia; one-third of the patients who were negative for BTX-B Abs at baseline became positive for BTX-B antibodies at the last visit.138

A new batch of Botox has been used since 1997. It has a higher activity per mg protein, but comparable unit efficacy150 and, because of the lower protein load, it promised to have a lower risk of antibody production. A double-blind, multicenter study crossover design of 133 patients compared the efficacy and safety of BTX-A (Botox) produced from both original and current bulk toxin sources for the treatment of CD.151 Adverse events were assessed at each visit. Efficacy was...
assessed at 2 and 6 weeks post-injection using the severity and pain-disability subscales of the TWSTRS. Efficacy and adverse effects and dosing were virtually identical after treatment with either batch of BTX-A. In our experience, this new preparation decreased the risk of antibody formation by a factor of six. In a retrospective comparison of 130 patients treated for CD with original Botox, 42 of whom were exposed only to the original BTX-A used before 1998 (25 ng protein/100 U), and 119 treated only with the current BTX type A (5 ng of protein/100 U), blocking antibodies were detected in 4 of 42 (9.5%) patients treated only with original BTX-A but in none of the 119 patients treated exclusively with current BTX type A (p <0.004). However, a patient with cranio-cervical dystonia injected with the new, lower-protein formulation (patients treated exclusively with current BTX type A), blocked antibodies in 4% (9.5%) of patients treated only with original BTX-A but in none of the 119 patients treated exclusively with current BTX type A

Detection of blocking antibodies

There are several methods for detecting blocking antibodies in patients who lose responsiveness to BTX. The gold standard is the highly specific, but relatively insensitive and cumbersome assay, the mouse protection assay (MPA), which evaluates the ability of increasing dilutions of a patient’s serum to protect mice from lethal doses of BTX-A. Another bioassay involves a unilateral brow injection (UBI) in which a test dose (20 U of Botox) is administered and, if the brow is paralyzed and the patient is unable to frown on the injected side this indicates that the patient is BTX responsive and, therefore, does not have blocking antibodies. Ever more sophisticated and quantitative bioassays have been developed using quantitative EMG and reduction of evoked or maximal motor unit amplitude, and reduction of sudomotor activity. One of these – the so-called EDB Test involves injection of BTX-A into an indicator muscle, the EDB, combined with amplitude measurements of compound muscle action potentials (CMAPs) elicited by electrical nerve stimulation of the peroneal nerve before and after the injection. A recent study concludes that:

the EDB test correlates better with the clinical response than the antibody assays and that EDB decrement does not always correlate quantitatively with the BTXA antibody titers. In patients with secondary nonresponsiveness, it is recommended that an EDB test is the initial investigation of choice. In those patients where the EDB test does not demonstrate resistance to BTX-A, a reexamination of the patients and carefully placed injections under EMG guidance may improve results.

Antibodies can be assayed directly in vitro; however, in vitro antibody assays, including the Western blot assay (WBA), do not correlate well with clinical responses because they do not detect specific blocking antibodies. More recently, an assay using immunoprecipitation of I-labeled BTX has been developed. Hanna et al compared the WBA to the immunoprecipitation (IPA) and bioassays. Both in-vitro assays had high specificity, although the sensitivity of the IPA was higher than the MPA. In addition, the IPA seems to display positivity earlier than the MPA, and as such, it may prognosticate future non-responsiveness. Eyebrow (and frontalis) test injections correlated well with clinical and immunologic results and are useful in the assessment of BTX non-responders and in an algorithm for management of BTX non-responders. In addition, several risk factors have been identified for the development of BTX antibodies, including short (<3 month) interval between treatments and ‘booster’ injections, high cumulative doses, duration of treatment, and possibly young age. Resistance with antibody formation has very rarely been reported in conditions other than CD, although rare cases of resistance (although not well documented by appropriate antibody assays) have been noted in patients with laryngeal dystonia. In order to evaluate the feasibility of low-dose treatments, Rollnik et al demonstrated that low-doses of Dysport, diluted with albumin, were effective without the development of antibodies in 115 patients suffering CD, blepharospasm, and HFS over a period of 2 years in an open-label, non-controlled pilot study. Antibody levels can decline after cessation of therapy, although they may not regain responsiveness (usually temporary) to the same type of BTX for at least 18 months. Thirteen patients with various dystonic syndromes and complete secondary therapy failure underwent monitoring period of at least 750 days after loss of response; two or more BTX-A antibody tests using the quantitative mouse diaphragm assay were performed. Eight of 13 BTX-A antibody titers decreased. The onset of decrease could be detected after approximately 500 and 1750 days. After 1250–2250 days, they had dropped below a level of 0.002 U/ml, where it is felt that secondary unresponsiveness is unlikely. However, 5 of 13 BT-A-AB titer did not decrease. The authors expressed their hopes that these patients might again become responsive to BTX-A, but there may well be an anamnestic response. Unfortunately, once patients develop blocking antibodies, even if the titer subsequently decreases, a rechallenge with the same type of BTX usually again stimulates the
production of antibodies. Even when these patients are reinfected with an alternate type of BTX, they are at a high risk of developing blocking antibodies to the second BTX, presumably because of cross-reactivity.\textsuperscript{167,168}

\textbf{SUMMARY}

Botulinum toxin provides a tool to perform selective chemical denervation. This has been shown to be effective in a variety of forms of dystonia. Although the dystonia can be generalized or multifocal, even the more widespread forms may display the most troublesome features for individual patients in a limited anatomic area. In general, BTX is very safe and primary toxicity is due to local spread. Systemic spread is very rare. Two different serologic subtypes of the toxin are available clinically, providing an alternative mode of therapy for patients that develop immunoresistance to one or the other. Various preclinical studies suggest that BTX-A is more potent and long-lasting than BTX-B, but this remains to be demonstrated in a clinical trial. Therapy has been limited by the development of blocking antibodies. This appears to be far less likely when using the newer preparation of BTX-A, which is more pure: i.e. has a greater neurotoxic activity per mg of total protein. Besides blocking neuromuscular activity by inhibition of ACh release, botulinum toxin appears to have effects on pain that may occur by different mechanisms, such as inhibition of peptide release.

\textbf{REFERENCES}

32. Dong M, Yeh E, Tepp WH et al. SV2 is the protein receptor for botulinum neurotoxin A. Science 2006; 312(5773): 592–6.
CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA


43. Giladi N. The mechanism of action of botulinum toxin type A in focal dystonia is most probably through its dual effect on efferent (motor) and afferent pathways at the site of injection. J Neurol Sci 1997; 152(2): 132–5.


69. Sloop RR, Cole BA, Escutin RO. Reconstituted botulinum toxin type A does not lose potency in humans if it is refrozen or refrigerated for 2 weeks before use. Neurology 1997; 48(1): 249–53.


INTRODUCTION

Surgical treatment options for patients with medically refractory dystonia are gaining increased attention and acceptance over the past few years.1–3 Surgery can provide more permanent relief of disabling dystonic movement disorders, and it can effectively prevent secondary complications of dystonia. More recently, there has been considerable reinterest in functional stereotactic neurosurgery to treat dystonia, and deep brain stimulation (DBS) has become one of the most important therapeutic tools.4,5 In the following sections, we provide a short overview on the history of surgical treatment of dystonia and discuss current treatment options.

HISTORY

The first operations for treatment of cervical dystonia (CD) were probably performed in ancient Greece. Early operative techniques consisted mainly of myotomies. Intradural denervation techniques were introduced in the late 19th century, and were popular throughout the 20th century.6 In the 1970s, the concept of selective peripheral denervation using extradural approaches, including posterior ramisectomy and spinal accessory nerve sectioning, was developed and popularized by Bertrand.7 Since side effects were clearly reduced with this technique, selective peripheral denervation has gained more and more popularity and has almost replaced intradural sectioning. In the 1970s, epidural dorsal column stimulation of the cervical spine was introduced to treat CD.8 Although this method was attractive from a theoretical point of view, it has been largely abandoned since independent evaluation of outcome could not confirm its therapeutic benefit.9

Surgery of the basal ganglia circuitry for treatment of movement disorders was not performed until Meyers, in 1939, pioneered his innovative techniques.10 After Spiegel and Wycis had introduced the method of functional stereotactic surgery in men in the late 1940s, ablative procedures targeting the thalamus and the pallidum were used in hundreds of patients with otherwise intractable dystonia.11 Thalamotomies and pallidotomies were also used with success in patients with CD, and the results of more than 300 patients were reported in the literature.12 In the late 1970s, functional stereotactic surgery for dystonia was almost abandoned for several reasons, including the general decline of movement disorders surgery at that time, the introduction of selective peripheral denervation, and the widespread and beneficial use of botulinum toxin (BTX) A soon thereafter. The reinterest in functional stereotactic surgery for dystonia followed the renaissance of movement disorders surgery for Parkinson’s disease (PD). Finally, the introduction of DBS has facilitated the performance of bilateral surgery in the same operative session without significant increase of side effects, and thus has replaced ablative surgery in many neurosurgical centers worldwide.

PERIPHERAL SURGERY FOR CERVICAL DYSTONIA

Peripheral surgery for CD, nowadays, is performed mainly in patients who do not achieve adequate benefit from BTX injections. The estimated frequency of primary non-responders to BTX injections is 6–14% of patients with CD, and BTX loses its efficacy with continued use because of the development of immunoresistance in about another 3–10% of patients.13,14 Patients with secondary immunoresistance may benefit from newer types of BTX. Surgical treatment should be considered both in primary and in secondary non-responders to BTX. It may also be considered an alternative in selected patients after years of successful trials with BTX, because it can provide more permanent relief. Surgical treatment, in general, is indicated in those patients with functional

19

Surgery for dystonia

Joachim K Krauss and Thomas J Loher
disability caused by their dystonic movement disorder. Restriction of social activities because of embarrassment related to CD can be a major driving force, particularly in younger patients, to seek more invasive therapies. The operations most commonly used today aim at selectively weakening the dystonic muscles by nerve sectioning or myotomy. Nowadays, extradural procedures are performed most frequently, and, to a lesser extent, intradural nerve sectioning procedures. The denervation of muscles that are not involved in the production of dystonia should be avoided. The basic difference between intradural anterior cervical rhizotomy and extradural posterior ramisectomy is shown in Figure 19.1. In the past, operative procedures for treatment of CD were often performed as ‘standard’ procedures, not taking into account the specific pattern of dystonic activity in the individual patient. One of the crucial points of contemporary surgery for CD is tailoring the approach to the specific dystonic pattern of the individual patient, which may involve several successive operative steps, and the combined use of different surgical techniques.\textsuperscript{15,16} Interestingly, it has been shown that dystonic activity in various combinations may result in a similar abnormal head posture, and that (actually) the pattern of activation of dystonic muscles may change in an individual patient.\textsuperscript{17}

We have evaluated the symptomatic and functional outcome in a retrospective series of 46 consecutive patients who were operated on according to this algorithm, with independent assessment using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS).\textsuperscript{15} In this group, 76 surgical procedures were performed, including selective intradural and extradural denervation, and muscle sections. Global improvement at long-term follow-up at a mean of 6.5 years postoperatively was rated as excellent in 21% of patients, as marked in 27%, as moderate in 21%, as mild in another 21%, and as nil in 11%. Almost all mean TWSTRS subscores for severity of CD, functional disability, and pain were significantly improved. Mild transient side effects were present in 10% of the patients and included swallowing difficulties, severe neck pain or headaches, psychotic decompensation, and cellulitis at the site of the skin incision. Persistent side effects, however, occurred in only one patient. In this series, there were no significant differences in the distribution of outcome scores between patients with idiopathic and secondary dystonia, nor were there significant differences between patients who primarily did not respond to BTX injections and those who had developed secondary immunoresistance. There was a significant difference, however, with regard to the number of procedures performed. Patients with an excellent outcome had a higher number of surgical procedures on average than those patients who had achieved no benefit.

**Selective peripheral denervation**

Extradural sectioning of the posterior primary division of the cervical nerves is also known as ramisectomy. It was Bertrand who coined the term \textit{selective peripheral denervation} for the combination of sectioning of the peripheral branch of the spinal accessory nerve to the sternocleidomastoid muscle combined with posterior ramisectomy from C1 to C6.\textsuperscript{7,18} In contrast to anterior rhizotomy, there is no need for laminectomy and opening of the dura in posterior ramisectomy. The approach can be performed either unilaterally or bilaterally, depending on the pattern of dystonia.

Patients are operated on under general anesthesia.\textsuperscript{19} There have been several modifications of the original Bertrand technique. With the patient in the sitting position, both the site for posterior ramisectomy and the site for sternocleidomastoid denervation can be draped. The disadvantage of this position is the danger of air embolism, which, however, occurs only rarely in daily practice.\textsuperscript{20} A useful alternative is to perform the
ramisectomies in the prone position, and then the sternocleidomastoid denervation in the supine position. Using a 5 cm skin incision over the posterior margin of the sternocleidomastoid muscle, the trapezius branch of the spinal accessory nerve is first identified in the lateral neck triangle. Injury to the greater auricular nerve is carefully avoided. When the main trunk of the spinal accessory nerve is reached, branches to the sternocleidomastoid muscle are identified by electrical stimulation, and then sectioned and resected. Since the sternocleidomastoid may also be innervated by branches of the spinal nerves C1 and C2 or by recurrent nerves branching from the trapezius branch of the spinal accessory nerve, we have modified the original Bertrand technique and always complete the procedure with a myotomy and partial myectomy of the sternocleidomastoid.

Posterior ramisectomy is performed via a midline incision in the plane of the ligamentum nuchae until the posterior rim of the foramen magnum and the spinous processes of C2–C6 are reached. Then the cleavage plane between the more superficially located semispinalis capitis muscle and the more deeply located semispinalis cervicis and multifidus muscles on the involved side is entered (Figure 19.2). The inferior oblique capitis muscle is detached from its origin at the spinous process of C2. The posterior branches C3–C6 are found lateral to the facet joints, and are identified with the help of the surgical microscope and bipolar stimulation. After the main branches have been identified, they are sectioned and resected. Bipolar stimulation is then used to detect small residual branches. The C2 spinal ganglion is embedded in a rich venous plexus. With a unilateral approach, we usually perform a ganglionectomy at this site, including both the distal extradural portions of the roots and the rami. Since the greater occipital nerve is formed by the posterior C2 ramus, there is invariably a hypesthesia in the distribution of this nerve, which, however, in general, causes only little discomfort to the affected individual. It is more demanding to identify the suboccipital nerve, which is located between the arch of the atlas and the vertebral artery (Figure 19.3). It is also embedded in a venous plexus, which can result in brisk bleeding; this can be managed easily, however, by the application of Surgicel.

Figure 19.2 Topography of the approach for posterior ramisectomy. The posterior branches of C1–C6 can be reached within the natural cleavage plane between the more superficial semispinalis capitis muscle and the deeper multifidus and semispinalis cervicis muscles. (Reproduced from Braun and Richter,19 with permission.)
Beneficial results have been reported in the range of 70–90% of patients in most series. In a follow-up study on 140 patients at a mean of 33 months after surgery, 18 patients reported complete relief of their symptoms, 50 had marked relief, 34 moderate relief, and 19 had only minor relief, while another 19 patients had no improvement. In this study, the result of surgery differed between primary and secondary non-responders to BTX injections. Whereas 80% of secondary non-responders were satisfied with their postoperative results, only 62% of the primary non-responders considered the operation had been helpful. Recurrence of CD was noted in 11% of patients. In a retrospective long-term study at a mean of 5 years after surgery, there was a reduction in dystonia by 30% in about one-third of patients. In most studies, head tremor and phasic dystonic movements were improved to a lesser extent than dystonic postures. Since denervation of laryngeal and pharyngeal muscles is largely avoided, the frequency of side effects, in general, has been low. Side effects may include infection, paresthesias, and hypesthesia in the territory of the major occipital nerve, pain, and rarely transient dysphagia. Chawda and colleagues demonstrated that patients with no or minimal degenerative changes of the cervical spine had significant improvement in pain and severity of CD after selective denervation, whereas no difference was found in those with more severe changes. The authors concluded that effective early treatment of CD had a protective effect. Munchau and associates confirmed that reinervation is not infrequent after initially successful selective peripheral denervation. In those cases, additional or repeat surgery can be useful. Occasionally, selective denervation can also be indicated in patients with fixed dystonic postures, with the goal not to correct the head position but to alleviate accompanying pain.

**Myotomy and myectomy**

Myotomies and myectomies are rarely used as a first step in patients with CD, but these techniques can be helpful as an adjunct to selective denervation or for treatment of dystonic activities in muscles that cannot be denervated completely with ease. Whereas the posterior neck muscles are denervated adequately by posterior ramisectomies, dystonic activity in the scalene muscles, the levator scapulae, and the omohyoid is not controlled by this approach. In such cases, selective myotomies/myectomies are useful. In patients who present with painful dystonic activity of the trapezius muscle that
results in elevation and protraction of the shoulder or contributes to ipsilateral head tilt, partial myotonia and myectomy of the upper portion of the trapezius muscle can be performed with an asleep–awake–asleep operative technique.26

Chen has published the largest series on more extensive myotomies/myectomies for treatment of CD which were combined with selective peripheral denervations in certain patterns of CD.27 Treatment algorithms included selective resections of dystonic muscles for various patterns of CD, such as rotational CD, tilt of the head, anterocollis, and retrocollis. In his series of 60 patients, excellent or marked improvement was described in 83% of patients. In a series of 15 patients with retrocollis, partial resections of the upper part of the trapezius muscles, the splenius, semispinalis capitis, and semispinalis cervicis muscles were performed bilaterally.28 Outcome at follow-up at 3–10 years postoperatively was reported as excellent or marked improvement in 87% of patients without persistent side effects. The long-term results of non-selective sternocleidomastoid sectioning in another series of 11 patients, in contrast, were less favorable.29

**Intradural rhizotomy and nerve sectioning**

Intradural anterior cervical rhizotomy was the most common operation for CD before the advent of peripheral denervation.30,31 Several variations of this procedure have been developed. The ‘standard’ procedure includes intradural sectioning of the C1–C3 anterior roots and those rootlets of the spinal accessory nerves which supply the sternocleidomastoid muscles. A small suboccipital craniotomy widening the posterior rim of the foramen magnum and laminctomies of the three upper cervical vertebrae are performed. After opening of the dura, the upper spinal cord, the medulla oblongata, the cerebellar tonsils, the upper cranial nerve roots, the spinal accessory nerves, and the blood vessels of the cervicomedullary junction and the upper cervical medulla are visualized with the operating microscope. The anterior roots are stimulated with a bipolar nerve stimulator and then divided. Any arterial blood vessels that accompany the nerve roots should be spared. Denervation with this approach, in general, is limited downward to the anterior root of C3 if it is performed bilaterally. The C4 root may be sectioned on one side but endangers functioning of the diaphragm. Thus, this intradural approach cannot control dystonic activity, which is mediated via the C4–C6 roots. Since the ‘standard’ approach was rather non-selective and resulted in high complication rates, modified techniques aimed to denervate the dystonic muscles and to preserve normal activity. Thus, for example in a patient with rotational CD, unilateral anterior rhizotomy would be combined with contralateral spinal accessory nerve section.

Both the reported results and the complication rates in different series were highly variable. Most studies claimed useful postoperative improvement in 60–90% of their patients.30,31 It has been unclear, however, to what degree symptomatic amelioration of the abnormal postures or movements translated to improvement in functional disability with regard to the relatively high number of side effects. In the series of Friedman et al, the head was described to return to a neutral position in 59% of the patients postoperatively.31 The likelihood of the head returning to a normal position postoperatively was inversely related to the duration of CD. Some studies have reported only very modest results after anterior intradural rhizotomy. Hernesniemi and Keränen, for example, reported no patient with an outcome considered as good based on their patients’ self-assessments for the surgical result, disability, and working capacity.32 Complications of the standard bilateral intradural denervation are frequent and may be persistent and disabling. Mortality with the standard procedure ranged between 0% and 1%, in general, but was as high as 12% in some series. Side effects include dysphagia, weakness of the neck, cerebrospinal fluid fistulas, and infection. Weak or unstable neck has been estimated to occur in about 40% of patients after bilateral rhizotomy, and transient dysphagia in about 30% of patients.32 Radiologic swallowing abnormalities were described in as many as 95% of patients postoperatively, frequently representing aggravation of pre-existing pharyngeal dysfunction.33 In rare cases, bilateral infarctions of the medulla oblongata with bilateral Wallenberg syndrome or ischemia of the upper spinal cord with tetraparesis were reported.34 The procedure is much safer and accompanied by far less morbidity with selective approaches.

**Microvascular decompression**

Microvascular decompression (MVD) of the spinal accessory nerve for treatment of CD has been used in analogy to the therapeutic benefit of this procedure in other cranial neuropathies such as hemifacial spasm.35 The existence of two pathogenetically different types of CD has been suggested by proponents of MVD. The first is CD of ‘central’ origin and the second is ‘spasmodic torticollis of 11th nerve origin’.36 However, it is difficult to understand how MVD of the spinal accessory nerve should work, both regarding the pathophysiologic concept of MVD and the fact that almost always other muscles than the sternocleidomastoid are involved in dystonic activity. Outcome data of MVD for treatment of CD are very limited. Often, nerve sectionings were performed in addition to MVD.37 Jho and Jannetta
claimed a cure of CD in 65% of their patients (13 of 20 patients), improvement considered as significant in 4 patients (20%), as moderate in 1 patient (5%), and as minimal in 2 patients on long-term follow-up between 5 and 10 years after MVD.35 In some series high rates of surgical morbidity were described. Thus far, no prospective studies using appropriate assessment with standard rating scales have been published. With the present available data, microvascular decompression cannot be recommended as a treatment option for CD.

**FUNCTIONAL STEREOTACTIC SURGERY**

Current functional stereotactic surgical options include lesioning and DBS of the globus pallidus internus (GPI) and the thalamus. The pallidum was rediscovered in the mid 1990s as a target for dystonia, whereas DBS for treatment of dystonia was introduced only recently.38–40 The indications for the different therapeutic options and the goals to be achieved depend on the distribution of dystonia, the severity, the etiology, the presence of other neurologic symptoms, and the patient’s age. Hemidystonia, which is frequently secondary to contralateral caudatoputaminal lesions, may be stable after delayed onset and progression over several years, whereas idiopathic dystonia may still progressively spread to other body parts later on and then limit the benefit of surgery. Owing to the relatively small number of patient series, the variations in surgical methods, and the inconsistent outcome assessments, no definite recommendations about the best surgical options and ideal targets can be made for many dystonic disorders. In general, the GPi appears to be the preferred target for idiopathic genetic and other primary dystonias. The focus on the treatment of dystonia these days has shifted more and more to DBS because of the lower risk of performing bilateral surgery in one session.4,5

**Thalamotomy**

The target for thalamotomy for treatment of dystonia has been much more variable among different surgeons than thalamic targets for tremor. Thalamotomy has involved the nucleus ventralis oralis anterior and posterior, the nucleus ventralis oralis internus, the ventralis intermedius, the subthalamic region, the centrum medianum/nucleus parafascicularis complex, and the pulvinar thalami.12 The comparison of the symptomatic and functional outcome of the reported series of thalamotomy is limited because of the heterogeneity of patients, variations of the target, differences in evaluation of outcome, and variable length of follow-up. Immediate postoperative improvement is less striking than in other movement disorders such as PD or essential tremor (ET). Often, further amelioration can be observed within months after the operation. Postoperative improvement has been reported, in general, in 25–80% of patients with generalized dystonia, and in 33–100% of patients with hemidystonia.41–43 Andrew and colleagues found moderate or significant overall improvement in 25% of patients with generalized dystonia and in 100% of patients with hemidystonia; the benefit was more significant in secondary dystonia than in primary dystonia.42 Tasker and associates described that 68% of patients with secondary dystonia had more than 25% clinical improvement, whereas this was the case in only 50% of patients with primary dystonia.43 Patients with secondary dystonia also appeared to have more sustained improvement than patients with primary dystonia with thalamotomy. In the series of Tasker et al, 65% of patients with primary dystonia, but only 31% of patients with secondary dystonia, gradually lost the initial postoperative benefit. Immediate postoperative side effects were described in 7–47% of patients in different series. Transient side effects most commonly included confusion and contralateral weakness; similarly, as with PD, postoperative speech impairment has been observed more frequently after bilateral thalamotomies. Long-term follow-up has been rarely available. Cardoso et al reported moderate or significant improvement in 50% of patients with secondary dystonia at a mean follow-up of 41 months, and in 43% of patients with primary dystonia at a mean of 33 months.44 Krauss et al observed sustained moderate improvement in 3 of 6 patients with post-traumatic hemidystonia at a mean follow-up of 18 years.45

**Pallidotomy**

The pallidal target for surgical treatment of dystonia is located in the posteroverentral lateral GPi, basically at the same site as that used for pallidotomy in Parkinson’s disease. Single-unit extracellular recording is helpful in our opinion to delineate the final target more precisely and to determine the external and internal borders of the pallidum. Most neurosurgeons place two radiofrequency lesions in the GPi, 2 mm apart, along the trajectory of the radiofrequency probe. Whereas improvement of phasic dystonic movements may be seen early after surgery, tonic dystonic postures improve over much longer time.

Pallidotomy has been reported to be effective in various dystonic disorders, including generalized dystonia, segmental dystonia, and hemidystonia, yielding about 50–80% improvement in most studies.46–50 In the Baylor College of Medicine series, 14 out of 16 patients with generalized dystonia or hemidystonia benefited from...
meaningful improvement after pallidotomy.41,48 Eleven patients had bilateral procedures, staged in 3 patients and concurrent in 8 patients. It was difficult to compare the efficacy of unilateral vs bilateral surgery, as the decision was clinically based upon the anatomic distribution of the dystonia. Patients with genetic dystonias (both DYT-1 positive and DYT-1 negative) consistently demonstrated marked improvement, whereas this was less dramatic and less consistent in secondary dystonia. At a mean of 1.5 years follow-up, improvement was sustained. Pallidotomy has been shown also to improve symptomatic dystonia resulting from other neurodegenerative diseases such as Hallervorden–Spatz disease and Huntington’s disease in single cases.51,52 In some studies, a partial recrudescence of dystonic symptoms over time has been noted. The response of dystonia to pallidotomy may depend on etiology, according to the experience made at different centers. It appears that patients with primary dystonia respond well to pallidotomy, whereas patients with secondary dystonia without structural lesions enjoy moderate improvement, and patients with secondary dystonia and structural brain lesions often have only minimal benefit.53 Nevertheless, single patients with secondary dystonia may gain substantial benefit from pallidal surgery.54 Overall, the response of secondary dystonia to pallidal surgery appears to be somewhat unpredictable, and many of these patients do not show much benefit.55 Functional stereotactic surgery for choreoathetosis secondary to cerebral palsy (CP) is difficult to evaluate. Bilateral pallidotomies yielded limited benefit in such patients, with objective improvement of the movement disorder of up to 42%; however, this was at a high rate of persistent complications.56,57

Yoshor and colleagues recently compared the effectiveness of thalamotomy and pallidotomy in a retrospective series of 32 patients with primary and secondary dystonias.50 Eighteen patients underwent thalamotomies, and 14 patients had pallidotomies. Although comparisons were limited according to various differences between the two surgical groups, patients with primary dystonia who underwent pallidotomy demonstrated significantly better long-term outcomes than did patients who underwent thalamotomy. In this series, patients with secondary dystonia experienced more modest improvement after either procedure, with little or no difference in outcomes between the two procedures.

Deep brain stimulation

Since its introduction a few years ago, pallidal DBS has become one of the mainstays in the treatment of medically refractory dystonia (for review see References 3–5). Pallidal DBS is performed with the quadripolar 3387 DBS electrode (Medtronic Minneapolis, MN, USA) which has 1.5 mm gaps between the single contacts. Patients with dystonia are stimulated continuously. For the initial programming we usually use bipolar settings with the deepest contact, most frequently contact 1 set to negative, and the next contact, usually contact 2 set to positive, while the other electrodes remain neutral. Initial stimulation settings include a frequency of 130 Hz, a pulse width of 210 μs, and amplitudes between 2.0 and 4.0 V as tolerated by the patient. During the next few months, the intensity of stimulation is gradually increased, staying below the threshold that elicits unwanted effects. The threshold for undesired effects such as perioral tightness, which also may involve some difficulty swallowing or speaking, dizziness, tingling, and capsular responses, tends to shift during progressive adjustment of stimulation amplitude. If no optimal benefit of the movement disorder is achieved upon chronic stimulation, alternative electrode contacts or combinations are activated. Some centers also start with monopolar stimulation, or use two contacts as cathodal with case or another contact anodal. DBS settings are adjusted within the first year after surgery. In general, only minimal adjustment, if any, is required later.

Sometimes it may take months before the full benefit of pallidal DBS is notable. In contrast, however, dystonia may reoccur within minutes or hours when the implantable pulse generators (IPGs) are switched off.58 Since both pulse width and voltage are higher in dystonia patients than in Parkinson’s disease, depletion of the IPG batteries may occur within 2 years. Amplitudes have ranged between 2.2 and 7.0 V in our dystonia patients. Most centers perform contemporaneous bilateral surgery to implant the electrodes. Failure of chronic GPi stimulation may result in a medical emergency, in particular in patients with the Kinetra, an IPG used for bilateral stimulation. Hardware failure caused by unilateral lead dysfunction results in a more gradual and progressive recurrence of symptoms, perhaps accounted for in part by the presence of the retained contralateral stimulation.

DBS has the advantages over lesional surgery of being reversible and adaptable. It avoids concern about the effects of lesioning on the developing brain in children and allows bilateral surgery to be undertaken more safely because of the reduced level of morbidity involved with DBS compared to lesions. However, DBS may include hardware failure, high costs, time-consuming follow-up as well as those related to the perioperative period, such as infection and possible intracranial hemorrhage. The overall rate of hardware-related problems has ranged from 8 to 65%.59

Several pilot studies have shown that DBS, in particular pallidal DBS, is reasonably safe and efficacious in a variety of dystonic disorders. DBS for treatment of
dystonia has received FDA (Food and Drug Administration) approval in the form of an HDE (humanitarian device exemption) in the USA and CE (Conformité Européenne) certification in Europe. Larger studies are underway to validate the observations on DBS for dystonia being made in smaller studies that have been published. A French multicenter study investigated the effect of bilateral pallidal DBS in primary generalized dystonia, including blinded assessment of clinical outcome. A German multicenter study is investigating the long-term outcome of GPi DBS for primary generalized and segmental dystonia by a randomized double-blind study design. Furthermore, multicenter studies are being conducted to study the effect of pallidal DBS on tardive dystonia and cervical dystonia. Preliminary results of the Canadian study have become available. It appears feasible now also to explore possible new indications for DBS, such as paroxysmal dystonia, blepharospasm-oromandibular dystonia, and other focal dystonias.

Cervical dystonia

Since CD is the most frequent dystonic movement disorder, DBS might be of special interest in this group of patients. In particular, pallidal DBS can be a very useful treatment option in those patients who do not respond satisfactorily to BTX injections and who are not good candidates for other less costly interventions. Serial selective peripheral surgery, as discussed above, is still considered the therapy of first choice in most of these patients. Peripheral surgery, however, is not indicated in a subset of CD patients, including those with head tremor and myoclonus, marked phasic dystonic movements, sagittal and lateral translation, anterocollis, and combined complex forms of CD. Although, at present DBS is limited mostly to such patients with more unusual manifestations of CD, it might be considered an alternative in other types of CD in the future.

Bilateral pallidal DBS is favored over unilateral DBS in CD for a variety of reasons. There is evidence from various studies that CD patients have bilateral basal ganglia dysfunction, regardless of the phenomenologic manifestation in the individual patient. Positron emission tomography (PET) investigations, for example, demonstrated higher glucose metabolism in the lentiform nucleus bilaterally in CD patients without significant differences regarding the laterality, the specific pattern, or the severity of CD. Bilateral basal ganglia involvement was also shown in a single-photon emission computed tomography (SPECT) study investigating striatal D2 receptor binding in CD patients. Furthermore, transcranial magnetic stimulation studies revealed that there is considerable bihemispheric presentation of neck muscles. Also, review of the early literature on ablative surgery for CD showed that patients who had bilateral surgery overall had better results than those who underwent unilateral surgery, although at a higher rate of side effects. When a unilateral approach was chosen, there were quite different opinions on the side to be operated on. Cooper, for example, recommended thalamotomy contralateral to the dystonic sternocleidomastoid muscle, while Hassler and Dieckmann thought that an ipsilateral thalamotomy should be performed. This discussion has been revived recently, when opposing suggestions were made for unilateral DBS in CD patients based on the experience in single cases.

Since the first patients with CD were treated by GPi DBS in the late 1990s, beneficial results have been reported by a number of centers. Bilateral pallidal stimulation produces both symptomatic and functional improvement, including marked relief of pain in the long term in patients with complex CD. In our series, the gradual amelioration of CD over months was reflected by improvement of a modified TWSTRS scale on subsequent follow-up examinations, and the mean scores were better at 1 year after surgery than at 3 months postoperatively. Formal follow-up evaluation, at 20 months after surgery, demonstrated a 63% improvement of the TWSTRS severity score, a 69% improvement of the disability score, and a 50% improvement of the pain score. These figures correspond well with those from the Oxford group, which showed similar amelioration for the subscores severity (64%), disability (60%), and pain (60%) at 19 months follow-up. Our first patient has reached 9-year follow-up meanwhile. She still has marked benefit from continuous stimulation, but she underwent a total of three revisions over the years to replace fractured leads. Overall, 4 out of 5 patients with CD for whom we have long-term follow-up of 3 years or longer had sustained improvement comparable to 1 year postoperatively. In some patients, relief of pain preceded improvements observed in the other aspects of the TWSTRS scale. Single patients were reported in whom relief of pain was the most prominent feature. Overall, there appears to be less interpatient variability in patients with CD than in patients with other dystonic disorders. We have used chronic pallidal stimulation also as an adjunct in patients with cervical dyskiniasias and secondary cervical myelopathy prior to performing spinal surgery or spinal stabilization.

The costs of chronic pallidal stimulation are relatively high for patients with CD. This is due to the relatively younger age of patients with CD as compared, for example, to those with Parkinson’s disease, but also to the higher energy needed for chronic stimulation.
In particular, in this group of patients it would be desirable to develop new DBS strategies to reduce costs. Possible alternatives could include the development of rechargeable IPG batteries, the production of batteries that have a longer duration, or the exploration of other stimulation modes.

**Generalized dystonia**

The most beneficial results with pallidal DBS were reported in children with genetic DYT1-positive generalized dystonia. In their first publication on this subject, Coubes and colleagues described a mean improvement of 90% in the Burke–Fahn–Marsden Dystonia Movement Scale (BFMDMS) at a follow-up of at least 1 year after surgery in 7 patients (mean age of 14 years at operation). Improvement was gradual within months after implantation of the electrodes. Six children managed to walk without assistance after surgery and became functionally normal. Drugs were reduced in all patients, resulting in improvement of alertness. All children returned to school. The Montpellier group recently reported follow-up data for a larger number of patients. In this study, there was a mean improvement of 71% in the Burke–Fahn–Marsden (BFM) motor scores of 15 patients with primary DYT 1-positive dystonia 1 year after surgery, and a mean improvement of 74% in a group of 17 patients with primary dystonia of unknown etiology. Adverse effects have been minimal. Several other groups have reported similar results. Nevertheless, single cases that did not achieve the expected dramatic postoperative benefit were also reported. Also, in adult patients with primary generalized dystonia, remarkable benefit is achieved with bilateral pallidal DBS. In two adult patients with a positive family history of dystonia, for example, BFM dystonia scores improved by 74% 3 months postoperatively, by 75% after 1 year, and by 74% after 2 years. The improvement of the motor scores was accompanied by a 67% improvement of disability scores. In 12 patients with generalized dystonia from the Oxford group, there was a mean 48% improvement in the BFMDMS severity scores, and a 38% improvement in the disability scores. The lesser improvement in this group was most likely due to several issues such as greater variability in clinical background, the effect of treatment duration, and the duration of disease onset to treatment, which was more than 12 years. Overall, the response of generalized dystonia to pallidal DBS seems to depend on etiology, similar to the experience with pallidotomy.

The recently published class III French multicenter study included blinded assessment of clinical outcome. The mean improvement of the BFM rating scale in this study was 54% on average, and the mean improvement of disability was 44% at 1 year postoperatively. In addition, general health and physical functioning scores were significantly improved according to the SF-36. There was no permanent morbidity. It was also shown in this group of patients that no behavioral or mood changes were found. Also, there were no cognitive changes, except mild improvement in executive functions. In the German randomized controlled multicenter study which included 40 patients, the range from baseline 3 months after randomization was significantly greater in the neurostimulation group (15.8 points on the BFM scale) than in the sham-stimulation group (1.4 points). Substantial improvement in all movement symptoms except speech and swallowing was noted 6 months postoperatively.

**Segmental and focal dystonia**

Substantial benefit has also been described in patients with primary but more confined segmental dystonia. Improvement with bilateral DBS in such cases ranged between 50% and 90% of dystonia scores. We reported on a 67-year-old man with risperidone-responsive segmental dystonia whose BFM motor scores improved by 86% at 9 months follow-up. In this case, a more complex interaction with medication and stimulation was found, an issue that has been rather neglected thus far in DBS for dystonia. Although it has been claimed repeatedly that tardive dystonia, which often manifests as segmental or focal dystonia, is a good indication for pallidal DBS, little has been published on this subject. Nandi et al reported marked relief of tardive camptocormia with pallidal DBS in a patient whose movement disorder was otherwise refractory to medical treatment.

Improvement of cranial dystonias was reported in patients who were operated on for segmental or generalized dystonia. In a patient with Meige syndrome, BFM subscores had improved by 92% for eyes, by 75% for mouth, and by 33% for speech and swallowing at 2 years postoperatively. Meige syndrome and other focal dystonias might be of interest to be further explored with pallidal DBS in the future.

In a recent study on a series of 14 patients with segmental dystonia who underwent pallidal or thalamic DBS, there were stable improvements of motor scores on follow-up at 17 months after surgery (preoperative BFM 53.8; at follow-up 13.5) which was paralleled by improved disability scores (preoperative BFM disability 6.0; at follow-up 3.9). In 3 patients stimulation-induced hypokinetica dysarthria occurred with higher voltages, which limited the therapeutical benefit in these patients.
In the subgroup of 10 patients with pallidal DBS, there was a significant decrease of the total SF-36 scores by 40% at a mean of 7.5 months after surgery and by 51% at 17 months after surgery.80

Secondary dystonia

DBS for treatment of secondary dystonia is much more complex than that of primary dystonia. Although thought to be less effective in secondary dystonia, pallidal stimulation was reported to be successful in some individual cases.81,83 Thalamic DBS has been suggested to be more useful in such cases, but data published thus far do not allow us to draw any conclusions. Before the routine use of GPi DBS for dystonia, patients with medically intractable dystonia underwent thalamic DBS in Grenoble.83 Although there was little change in formal dystonia scores, about half of the patients achieved a good functional result. Thalamic stimulation was also efficient in patients with post-traumatic hemidystonia, postanoxic dystonia with basal ganglia necrosis, paroxysmal dystonia, and for the myoclonic component of myoclonic dystonia91 (for review see References 4 and 5).

Promising results were described in 2 patients with choreoathetosis after bilateral GPi DBS.92,93 Our experience with pallidal DBS in adult patients with cerebral palsy (CP) was more varied, and the benefit was minimal or irrelevant in some patients.80 The mean improvement in BFM scores in 4 patients with choreoathetotic CP was 12% at 3 months postoperatively, 29% at 1 year, and 23% at 2 years, which was not significant as compared to preoperatively. Two of these patients thought they had achieved marked improvement at 2 years postoperatively, although results of objective evaluation were less impressive. In these 2 patients there was a minor but stable improvement in disability scores. This discrepancy between the objective and the subjective evaluation is remarkable, and is most likely due to the fact that even slight improvement may mean a lot for these severely disabled patients. Given the modest objective improvement, if any, in patients with choreoathetosis, however, it is difficult to recommend pallidal DBS for this indication, despite the positive self-rating of individual patients. Further studies are necessary before DBS is applied more widely for this indication.

Hemidystonia is a typical manifestation of secondary dystonia. As discussed above, the thalamus was the target of choice for ablative surgery in hemidystonia.41,55 The results with pallidal DBS are rather heterogeneous. Whereas there was no or little improvement in some studies,70 unilateral DBS contralateral to the hemidystonia resulted in sustained marked improvement of dystonia-associated pain, phasic dystonic movements, dystonic posture, and functional benefit at long-term follow-up in other patients.54,83

INTRATECAL BACLOFEN

Intrathecal baclofen (ITB) has been used now for more than a decade to treat patients with dystonia.94,95 In particular, patients with generalized secondary dystonia, and patients with both dystonia and spasticity are considered good candidates for this treatment option.96,97 The mechanisms of action by which ITB treatment alters dystonia may involve both spinal and cranial levels. Intrathecal delivery of baclofen in dystonia patients results in reduction of dystonia and associated pain. In contrast to patients with spasticity, patients with dystonia require higher dosages of baclofen, they are more likely to become resistant to baclofen, and they are less likely to experience substantial improvement in function.

ITB is administered on a long-term basis through an implanted infusion pump. Pumps can be implanted in adults and in children weighing at least 20 lb (9 kg). Prior to pump implantation, patients may be screened with bolus injections of baclofen via lumbar puncture or by continuous infusion via an external micropump and an intrathecal catheter. Responses are expected within 6–12 hours. When the dystonia responds to the testing, a pump is implanted subcutaneously, usually in the right or left lower quadrant of the abdomen, and connected to an intrathecal catheter, which is inserted at approximately L2–3 and advanced cephalad to C7–T1. Regarding the need for numerous dose adjustments during chronic treatment, programmable pumps are clearly advantageous. Pumps are programmed postoperatively. Daily dosages for dystonia range from 200 to 2000 µg baclofen, usually between 500 and 1000 µg, which is higher than the dose needed to treat spasticity.

Sustained improvement of dystonia was reported in about 70% of published cases.94 In a series of 86 patients with generalized dystonia ranging in age from 3 to 42 years (median age, 13 years), dystonia was associated with cerebral palsy in 71%.98 Response to ITB was tested by continuous infusion in 72% of patients, and by bolus injections in 17%. Pumps were implanted in 77 patients. Dystonia scores were significantly decreased during follow-up up to 24 months. Patient questionnaires indicated that quality of life and ease of care improved in 86% of patients. Speech improved in 33% of patients, swallowing in 26%, upper limb function in 34%, and lower extremity function in 37%. Overall, surgical complications occurred in 38% of patients, including Cerebrospinal fluid (CSF) leaks, infections, and catheter problems, and ITB side effects in 26% of patients.
including constipation in 19%, decreased neck/trunk control in 8%, and drowsiness in 6%.

SURGERY FOR BLEPHAROSPASM

The mainstay in the treatment of blepharospasm is the local injection of BTX in the affected muscles. Surgical interventions are reserved for those patients who do not achieve adequate relief by the injections, or those who develop resistance with repeated injections. It is important to note that patients with blepharospasm who do not benefit adequately from BTX injection may have a component of apraxia of eyelid opening. While Jordan and colleagues reported a 7% incidence of apraxia of eyelid opening in essential blepharospasm, approximately 50% of patients with BTX failure who were referred for myectomy procedures were diagnosed with this condition. Since patients in advanced stages of blepharospasm may become functionally blind and unable to care for themselves, contemporary surgery can be a valuable treatment option. Neurectomies and selective nerve avulsions directed at the denervation of the contracting muscles in blepharospasm have been largely abandoned because of their relatively high recurrence rates and frequent side effects. Since Anderson and colleagues introduced and popularized selective myectomy procedures in the late 1970s, these approaches have been adopted more widely. Currently, extended limited myectomy and full myectomy are the procedures of choice. Full myectomy is technically more demanding and complication rates are higher with this procedure.

The extended limited myectomy procedure has been suggested as the first step when considering myectomy operations. The myectomy is performed through an eyelid crease incision, and involves the removal of the pretarsal orbicularis muscle, the preseptal orbicularis muscle, part of the orbital orbicularis muscle, and part of the corrugator supercilialis muscle. In patients with apraxia of eyelid opening, the levator aponeurosis can be tightened to correct upper eyelid position, and also the lateral canthal tendon. This results in improvement of function and cosmesis while reducing squeezing in the upper eyelid. Few of these patients may require a frontalis suspension as a second procedure if the eyelids still do not open well enough. Extended limited myectomy has been described to result in less lymphedema, ecchymosis, and supraorbital hyperesthesia, and patients recover much faster as compared with those after the full myectomy procedure. Also, this approach results in fewer corneal surface exposure problems and dry eyes. Often, patients in whom BTX injections had failed preoperatively respond to residual blepharospasm after extended limited myectomy.

Full myectomy is indicated in patients who did not achieve sufficient benefit with the more limited myectomy approach. It is performed through a brow incision above and a blepharoplasty incision in the lower eyelids. Then, the remaining orbicularis oculi muscles, and the procerus and corrugator muscles are removed as well, and the lateral canthal tendon is again tightened. Upper eyelid lymphedema is of utmost concern since it may last for weeks, months, and even years. Such patients may not be able to open their eyelids because of mechanical resistance, and the chronic swelling can be a difficult problem to resolve. The occurrence of chronic lymphedema is much rarer with the use of newer techniques. Other potential complications of the myectomy procedures include infection, hematoma, brow hair loss, eyelid retraction, trichiasis, and canthal deformity.

In a study from the Mayo Clinic, 94% of patients thought that myectomy procedures had provided both short-term and long-term benefits. The long-term need for BTX injections was decreased in about 30% of patients, and increased efficacy or longer-lasting effects were noted, postoperatively. Patients with severe disability from blepharospasm benefited more from myectomies than did patients with relatively mild symptoms.

An alternative procedure, the so-called frontal sling operation, consists of frontalis suspension, which has been used earlier for treatment of ptosis. In a series of 132 patients, improvement after surgery was achieved in 73% of patients. No serious corneal complications were observed. The beneficial effect of surgery, in general remained stable over the years. Most patients continued to have additional botulinum toxin injections. Frontalis suspension may be considered less-invasive surgery that is reversible upon removal of the silk or Gore-Tex sutures used in this procedure.

With regard to the recent development of pallidal DBS for treatment of dystonia, this new therapeutic modality might also be envisioned as an option in patients with severe and otherwise intractable blepharospasm. As outlined above, it has been used thus far successfully in single patients with Meige syndrome, where it improved both orofacial dyskinesias and blepharospasm.

REFERENCES

3. Albanese A, Barnes MP, Bhatia KP et al. A systematic review on the diagnosis and treatment of primary (idiopathic) dystonia and


Role of the physiotherapist

Jean-Pierre Bleton

INTRODUCTION

The usual treatment for pathologies affecting motor control involves motor rehabilitation, which explains the wide consensus of the medical profession regarding the use of rehabilitation to treat dystonia. This therapy, which is now well developed and structured, aims to give patients as much independence as possible, in a palliative or curative way. Although physiotherapy seems to play an important role in the treatment of people suffering from dystonia, rehabilitation professionals have few reliable scientific studies upon which to build their approach, apart from the recent studies of Byl and McKenzie for writer’s cramp and an earlier study by Pierre Rondot on spasmodic torticollis. Nevertheless, from the different approaches presented in the literature dealing with the rehabilitation of dystonia, it seems that rehabilitation focused on correcting the clinical abnormalities observed in dystonia reduces its severity.

Despite there being a great deal of similarity between the different forms of dystonia, each case is unique and requires its own rehabilitation program based on clinical evaluation.

REHABILITATION OF CERVICAL DYSTONIA OR SPASMODIC TORTICOLLIS

Many patients suffering from cervical dystonia (CD) or spasmodic torticollis (ST) are now referred to a physiotherapist by their neurologist to complement the effect of medical treatment and botulinum toxin injections. The specific rehabilitation of CD has long been a source of interest and comment, with the prescription of specialized exercises by such famous neurologists as Duchenne de Boulogne in 1862, Brissaud in 1895, and Meige and Feindel in 1901. Today, rehabilitation is still recommended in association with medical treatment.

No one physiotherapy treatment has been found to be universally effective. Rather than one single method, there are several strategies, which deal with the various clinical presentations. The exercise program is selected in the light of the pathophysiology.

Elements of pathophysiology relevant to the development of rehabilitation programs

Muscular contraction is abnormal in dystonic patients. Dystonic movement reveals excessive co-contraction between agonistic and antagonistic muscles. This pathologic muscular activity reduces the speed and force of the movement. The rehabilitation strategy consists of rebalancing the activity between dystonic muscles and underperforming antagonistic muscles.

Continuing activity of the dystonic muscles leads to a deficit of the strength of their antagonists. The rehabilitation program tries to focus selectively on the underperforming muscles and not to overflow on other muscles.

Electromyographic (EMG) recording of passive neck movement shows a prominent paradoxical muscular activity of the dystonic muscles during their shortening. This pathologic localized postural reflex is called the ‘shortening reaction’ or Westphal’s phenomenon. Therefore, the objective of physiotherapy is to keep the head in the opposite direction, away from the torticollis side.

CD leads to abnormal reorganization of voluntary gestures. Instead of calling on synergistic muscles to carry out a movement, patients involve dystonic muscles that disturb the correct execution of the neck movements. This phenomenon is called overflow.

The orientation, speed, localization, and intensity of the motor exercises are selected in order to obtain the specific intended contraction.
The intensity of dystonia varies according to the muscular effort, the degree of tension, and the position of the body. CD is less important or even disappears when the body is relaxed. Thus, the physiotherapist chooses working positions (lying, sitting, or standing) adapted to the capabilities and tonic state of the patient.

Cutaneous stimulation of the dystonic muscles reinforces the pathologic activity. The close spatial relationship between the site of cutaneous stimulation and the contracting muscles explains why massage is not recommended in the treatment of dystonia. On the contrary, EMG recording shows reduction of myoelectric activity during an antagonistic gesture or sensory trick (e.g. there is frequent reduction of myoelectric activity when the head is supported or leaning against a wall).

### Development of a specific rehabilitation program for cervical dystonia

Every CD case is unique, and therefore the physiotherapy approach must take into account the specific clinical presentation. The physiotherapy management of the tonic forms aims to recover the balance between the actions of the different muscles that play a role in the position of the head. On the other hand, the physiotherapy treatment of the myoclonic forms aims to remove involuntary and inappropriate head movements, by conscious and coordinated movements.

As the aim is to obtain stability of the head on midline, the physiotherapist develops an approach to treatment with realistic steps to be reached within a reasonable time frame. For some patients, treatment of pain is the priority, whereas for others it is stiffness of the neck or reawakening of specific muscles. Regular assessments allow the treatment to be constantly reshaped to fit the clinical evolution (Table 20.1). When possible, physiotherapy assessment is performed before the botulinum toxin injections have modified the clinical presentation. The muscles identified as causing CD are a target for the botulinum toxin injections. This identification is also relevant to the physiotherapy treatment, which aims principally to relax the tension in the dystonic muscles and to reinforce the activity of the corrective muscles.

### Pain management

Patients often complain of a sore neck or cervical discomfort. This seems to be due to the hyperactivity of the dystonic muscles. The most common sites of pain are located on the sternoclavicular joint, acromioclavicular joint, spinous processes of lower cervical vertebrae, on the insertions of the sternocleidomastoid muscle (SCM) on the clavicle, and on the insertions of the trapezius muscle on the occipital bone. This kind of pain is often reduced by stretching the muscles concerned and by careful mobilization of the painful joints. Electrotherapy, in particular ultrasound therapy, is used for its thermic, vasomotor, and fibrolytic properties.

### Orthopedic consequences

During the sessions, the physiotherapist should attempt to preserve the range of the different cervical and shoulder girdle movements and to decrease the tone of the involved muscles by using local or general relaxation techniques, gentle manual tractions of the cervical region, and deep breaths. Because the cervical region is a vulnerable area, mobilization must always be carried out with care.

### Rehabilitation of the clonic form of cervical dystonia

Rehabilitation of the clonic form involves two stages of treatment.

The first stage consists of maintaining immobility for a gradually increasing length of time. Initially, this immobility is sustained locally in the cervical region, then progressively during activities such as walking or moving the arms. The head can be kept immobile with the use of techniques such as a light touch on the cheek (equally effective whether performed by the patient or the physiotherapist), electrical or manual stimulation of the corrective muscles (often the SCM on the side of the pathologic rotation), or even rotation of the gaze to the side opposite to the CD (oculocephalogyric reflex), which induces contraction of the corrective cervical muscles. Patients train themselves to maintain immobility in front of a mirror or with the help of a myofeedback apparatus. The supine position abolishes the spasms or noticeably moderates them. The support of the occipital bone against the horizontal plane of the table seems to play the principal role. The posture ‘hands folded behind the head’ decreases the intensity of the spasms and is taught as an exercise to repeat during the course of the day. Repetitions being a strong factor of improvement, patients are encouraged to constantly fight against the spasms and to organize their environment in order to facilitate corrective action.

The second stage of treatment is applied when patients are capable of maintaining their head immobile on their own. The aim is to suppress automatic and pathologic gestures and to develop conscious and natural movements. It relies on two basic principles: reinforcement of the weakened corrective muscular activity and...
Table 20.1 ST Report Form. (Reproduced from Bleton, with permission.)
recovery of normal synergy between the muscles involved. Myofeedback is a useful complement to the physiotherapy treatment, but, today, this approach has lost some of its appeal compared to current practice, which favors the development of the interaction between the patient and the physiotherapist.

Rehabilitation of the tonic form of cervical dystonia

In this presentation of CD, the rehabilitation strategy aims to reduce tension in the muscles responsible for the CD while reinforcing the action of the corrective muscles. By acting upon both the hyperactive, dystonic muscles and their weakened antagonists, physiotherapy creates conditions which favor the maintenance of the head in a balanced position and prolongs the action of botulinum toxin injections carried out to weaken the muscles responsible for the CD.

The dystonic muscles relax in response to gentle but sustained traction of the neck. It then becomes possible to obtain a contraction of the corrective muscles, benefiting from the relaxation of their antagonists. The tractions are repeated as soon as the spasms reappear.

These mobilizations are carried out with the patient relaxed, lying on the back with the head resting on the plinth. In the rare situations where pressure on the occipital region triggers or increases spasms, the mobilizations can be carried out with the patient in prone position or on all fours.

The muscular approach consists of stretching each of the muscles responsible for the CD and controlling spasms by using ‘favorable activities’ – such as the direction of the gaze – that play a significant role in the correction of the cervical movement. The spasm intensity diminishes if the eyes are turned away from the spasm side. The positive effect of this oculocervical coordination is used in daily activities. Other favorable activities are tactile inputs. Gentle friction on the jaw on the opposite side to the CD makes the head turn towards the stimulus as if pulled by a magnetic field.

Deficient muscles are reinforced by voluntary contraction (Figure 20.1). Static contractions in the inner range of movement are carried out in order to avoid muscular overflow and prevent the effect of the shortening reaction. The head is gradually shifted from the opposite side of the CD to the neutral position. Coordination of the action between deficient and dystonic muscles re-establishes localized postural balance. Patients learn how to immobilize the head in a lying position, then sitting, and finally upright. When patients have managed to control the head in the physiotherapy context, they then attempt to transfer this control to everyday life.

Once the head is well positioned, one deals with the compensatory attitude of the upper body. The torso and shoulder girdle are frequently involved in the pathologic posture. Electrical muscle stimulation provides a boost to this muscular reinforcement. The duration of the current, along with its onset and offset, are regulated so as to avoid sudden muscle jerks. The patient improves, not by remaining passive, but by accompanying the electrical stimulation with a voluntary corrective movement.

Patient involvement

As a matter of course, all sensory tricks and orthopedic appliances must be removed. Sensory tricks are a constant reminder of cervical dystonia and rigid cervical collars provoke nociceptive stimuli, which create spasms or increase their intensity. Patients must understand their condition and recognize the muscles involved in their particular case in order to correct their abnormal activity. Patients are advised about the organization of their environment in order to stimulate the contraction of the corrective muscles and to turn the gaze to the same side. Between treatment sessions, patients must respect the don’t-make-it-worse rule by avoiding activities that increase the CD. This is one way to facilitate control.

Physiotherapy and botulinum toxin

Even before the use of botulinum toxin, positive results had been observed after long months of treatment with
myorelaxant drugs, intramuscular injections of alcohol, and rehabilitation. The use of botulinum toxin has changed the prognosis of CD; the short-term improvements are surprising, even if occasionally the long-term outcome is variable and sometimes inconsistent.\(^{10}\) Pierre Rondot has shown in a review of 220 patients with isolated and idiopathic CD treated over a 14-year period that the best therapeutic results were obtained by combining anticholinergic drugs, local injections, and physiotherapy.\(^3\) The weeks following the course of botulinum toxin injections are the ideal time to carry out physiotherapy treatment. Given the weakness of the dystonic muscles, the antagonistic muscles are more able to contract. At the end of the toxin’s effective period, when muscular activity begins to interfere once more, rehabilitation continues unchanged. While awaiting the next injections, physiotherapy focuses on muscle relaxation.\(^{35}\)

Although a prognosis cannot be reached during initial assessment, it can be suggested. Certain rules have been repeatedly confirmed through experience. Tonic form and simple CD in particular have a more positive outcome. Conversely, tremor forms and complex CD respond to a lesser degree to physiotherapy. Nevertheless, application of transcutaneous electrical nerve stimulation (TENS) can be an effective technique on dystonic tremor.\(^{36}\)

Given that so few recent scientific studies have been published, it would be useful to investigate further the effectiveness of physiotherapy for CD.

**TASK-SPECIFIC DYSTONIA: REHABILITATION OF WRITER’S CRAMP AND MUSICIAN’S CRAMP**

**Development of a specific rehabilitation program for writer’s cramp**

The treatment of writer’s cramp is essentially very similar to that of CD. Botulinum toxin, combined with physiotherapy, is currently the best therapeutic approach.\(^{37,38}\)

The effectiveness of rehabilitation depends on the capacity of patients suffering from writer’s cramp to modify the sensorimotor program of writing through training.\(^{39}\) In a preliminary study based on the publications of Byl et al.,\(^{40}\) EMG recording has shown disorganization of the representation of the fingers’ somatotopia in the primary somatosensory cortex (S1) in patients suffering from a functional dystonia of the dominant upper limb.\(^{41}\) The second study compared a cohort of patients who had been suffering from writer’s cramp but were now clinically healed, and who had received only physiotherapy treatment, with a cohort of patients who also suffered from writer’s cramp, but were not treated. This showed a reorganization of the somatotopic representation of the fingers at the level of S1 of the dominant upper limb in patients who had received physiotherapy treatment.\(^{42}\)

The idea that rehabilitation is a legitimate treatment of writer’s cramp has been gaining credibility since the middle of the 19th century, especially following the publications of Henry Meige, whose advice to write little, but slowly, in large, round, and straight movements still applies today.\(^{43}\)

The aim of rehabilitation is not to enable patients with writer’s cramp to write as they used to, but to help their dysgraphia evolve towards a more relaxed movement that is more fluid, legible, and better controlled. One of the foundations of rehabilitation relies on the principle of target muscles, the action of which is considered to be particularly pathogenic and the cause of the abnormality.\(^{44}\) Once identified, these muscles undergo various relaxation techniques (stretching and corrective postures). The aim is to neutralize the muscles in order to break up the dystonic posture. Thus, rehabilitation adds its effects to those of botulinum toxin. Furthermore, the relaxation of the target muscles facilitates the corrective effect of the antagonists.

The lack of muscular coordination and of movement precision are not the only symptoms causing writer’s cramp. The examination of some patients reveals signs of sensory impairment of the hand, which may be reversed with sensory training.\(^{45,46}\) The inability to relax at will also plays an important part. de Ajuriaguerra has shown the benefits of relaxation for particularly anxious people, as well as when and how to use it.\(^{47}\) Once patients are able to actively reach a state of muscular relaxation again (a feeling of heaviness in the arm), they are shown how to hold the writing instrument ergonomically. They then practice under supervision. Patients are given various exercises to develop the nimbleness of the fingers and, using a pencil, to regain fluidity and comfort in holding the writing instrument. It is then a matter of exercising the muscles in order to correct the dystonic posture by involving them in the drawing of curves, convex and concave lines, and complicated patterns.\(^{48}\) The more the practice context is varied, the more the activity of writing becomes simple, precise, and comfortable. The picture-writing exercises and the materials used (long-bodied pencils, multisided pencils, large sheets of paper) are chosen to avoid reproducing the situation to which writer’s cramp is initially linked.

Finally, the aim of the rehabilitation is not to improve one or more muscle actions, but instead to correct a gesture and modify a motor program (Figures 20.2 and 20.3). Hence, Kouindjy’s suggestion, quoted by Macé de
Lépinay, to write with the wrist bent in flexion above the line of handwriting (poignet renversé) to overcome particularly persistent abnormalities in extension.49

Everyone’s handwriting presents thoroughly individual characteristics. However, for the correction of writing dystonia, cursive handwriting is chosen, one of the essential characteristics being to encourage the linking of the letters with the effect of creating a synergy between the cursive movement of the shoulder and the writing movement of the hand.50

During the writing exercises, patients must take care to keep arms, shoulders, and chest relaxed, as well as to maintain calm and regular breathing. They must also try to avoid fragmenting words and separating letters. They must try to keep a balance between humps, ascending and descending loops, yet avoid too much pressure of the point of the writing instrument on the paper. The usual approach relies on a progressively more complex program. During this stage of the training, one must often exaggerate the size of the letters and slow the speed of the writing in order to enable patients to acquire control of the writing gesture. With practice, the handwriting returns to a normal size and speed. Given the very individualized nature of the exercises, sessions are on a one-to-one basis and require from patients a great deal of concentration. Therefore, exercises must be interrupted before signs of fatigue or discomfort appear. Sessions usually last between 30 and 45 minutes and end with relaxation techniques for the muscles. Patients are advised to practice the prescribed exercises regularly each day.

It takes 6–8 months to correct a writing dystonia. There is the risk of causing a relapse if rehabilitation is stopped too soon. A completed or successful rehabilitation is characterized by the disappearance of the abnormal posture, a more relaxed and faster movement, as well as an easier initiation of writing. The handwriting is rounder, more regular, and more legible. Patients can once again enjoy writing.

If the treatment fails, options are limited, apart from the use of information technology. Using the other hand may displace the problem, as the dystonia may in time affect that hand too. There are many special pens and devices offered to people suffering from writer’s cramp. Few, however, have proved to be really effective.51,52

Development of a specific rehabilitation program for musician’s cramp

This form of dystonia is a condition feared by musicians, as it leads to movement control problems that can interrupt their career, occasionally permanently. As in the case of writer’s cramp, the dystonic posture is often one of rotation (e.g. hyper-pronation of the hand, excessive flexion of the wrist, arm internally rotated), and only appears during use of the musical instrument. Musicians lose mastery of the movement of their fingers and this is at the root of their distress. Examination frequently reveals musculoskeletal dysfunctions affecting not only the upper limbs but also the shoulder girdle and often the spine, as well as weakness of certain intrinsic muscles of the hand and an imbalance between the actions of agonistic and antagonistic muscles.53

The resemblance between writer’s cramp and musician’s cramp suggests a similar management, with rehabilitation being of primary importance.

Pain management

Although pain is not a predominant feature of musician’s dystonia, some patients complain of pain related to muscular spasms. The treatment of these painful dystonias consists of resting the most affected part of
the limb, often with the use of an orthosis. Prolonged immobilization is to be avoided, as it weakens the musculature and can be disheartening for the musician. One has often recourse to a rest, alternating the wearing of removable splints and gentle rehabilitation. In all cases, the resumption of playing the musical instrument occurs very gradually and is controlled by the physiotherapist, once pain is no longer present.

**Correction of poor postures**

It is important to watch patients playing their instruments in order to correct faulty postures. Rehabilitation is not limited to the hand, but addresses the whole of the upper limb and spine. Musicians must become conscious of the faulty postures that are at the origin of their dystonia. They must learn to relax the affected muscles, to deprogram the harmful movements, to correct the musculoskeletal dysfunctions, and eventually to relearn normal physiologic movements.54 In front of a mirror, patients gain an awareness of their body and learn how to correct the abnormal postures. A muscular balance must be achieved, followed by relearning how to play the instrument with correct use of the body and of the adapted postures.

It takes at least 1 year to correct a musician’s cramp. The quality and regularity of the treatment are important as is the active participation of patients in their own rehabilitation. With long and comprehensive rehabilitation programs, ‘improvement of the symptoms is attained in most cases’ of musician’s cramp.55 The satisfactory results obtained by correcting the pathologic postures and by teaching ergonomic positions highlight the importance of local factors in the appearance of task-specific dystonia, especially musician’s cramp.56

**GENERALIZED DYSTONIAS: REHABILITATION OF PRIMARY OR IDIOPATHIC TORSION DYSTONIA**

The primary or idiopathic torsion dystonia (ITD) arise almost always in childhood. They begin very often with involuntary muscle contractions of the lower limbs, which spread progressively to the whole body. In general, they stabilize after adolescence, but having caused a significant motor handicap (loss of, or severe difficulties with walking, extension, or rotational spasms of the trunk and limbs, which greatly limit most functional activities).

The slightest movement provokes the dystonic muscle cramps, which may become permanent. Even if the cramp is continuous, its intensity is influenced by changes in position of the body, such as lying to sitting.57 Emotion and stress are also aggravating factors. These clinical signs are diminished by sleep and by certain sensory tricks.

Children and adolescents with ITD pose a major therapeutic challenge, exceeding the limits of physiotherapy alone and requiring a multidisciplinary approach to deal with all of the psychological and educational issues and difficulties of daily life. Rehabilitation is an important part of the management of the dystonic child. Goals must be functional and the vision global. Treatment does not claim to make the symptoms disappear, but only to limit them to allow the child to lead as independent an existence as possible with the widest possible range of activities.

**Development of a specific rehabilitation program for idiopathic torsion dystonia**

The motor problems and the handicapping factors must be identified for each patient.58 Solving these problems will involve not only the therapists but also the family and teachers. The rehabilitation of these children is different to that of children with cerebral palsy. Dystonic children have usually completed their neuromotor development before the appearance of the condition. Therefore it is not a question of facilitating a process of acquisition of motor skills, but one of reducing the involuntary muscular contractions that prevent children from using their motor potential. The activities of many of these children regress and reimprove due to variations in treatment efficacy or as a result of good and bad periods.

**The search for physical comfort and painlessness**

Pain only affects a small percentage of dystonic children. It occurs most with paravertebral muscle spasms, or with isolated intense cramps of certain muscles such as the hip adductors or biceps brachii. The asymmetrical distribution of cramps and of torsion postures leads to pain related to positioning. Traumatic lesions resulting from uncontrolled movements or falls may also cause pain. The treatment of pain is a priority as it disturbs rest, appetite, and schoolwork, and is the cause of anxiety and alterations in mood.

Muscular relaxation is obtained by:

- Placing the child in comfortable positions that require little effort and that maintain the body in flexion, as in sitting or lying on the side with knees against the chest. The spasms are sometimes less marked on all fours or in prone position, which can be considered as optimal rest positions for the patient.
- The use of relaxation techniques for the whole body, associated with deep breathing.
• The release of muscle tension in the ‘starter muscles’, the source of the spasms.

Rest and hydrotherapy in warm water favor muscular relaxation. The subject can then profit from this relaxation to attempt to produce voluntary muscle contractions that correct the worst deformities.

Prevention of orthopedic problems

Dystonic postures lead spontaneously to limb deformities and joint stiffness, which if not treated early may become irreversible. By acting upon the balance between the hyperactive dystonic muscles and their ineffective antagonists, it is possible to maintain and occasionally improve deformities. Orthopedic appliances such as corsets are poorly tolerated. The constraints they impose favor the appearance of muscular spasms or increase their intensity.

Physical activity

Physical activity includes localized exercises for the corrective muscles, dynamic in nature as well as exercises for the whole body, avoiding or limiting the onset of spasms. Placing the entire body in a flexed position diminishes the intensity of the spasms. It is then possible to benefit from this state of reduced pathologic tonic activity in order to obtain voluntary muscular contraction without triggering spasms.

Functional activity

Rehabilitation must help patients carry out activities essential to daily life, such as moving around independently, dressing, eating independently, and meeting basic hygiene requirements. This functional independence is necessary but not in itself sufficient, as the young patient must also go to school and have a social life and hobbies. Commonsense solutions can often overcome the difficulties associated with locations unadapted for persons with a handicap. Care must be taken to ensure that the time spent in rehabilitation does not disturb schooling.

Problems of written and verbal communication pose a major problem to the pursuit of studies:

• Writing is most commonly made possible through the use of school furniture adapted to the postural deficits of the child, and computer technology is overcoming the difficulties involved in holding a pen (digital recording, voice recognition software, or simplified keyboards).59

Although limited in what it can achieve, rehabilitation gives positive results in preventing joint deformity, in improving stability and comfort in different positions (lying, sitting, standing), and in allowing the patient, in many cases, to preserve or rediscover a certain degree of autonomy in walking. However, rehabilitation must not be considered merely as a treatment, but as a way of helping patients pursue their interests and passions and of allowing life to be lived to the full.

In the face of a condition with such a perplexing evolution, the slightest chance of improvement of any aspect of the handicap must be seized upon and made the object of a specific rehabilitation.60 The contribution of family, friends, and teaching staff is of utmost importance for the successful integration of the child into everyday life.

CONCLUSION

The rehabilitation of dystonia is not restricted to the application of a few standard exercise programs. The objective is to correct the affected function through willful intervention. Such a rehabilitation program is as demanding for the patient as it is for the physiotherapist. Patients need information, stimulation, and motivation in order to find the inner resources to overcome their abnormality or handicap. In addition to correcting, or compensating for, the sensorimotor abnormalities, physiotherapy treatment must enable the reinsertion of patients with dystonia into family, social, and professional life as well as help them find within themselves a new dignity to their lives.

ACKNOWLEDGMENTS

I would like to thank Kari Hanet MD BA and Laura Prendergast MSc Physio for their help in translating this text into English.

REFERENCES

22. Cruchet R. Traité des Torticolis Spasmodiques, Spasmes, Tics,
21. Monnier M. Le torticolis spasmodique; ses variations sous l’influ-
18. Rondot P, Bleton JP. Syncinésies et mouvements involontaires
16. Van Zandijcke M. Cervical dystonia (spasmodic torticollis). Some
15. Dykstra D, Ellingham C, Belfie A et al. Quantitative measurement of
cervical range of motion in patients with torticollis treated with
botulinum A toxin. Mov Disord 1993; 8: 38–42.
14. Feve A, Bathien N, Rondot P. Abnormal movements related
potentials in patients with lesions of basal ganglia and anterior
13. Bleton JP. Physiotherapy for spasmodic torticollis. In: Bouvier G,
et fils; 1862.
11. Westphal CFO. Uber eine dem Bilde der cerebrospinalen grauen
Degeneration ähnliche Erkrankung des centrlen Nervensystems
mit neurologischen Symptomen. Arch Psychiatr Mentaler Krankh 1895.
by local injections of botulinum toxin. Rev Neurol (Paris) 1990;
8. Berardelli JC, Rothwell JC, Hallett M et al. The pathophysiology
7. Rondot P. [Clinical and physiopathological study of contrac-
tures]. Rev Neurol (Paris) 1968; 118: 32–42. [in French]
6. Meige H, Feindel E. Traitement des tics. Traitement par l’immo-
bilisation des mouvements et les mouvements d’immobilisation.
5. Zati A, Crémonini P. Le training autogène de Jacobson dans le
traitement du torticolis psychogène. J Réadapt Méd 1993; 13:
3–6.
4. Duchenne (de Boulogne) GB. De l’Électrisation Localisée et Son
Application à la Pathologie et à la Thérapeutique. Paris: Baillière
et fils; 1862.
3. Rondot P, Marchand MP, Dellatolas G. Spasmodic torticollis:
2. Cruchet R. Traité des Torticolis Spasmodiques, Spasmes, Tics,
1. Béclère J. [Traité des torticolis paralysiques, spasmodiques et
familiaux]. Rev Neurol (Paris) 1891; 2: 139–50. [in French]
232 CLINICAL DIAGNOSIS AND MANAGEMENT OF DYSTONIA

INTRODUCTION

The development and implementation of the dystonia specialist nurse (DSN) role represents a valuable step forward in the creation of a more patient-focused service. The role includes one of educator, leader, researcher, resource manager, and clinician. It is suggested that a specialist nurse is able to see more patients in conjunction with the consultant, thereby reducing the consultant’s work load, as well as decreasing the waiting list.\(^1,2\) It enhances the service by reducing the number of complaints and waiting times for treatment, provides a more informal approach, and ensures up-to-date evidence-based practice. It also increases job satisfaction for the nurse, due to the dedicated nature of the role and ability to lead the service/practice development. This chapter highlights the advantages and disadvantages of a dystonia specialist nurse, as assessed within the UK healthcare system.

This chapter also provides a brief description of dystonia, the historical background to the treatment of dystonia, and the development of the DSN. It also looks at the reasons why the DSN role has developed and outlines the governmental influences on dystonia. Also discussed within the chapter are the reasons why patients with dystonia have had bad experiences and long waits for treatments. This all leads to why patients with dystonia need a service that is informal and predominantly patient-focused.

Clinical neuroscience is an expanding area of health care, and numerous specialist nurse posts are being developed. The expansion of these positions are part of the UK government’s plans in bringing the health service into the ‘twenty first century’.\(^3\) According to the Code of Conduct for National Health Service (NHS) managers, the NHS plan will deliver services designed around the needs of the patients.\(^4,5\) There is, however, the opportunity to be proactive in the development, implementation, and evaluation of specialist nurse posts, and the DSN is representative of this.

Dystonia is a movement disorder that has been poorly managed in the past. Many patients were (and are) misdiagnosed, and therefore receive inappropriate treatment.\(^6\) Patients with chronic movement disorders, in whom no physical cause could be identified and therefore believed to be psychogenic in origin, were often referred to psychiatrists.\(^6\) It was not until the latter part of the 19th century, with the development of neurology as a separate field of medicine, that patients were diagnosed as having a distinct neurologic conditions. The two World Wars, however, brought pharmacologic advances and, as a result, neurologic conditions such as epilepsy and Parkinson’s disease were treated much more successfully.\(^6\) With developments in neurologic medicine, there was also greater recognition of relatively rare neurologic disorders such as dystonia.\(^6–8\)

Although dystonia is the third most prevalent neurologic movement disorder after essential tremor and Parkinson’s disease,\(^7,8\) many general practitioners (GPs) and other primary care physicians may never have seen anyone with dystonia. It is therefore not surprising that patients with dystonia have been misdiagnosed. Consequently, and also because many individuals with milder focal dystonia do not seek medical attention, the number of people with dystonia is probably higher than these estimates.\(^6,8–10\) The need for people to acknowledge and understand dystonia is important: increased awareness leads to a more positive outlook for these patients.\(^11\) As with any specialist nurse role, that of networking and communicating with other professionals is vital. A specialist dystonia nurse can be the link needed for better liaison between the primary care trusts (PCTs) and other healthcare professionals. This can be achieved by an increase in communication between primary and secondary care and by the development of various written leaflets and protocols. This is therefore a step in the right direction in increasing the awareness of the condition.

In this changing world of healthcare, the move towards more specialized areas of nursing is paramount
due to the advances in technology education and extended nursing skills. Specialist nurses are the most suitable professional for raising awareness; they are best placed to take on the responsibilities of their patients, as they understand their needs and requirements. Specialist nurses and nursing in general are concerned with health and the environment, which involves direct outcomes influencing patients, families, and communities.

THE ROLE WITHIN NEUROSCIENCES

Within the UK, dystonia nurse specialists are relatively new roles which are evolving within neurosciences, ophthalmology, and ENT (ear, nose, and throat) departments. Specialist roles are developing in these areas due to the nature of the disease. The development of DSNs in the UK began approximately 8 years ago, when one nurse had an overwhelming interest in dystonia. This nurse began his role funded as a university research nurse practitioner. The research was to test the theory that a fully qualified nurse could deliver botulinum toxin treatment and supportive care as effectively as the standard medical model. The project was successful; the nurse is now employed as a full-time outreach nurse for patients with dystonia and runs his own clinics. This nurse’s work involved a more informal approach to dystonia.

Dystonia services expanded within neurology, ophthalmology, and ENT approximately 20 years ago when botulinum toxin was more widely used for the treatment of dystonia. These clinics ran for many years, treating patients with dystonia, strabismus, laryngeal dystonia, and hemifacial spasm, and seeing only about 10–15 patients per month. With the increasing number of cases of diagnosed dystonia, this inevitably led to an increase in number of patients in these clinics. Interestingly, however, dystonia services had never been formally audited until the late 1980s.

At this stage, purchasers of services did not realize that they were paying for expensive treatments. Treatment had been provided without specific allocation of resources to fund it. Increased number and throughput of botulinum toxin clinics further increased pressure on funding and led to increased follow-up intervals for patients receiving botulinum toxin. A more recent review of the service identified the need for additional funding, and the possibility of involving private finance. The number of dystonia referrals continues to increase, as a result of better recognition of the condition by GPs and awareness of the disease through access to the Internet. In addition, increased involvement of patient support groups and more active involvement of neurologists and specialist nurses with interest in dystonia has played a role. To deal with the greater numbers of patients with dystonia referred for assessment and treatment will require a proactive approach, and DSNs can play a key role in this.

STRUCTURED APPROACH TO DYSTONIA SERVICES

Dystonia presents differently in each individual and the degree of disability can fluctuate from person to person and from month to month. The disease can cause profound deterioration in individual’s health as well as severe social and financial difficulties. With the absence of cure or prevention, dystonia needs a well-coordinated case management. Figures 21.1–21.3 show the structured approach adopted in Neurosciences at Lancashire NHS Trust in the UK, where the key role for the nurse is assessment, counseling, and treatment of patients with botulinum toxin.

QUALITIES NEEDED FOR A DYSTONIA SPECIALIST NURSE

Patients’ families and carers must be offered the widest possible range of support, treatment, and care. This includes not only sensitivity to the needs of patients and others that may be involved in their care, but also an understanding of the roles of other interdisciplinary healthcare professionals who may need to be involved.

Figure 21.1 Organization of dystonia care team.
ROLE OF THE SPECIALIST DYSTONIA NURSE

With regular meetings and liaison with all these people, the DSN can provide a holistic approach to the care provided. The role of the DSN, therefore, would be to bring all these professionals together and provide a collaborative care pathway, continuity of care, and a high-quality service.

A specialist nurse needs extensive knowledge of his/her subject. Attending the Dystonia Society and support group meetings is an invaluable forum to meet patients and their carers who can keep up to date with new treatments. These meetings ensure a patient-led service by discussing patients’ requirements. Therefore the role of the DSN is to listen to the patients and become their advocate. In doing so, the nurse also becomes an expert in dystonia, providing information, support, and guidance. Individuals with dystonia need alternative coping strategies: not only self-help but also involvement of other disciplines. The Commission for Health Improvements (CHI) recommends that hospitals need to improve patients’ involvement in the care they receive and have proposed that written strategies be developed to address this. The UK government policy ‘The Expert Patient’ states that ‘patients with chronic illnesses know their needs best’. These individuals need an advocate, and the DSN can do this, but they can only be patients’ advocates by listening and working closely with them.

Part of the role is to educate others; therefore, presentations at conferences such as dystonia awareness days and neuroscience meetings, both locally and nationally, is a strategy to enhance this education role. The education of future dystonia nurses is very important to ensure quality services for all dystonia patients. According to the Royal College of Nursing (RCN) presentations are part of the specialist education strategy. It is at these conferences that nurses often increase their knowledge and exchange and develop networks with nurses in the same and different specialities, sharing information and practice. The DSN needs therefore to be able to educate others: not only patients but also other health professionals. They need to be able to liaise with all involved in providing a high-quality holistic approach.

Literature on nursing roles in dystonia is scarce. Literature about specialist nursing, in general, helps to define the role, looks at the qualities needed for the specialist role, and highlights the educational needs necessary. According to the UKCC (UK Central Council for Nursing and Midwifery) standards, there are no specific qualifications necessary; however, the document does

Figure 21.2 Organization of referral process.

Figure 21.3 Organization of structured plan in treating patients with botulium toxin.
highlight the need for nurses able to perform higher levels of judgment, discretion, and decision-making.21 These higher levels lead to improved patient care by ensuring supervised practice, audit, research developments, and the teaching of others. This is achieved by having skilled leadership. These higher levels of judgment and decisions are based on:

- clinical practice
- care management
- clinical practice development
- clinical leadership.

As specialist nurses increase in numbers and evidence-based practice brings changes to patient care delivery, the role of the specialist nurse should be to sustain and spread knowledge so that those involved in healthcare delivery benefit:

The need for the specialist practitioner to be expert in their field is essential, as the need to transform research into practice requires interest in the subject, organisation, intellectual vigour, clinical judgement skills and endurance.19

However, to ensure that the gap between theory and practice is closed, there must be closer links between knowledge generated and its implementation.22 It is important, therefore, that specialist nurses are fully prepared for the roles and to ensure support, evaluation of the role, and further education. The right to claim such a status and all that it implies will only be given to those who are prepared to take up the heavy responsibilities for the continued development of both their knowledge and skills beyond that of initial qualifications and appointment to practice. Benner states that nursing develops in five stages from novice to expert.21 Although Benner’s ideas are correct, with each new situation we all become novices and one should never class oneself as a total expert since there are always new ways or ideas to explore. By involving others, the patient, is given the opportunities to have ‘experts’ in all fields. Therefore, the specialist nurse although never classed as a complete expert, will have the necessary expert knowledge and know where to find extended knowledge to teach others and be in touch with up-to-date advances in treatments.

Specialist nurses are involved with the delivery of direct and indirect patient care, becoming the coordinator of care between the primary and secondary delivery and ensuring continuity and providing emotional and psychological support.10,12 Specialist roles were often developed because of local need, and, according to the RCN, they improved and increased information and developed a service that patients found acceptable.19 This is, however, difficult to measure because of anecdotal and descriptive reviews.24 There are few quantitative data available, although qualitative data show that specialist nurses are valuable in the care management of patients.24,25

The reason for such poor quantitative data is that peoples’ interpretations are difficult to quantify; often they find it difficult to explain why they think a service is good or bad. With the importance of audit and nursing governance, this quantitative data will become available and provide the evidence needed to demonstrate that the role is beneficial, cost-effective, and an improvement to services.1,2

Many individuals with dystonia have been treated unfairly in the past due to misdiagnosis and misreferral, and so there is a need for support and guidance. Providing information and listening may be all that is necessary for these patients to access and respond to treatment. One can argue then that this type of support could be offered by any nurse, although a nurse with extended knowledge and commitment to a service must be better equipped to deal with associated dystonia problems. One review states that the qualities needed to be a specialist nurse are ‘adaptation to meet the challenging and changing needs of patients, families, nurses, physicians, trusts and to assist the government proposal’.26 This commitment to a service brings added pressures to the post and the need for support from others is essential, and is best achieved by clinical supervision.27

Thus, specialist nurses need the support of doctors, colleagues, and managers. Working with others is paramount, especially nurses within the same directorate and speciality, as this creates a learning environment as well as support and guidance.27

Education to practice has been debated extensively,19,26,28,29 and many argue that education to degree level is essential, whereas others say experience and post basic education is all that is required. However, education improves knowledge, not only in the specialist subject but also in health politics, nursing research, and teaching methods.30,31 For instance, education is invaluable when evaluating a business plan. This evaluation of the role provides evidence as a structured case/argument that the role is beneficial. Experience is also a critical requirement as it provides direct care delivery by teaching, assessing, and evaluating care given and also by providing consultation, change management, and providing advocacy for the patients.24

Many specialist nurses in the UK have, or are working towards, degree-level qualification, which brings them in line with other countries and will assist with consultant nurse posts in the future.30–32 Without these skills, the role of the specialist nurse cannot be fulfilled. A clinical nurse specialist will assist in closing the theory practice
gap, as the demand for evidence-based practice increases. Specialist nurse practitioners are often the contact between academia and practice, which can only be an advantage to nursing.\textsuperscript{31–34}

According to many authors, nurse specialists deliver low-cost, high-quality care, providing medical intervention and alternative treatments for health care continually not only through illness but also during healthy periods.\textsuperscript{1,32,35,36} Cost-effectiveness for specialist nurse service is a controversial area, as there may be an increase in cost through the initial setting up of a service, improved knowledge and uptake among patients and carers of possible services, and benefits for which they are entitled.\textsuperscript{2} There will also be the extra patient referrals as the service improves and as dystonia becomes increasingly recognized. Many studies, however, have reported that specialist nurses are cost-effective by reducing hospital admissions and consultant-led outpatient appointments. This is achieved by working with set protocols, having nurse-led clinics, and managing their own patients.\textsuperscript{1,24–26,34,37,38}

Although some studies have found no significant difference between medical and nursing treatment, the nurse’s input appeared to be an effective innovation in care delivery.\textsuperscript{1,2,24,38,39} Specialist nurses, in general, have more dedicated time with individual patients, compared with physicians, which may have a beneficial effect on the therapeutic experience and is felt to be an asset to any service.\textsuperscript{40}

All nursing encourages patient-focused care, as nurses provide care based on the needs of patients after listening to them and involving them in decisions over care. However, this can have disadvantages, as patients seeing a specialist nurse can become focused only on their own illnesses and want treatments that they have seen on the Internet or have spoken with others about, which can sometimes be denied due to lack of evidence or lack of funding.

Figure 21.4 highlights the role and responsibilities of the specialist nurse practitioner and all are essential to ensure a smooth and successful dystonia clinic.

**HOW THE SPECIALIST NURSE HELPS SERVICE DEVELOPMENT**

Practice development, which is essential for the clinical nurse specialist role,\textsuperscript{41} includes having some firm evidence-based criteria. Practice in the UK has been developing since nursing as a profession developed, but it has...
been accelerated since the introduction of the Post-Registration Education and Practice Project (PREPP). PREPP guidelines also assist in the education and expert knowledge needed for such positions. Nurses need to prove they are committed to lifelong learning by providing evidence that they ensure at least 5 study days within 3 years.

With the development of dystonia specialist nurses came the introduction of nurse-led clinics. These provide better access to the service due to the specialist nurse taking on her own case load, which increases patient throughput and in turn leads to a decrease in the waiting times for patients with dystonia and an improvement in the services provided. The nurse-led clinics have smaller numbers, therefore creating more time for each patient instead of clinic appointments with a busy consultant. This can lead to fewer complaints. One may question that if the patients seen are smaller in number, how does this improve service? The answer that a nurse’s time is not restricted and therefore she is able to see more patients on extended days/hours and the patients have direct access to a telephone answering service. There is a minimal waiting list and patients referred to the dystonia clinic will not have to wait for months for treatment, as they have done in the past. Future developments could include the introduction of outreach clinics, meaning that patients will have access to the service near to their own homes and therefore minimize traveling times. Minimizing traveling time minimizes the stress of attending hospital, which may involve travel of over 50 miles. Elderly patients without a mode of transport are reliant on hospital transport, which often cannot guarantee the requested time of pick up and return journeys. With all these advantages to the service, patient satisfaction should increase, with complaints conversely decreasing. Research is another important aspect of clinical practice. Nursing is said to have a poor track record in implementing research findings and the development of specialist practitioners has improved this. Specialist nurses can be the innovators of research findings, liaising with other health professionals and ensuring evidence-based practice. All specialist nurses are indirectly involved with the pharmaceutical companies who promote new treatments. Specialist nurses should have the skills to analyze trial data for new treatments and are often also directly involved with drug trials. Nurses feel that when implementing research they come across barriers in the form of managers, doctors, and other nurses, and have felt hampered by the medical profession in the area of research. Nurses cannot afford to be submissive, as they need to be looking at research and using best practice for their patients. This is highlighted with nurse governance, as nurses are now involved with decisions, therefore extending their authority in care giving. Now that the basic nursing qualification is to diploma or degree level, nursing is working towards a professional status. Nurses are gaining a greater understanding of research and of the research process. With this education, they are more likely to question procedures rather than just complete tasks.

To ensure best practice, there must be good evidence-based protocols in place. With the introduction of standards, protocols, and competencies, and using audit to monitor the service, it can be ensured that what is said is being done is carried out. Design of protocols and standards for the dystonia specialist have been developed by a number of specialist nurses working together to achieve the best for patients. Benchmarking and networking are strategies to ensure best practice is maintained. Benchmarking is a system developed to ensure that guidelines are written to enhance a better quality of care delivered to each patient. There are also national guidelines based on research evidence which are developed by a benchmarking group, which should be multiprofessional and include patient representatives. Shared care protocols are key developments that involve the patients’ GP to help with awareness of the disease and to involve others in the treatment and outcome of these patients. Writing these protocols enables the service to be evaluated each year, and if the standards are not being achieved, the service must be amended. It also gives the specialist nurse evidence to support the notion that the service is an asset to directorates and trusts and other funding bodies.

The development of the dystonia service protocols has been paramount in the success of the service in other areas. These written guidelines provide a guidance for others who wish to develop such roles. However, they should be considered as active documents, as there are always changes and innovations that must lead to the guidelines being reviewed and revised accordingly. The implementation of any guidelines must be patient-centered, which means that one must recognize the patient’s health problems and evaluate the outcomes and implement the evidence-based care within these guidelines. Guidelines for patients are best when patients have their say in what’s best for them. This leads to guidelines that will be beneficial to nurses, patients, and doctors.

The development of clinical competencies for a specialist nurse are vital and, with the guidance of others in the same field and the consultant in charge, these written competency statements act as legal documents to practice. They also act as teaching material for others. It is essential that these protocols, standards, and competencies are written jointly with other dystonia nurses and
with the patient’s perspective in mind. Multiprofessional networking via the Internet offers opportunities for the development of competencies. In addition, it facilitates problem sharing and solving. The Nursing and Midwifery Council (NMC) expects nurses to behave according to the standards and guidelines written. It is therefore important that these developments are measured against NMC standards and good practice is upheld. These protocols will ensure that evidence-based practice in dystonia care is implemented, which, in turn, will improve patient satisfaction.

Specialist nurses also have a key role in assessing research developments to identify practice that may not only be beneficial to patients but may also be financially and clinically effective. After analyzing the research, specialist nurses need to instigate change. This change then needs to be part of an audit cycle to analyze the results and evaluate the effectiveness of change, with the ultimate goal of improving patient care.

Dystonia specialist nurses need good leadership skills. These are enhanced by added education, experience, and commitment. Practice development tends to happen to nurses without thinking about it. The introduction of PREPP ensures all nurses are committed to lifelong learning, developing their skills so as not to be left behind. While working towards the specialist dys-tonia nurses position, leadership skills develop naturally as there is the need to be able to liaise with others and take peoples’ opinions and experiences on board. Therefore, the specialist nurse needs to be an innovated change agent, researcher, teacher, counselor, and lifelong learner, so as to ensure quality care is given to each patient.

In the UK the government plays a large part in how the NHS develops. They have found that specialist nurses improve the quality of care delivered to patients economically. We can argue then that the government has pushed nurses into specialist roles by introducing targets, as one of the advantages with these roles is that they lower the waiting times to see a consultant. However, specialist roles have not always been developed by medical influence; nurses themselves have often been the instigation for these roles, by developing a particular interest within a specific field. Specialist roles may have been instigated from the extended roles developed within the NHS such as continence link nurses, infection control nurses, and pain management nurses.

Specialist nurses, as highlighted in many reviews, are an asset to the service, providing holistic care to patients. Owing to the lack of quantitative evidence, the reason for this is hard to establish. However, a patient who has a personal nurse giving information and support, who sees them every visit and is at the end of a phone, appears to have enhanced outcome compared with one who does not have access to a specialist nurse. Information has been highlighted as an improvement seen by the majority of patients, although not by all.

To summarize, a specialist nurse’s role is one of direct and indirect caregiver with experience in a specific field, performing higher levels of judgment and decisions with discretion. These nurses should be capable of degree-level education and have the responsibility to supervise evidence-based practice, oversee audit, develop research strategies, and be seen as an educator. The specialist nurse’s role will also enhance the service development by ensuring government targets are met and being economically viable and that patients are given the treatment when and how they deserve.

REFERENCES

13. Ipsen. Selected In Effectiveness Proven In Us. 2000.
Outcomes of dystonia have been traditionally evaluated using objective clinical indices measuring disease markers such as head movement, shoulder elevation, and tremor. Although such indices provide important data, they are limited as they do not give valuable information regarding patients’ perceptions of their condition. Therefore, patient-reported rating scales are used to measure broader health outcomes such as quality of life (QL). This chapter provides information on dystonia and QL. It has three aims:

1. To provide an introduction to QL.
2. To describe QL research in dystonia.
3. To critically appraise current research with the view to recommendations for future studies.

AN INTRODUCTION TO QUALITY OF LIFE

Background

During the past two decades, there has been a transition from solely measuring traditional clinical outcomes to the inclusion of a wider range of health variables, including QL. This shift has occurred for a number of reasons. The narrow definition of health in terms of morbidity and mortality has been replaced by the broader definition: a ‘complete state of physical, mental and social well-being and not merely the absence of disease or infirmity’. In addition, rising standards of living, aging populations, and the development of health technology have led to a shift in attention from curing acute diseases to the management of more complex, chronic conditions, including many neurologic disorders such as dystonia. Additionally, healthcare providers increasingly demand that clinicians demonstrate evidence of cost-effectiveness, in which the benefits of treatment are weighed against the costs of that intervention.

What is quality of life?

Health cannot be measured directly. The complex and abstract nature of health has led to a continuing debate on how best to measure it. Health measurement relies on the use of health indicators to represent various dimensions of health, and so researchers have developed measures to elicit patients’ opinion about various aspects of health such as QL. Health measurement, therefore, can be described as the field of study concerned with the development of methods for measuring patient-reported outcomes.

The terms QL, health-related QL, health status, and functional status are often used interchangeably in the health measurement literature. Although there is a lack of conceptual clarity regarding these terms, there is broad agreement on the core minimum set of health concepts that should be measured. These include physical and mental health, social functioning, and general health perceptions.

Why measure quality of life?

Despite the recent acceptance of QL data, some clinicians have regarded these as ‘soft science’ preferring ‘hard data’ such as tangible variables measured with mechanical instruments (e.g. blood counts) or clinician judgment. However, it can be argued that many of the so-called ‘hard outcomes’ reported in the literature are actually ‘softer’ than first supposed. For example, data obtained from medical records contain information about subjective states that have been collected using non-standardized methods. Also, traditional disease-staging techniques are observer-dependent and subject to considerable variation. In contrast, it has been shown that patient-based data are good predictors of long-term outcome. For example, QL data are accurate predictors of outcome in hypertension, diabetes, chronic obstructive pulmonary disorder, and ischemic...
heart disease,¹¹ and mortality in the general population.¹² Thus, patients’ views and perceptions of their own health are an essential part of healthcare evaluation.¹³

How is quality of life measured?

Two main conceptual approaches to health measurement have been identified.¹⁴,¹⁵ The standard needs approach describes measuring QL as the extent to which certain universal needs are met. This approach advocates that there are a standard set of life circumstances that are required for optimal functioning. Although a subjective phenomenon, QL is viewed as an objective characteristic of an individual. In contrast, the psychological processes approach views QL as constructed from individual evaluations of personally salient aspects of life. This approach sees QL as being made up of perception of life circumstances, dependent on the psychological make-up of an individual, rather than on their life circumstances alone. The central assumption of this approach is that each person is the best source of judgments about QL and one cannot assume that all people will value different circumstances in the same way.

Many types of patient-reported rating scales can be classed as following the standard needs approach, including generic (e.g. Medical Outcomes Study Short Form-36),¹⁶ disease-specific (e.g. the Cervical Dystonia Impact Profile),¹⁷ and site-specific measures (e.g. Oxford Hip Score).¹⁸ For more details on different types of measure see Chapter 23 on dystonia rating scales.

In contrast to using generic or specific measures using predetermined content, proponents of the psychological processes approach argue that listing items in measurement scales does not capture the subjectivity of human beings and the individual structure of values. In short, prescribing items using a preordained definition of QL and matching the person to the definition (i.e. ‘goodness of fit’), does not let us know whether all the domains, pertinent and meaningful to each respondent, are included. This viewpoint has influenced the development of ‘individualized’ measures such as the Schedule for the Evaluation of Individual Quality Of Life (SEIQoL).¹⁹ This measure allows individuals to nominate important domains of QL and weight those domains in order of importance. Another measure, the Patient Generated Index (PGI), asks individuals to identify those aspects of life that are personally affected by health.²⁰ The advantage of these measures includes a claim for validity, as the areas of importance are selected by the individuals involved in completing the measures. The main disadvantages are that some of these measures require trained interviewers, which translates into a need for greater resources, and lower practicality. Also, it is not easy to produce population-based comparative or normative data given the variation in each individual completed measure.²¹

The majority of existing patient-reported rating scales follow the standard needs approach. Research into individualized measures is still in its infancy and more work is required before the relative advantages and disadvantages of the two approaches can be discerned.²¹ There is no existing dystonia research using individualized measures and, as such, the studies presented in this chapter follow the standard needs approach.

QUALITY OF LIFE RESEARCH IN DYSTONIA

This section focuses on generic patient-rated scales used to measure QL or aspects of QL in dystonia research. Dystonia and QL study descriptives are presented, followed by measures and QL domains, and a summary of main findings. Chapter 23 on dystonia rating scales describes disease-specific measures in greater detail.

Study descriptives

Twenty-six studies have investigated aspects of QL in generalized dystonia, cervical dystonia (CD), and blepharospasm using generic patient-reported rating scales. The majority of studies have analyzed cohorts of CD patients. Sample sizes ranged from 6 to 289, with a median sample size of 64 (85% of the studies included less than 100 patients). In general, response rates were not reported, but when they were, they were generally high (≥84%). Mean age ranged from 41 to 57 years. The percentage of women in the samples ranged from 48% to 81%, which reflects the preponderance of females with focal dystonias.²²,²³

Domains and measures

Eighteen generic rating scales have been used: the most commonly used were the Beck Depression Inventory, Medical Outcomes Study Short-Form-36, and the Rosenberg Self-Esteem Scale. Table 22.1 shows the type of measures and domains measured. Studies have predominantly focused on psychological outcomes such as depression, anxiety, and self-esteem. Table 22.2 shows domains measured.

Findings

As described above, QL measures should include a number of physical, psychological, and social dimensions. Dystonia research has included aspects of all of the following areas.
Physical health

Pain is described as an important symptom, with CD patients using descriptors such as 'tiring', 'continuous', and 'tugging'.

Mental health

The majority of studies using generic measures have evaluated the psychological impact of dystonia. Studies have described CD patients as similar to cervical spondylisis patients on anxiety and negative expectancies, but experiencing more depression. Long-term follow-up has revealed that levels of depression do not change over time. Levels of self-esteem and self-deprecation are similar to patients with Parkinson's disease, but CD patients believe in internal locus of control (i.e. they feel personal control over their own lives and health as opposed to being controlled by others or outside forces). However, there is some contradiction in the literature. For example, whereas one study emphasizes the need to consider psychological well-being in the treatment of CD patients, another argues that CD patients experience low psychological distress, although the last study included patients with dystonia as part of a complex regional pain syndrome and therefore is not a form of primary torsion dystonia.

General health-related quality of life

The most common health-related QL measure used to assess the impact of dystonia has been the Medical Outcomes Study Short Form-36 (SF-36). The SF-36 contains questions on general health and well-being in 8 multi-item scales. Each scale is scored from 0 (indicating worst possible health) to 100 (indicating best

---

<table>
<thead>
<tr>
<th>Domain</th>
<th>Measure</th>
<th>Study references</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>Beck Depression Inventory</td>
<td>27–29, 31, 32, 40, 50, 53, 54</td>
</tr>
<tr>
<td>Health-related QL</td>
<td>Medical Outcomes Study Short Form-36</td>
<td>28, 30, 32, 34, 47, 53</td>
</tr>
<tr>
<td>Self-esteem</td>
<td>Rosenberg Self-Esteem Scale</td>
<td>31, 32, 40, 50</td>
</tr>
<tr>
<td>Psychological functioning</td>
<td>Sickness Impact Profile</td>
<td>42–44, 51</td>
</tr>
<tr>
<td>Health-related QL</td>
<td>Medical Outcomes Study Short Form-20</td>
<td>35, 39</td>
</tr>
<tr>
<td></td>
<td>Euroqol-5D</td>
<td>34, 36, 46</td>
</tr>
<tr>
<td></td>
<td>Nottingham Health Profile</td>
<td>37, 38</td>
</tr>
<tr>
<td>Disease acceptance</td>
<td>Acceptance of Illness Scale</td>
<td>32, 50</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Spielberger Trait Anxiety Scale</td>
<td>25, 50</td>
</tr>
<tr>
<td></td>
<td>Beck Anxiety Inventory</td>
<td>32, 46</td>
</tr>
<tr>
<td>Negative expectancy</td>
<td>Hopelessness Scale</td>
<td>26</td>
</tr>
<tr>
<td>Locus of control</td>
<td>Multi-Dimensional Health Locus of Control Scale</td>
<td>31</td>
</tr>
<tr>
<td>Psychological functioning</td>
<td>Bradburn’s Present Feelings Scale</td>
<td>50</td>
</tr>
<tr>
<td>Psychological distress</td>
<td>Symptom Checklist-90R</td>
<td>33</td>
</tr>
<tr>
<td>Pain descriptors</td>
<td>Finnish Pain Questionnaire</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td>McGill Pain Questionnaire</td>
<td>46</td>
</tr>
<tr>
<td>Health State</td>
<td>Euroqol-5D</td>
<td>34</td>
</tr>
<tr>
<td>QL</td>
<td>Nottingham Health Profile</td>
<td>37</td>
</tr>
</tbody>
</table>
Table 22.2 Domains measured using generic measures by author and measure

<table>
<thead>
<tr>
<th>Study references</th>
<th>Personality</th>
<th>Anxiety</th>
<th>Depression</th>
<th>Psychological functioning</th>
<th>Self-esteem</th>
<th>Locus of control</th>
<th>Pain</th>
<th>Health state</th>
<th>Health-related QL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jahanshahi and Marsden25</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jahanshahi and Marsden27</td>
<td></td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jahanshahi and Marsden29</td>
<td></td>
<td></td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jahanshahi and Marsden31</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jahanshahi and Marsden40</td>
<td></td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jahanshahi et al50</td>
<td></td>
<td></td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kutvonen et al24</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>♦</td>
</tr>
<tr>
<td>Brans et al39</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gudex et al34</td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindeboom et al35</td>
<td></td>
<td></td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Van der Laan et al33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Brefel-Courbon et al37</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ben-Shlomo et al32</td>
<td></td>
<td>♦</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Muller et al38</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Camfield et al30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bereznai et al47</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
possible health). Two component scores make up overall physical and mental dimensions. In a study of blepharospasm, women were found to score lower (i.e. poorer health-related QL) in all SF-36 domains than male patients.\textsuperscript{28,34} In addition, 37\% of patients were found to be depressed. Patients with CD have been found to have poorer health-related QL than UK controls, particularly in the areas of SF-36 physical role limitation (42 vs 86), pain (55 vs 82), and health perception (46 vs 74).\textsuperscript{30} This trend has been supported in other studies.\textsuperscript{28,34} Dimension scores are comparable to data from patients with mild to moderate multiple sclerosis (EDSS 3-6), moderate Parkinson’s disease, and moderate epilepsy.\textsuperscript{30}

One study has attempted to model QL variables in CD patients.\textsuperscript{32} Patients with CD (n = 289) were recruited from seven European countries. Data on QL were collected using the SF-36. It was found that SF-36 physical and mental component scores were predicted by self-esteem and self-deprecation, educational level, employment status, social support, response to botulinum toxin, disease severity, social participation, stigma, acceptance of illness, anxiety, and depression. The strongest predictors of QL were found to be anxiety and depression. The authors also present a conceptual scheme in which QL is associated with a number of explanatory and intermediary variables (Figure 22.1).

Finally, a recent study has provided evidence-based guidelines for using the SF-36 in CD research.\textsuperscript{52} To do this, the hypothesized relationships between items, scales, and summary measures of the SF-36 were tested using psychometric analyses in data from a postal survey of 235 people with CD. Although the majority of subscales performed adequately, the Role Physical and Role Emotional subscales had substantial floor and/or ceiling effects. Evidence did not support computing SF-36 Physical and Mental Component summary scores. Guidelines were proposed that include the recommendation that these subscale and summary scores should be reported with caution.

**Treatment effects**

The majority of studies investigating treatment have focused on the use of botulinum toxin type A (BTX-A) in CD,\textsuperscript{28,34-41} with a few studies investigating the impact of type B (BTX-B).\textsuperscript{42-44} These studies have used generic measures to focus on the impact of treatment on aspects of psychological functioning and general health-related QL. Fewer studies have investigated surgery, including muscle sections,\textsuperscript{45} denervation,\textsuperscript{46} or deep brain stimulation.\textsuperscript{47,53,54} Surgical studies have focused on aspects of psychological functioning, pain, and general health-related QL, although one study used

---

**Figure 22.1** Conceptual scheme of the influence of factors on quality of life in cervical dystonia. (Reproduced from Ben-Shlomo et al,\textsuperscript{32} with permission.)
a Parkinson’s disease self-report scale (PDQ39) as there was no specific dystonia measure available. Interpretation of data from this measure should be treated with caution.

Most studies report improvement, but have either been unable to discriminate between patients or have described small changes post-treatment. For example, whereas one study found that the Medical Outcomes Study-Short Form-20 detected improvement in CD patients following BTX-A, a study assessing the efficacy of BTX-B showed no significant improvement as measured by the Sickness Impact Profile. A large French study of deep brain stimulation in primary generalized dystonia showed improvements in global health as determined by the SF-36. Table 22.3 shows a summary of the findings of treatment effects by measure.

### Table 22.3 Treatment effects

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Measure</th>
<th>n</th>
<th>Assessment period (range)</th>
<th>Percentage of studies reporting significant improvement (p &lt; 0.05)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BTX-A (type A)</td>
<td>Beck Depression Inventory</td>
<td>26 to 131</td>
<td>B, 30 weeks P</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Euroqol-5D</td>
<td>196</td>
<td>4, 6 weeks P</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>MOS-20</td>
<td>54 to 64</td>
<td>3, 12 months P</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>NHP</td>
<td>20 to 21</td>
<td>B, 7 months P</td>
<td>50</td>
</tr>
<tr>
<td></td>
<td>Rosenberg Self-Esteem Scale</td>
<td>26</td>
<td>B, 30 weeks P</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>SF-36</td>
<td>131 to 196</td>
<td>4, 6 weeks P</td>
<td>50</td>
</tr>
<tr>
<td>BTX-B (type B)</td>
<td>Sickness Impact Profile</td>
<td>122</td>
<td>B, 4 weeks P</td>
<td>0</td>
</tr>
<tr>
<td>Surgery (denervation)</td>
<td>Beck Anxiety Index</td>
<td>62</td>
<td>B, 3, 18 months P</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Beck Depression Inventory</td>
<td>62</td>
<td>B, 3, 18 months P</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Euroqol-5D</td>
<td>62</td>
<td>B, 3, 18 months P</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>McGill Pain Questionnaire</td>
<td>62</td>
<td>B, 3, 18 months P</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>Rosenberg Self-Esteem Scale</td>
<td>62</td>
<td>B, 3, 18 months P</td>
<td>0</td>
</tr>
</tbody>
</table>

B = baseline; P = post-treatment.

### CRITICAL APPRAISAL OF QUALITY OF LIFE RESEARCH

QL research in dystonia is a growing field and many widely accepted generic measures have been used to assess aspects of QL. However, sample sizes have been low, and much of the research into patient reported outcomes of dystonia is limited, focusing primarily on psychological dimensions of patient well-being. Also, none of the generic measures have been psychometrically tested for suitability with dystonia patients. There is little conformity in the number and types of measures used in each of the studies, reducing the extent to which findings can be compared. The vast majority of research focuses on CD, with few or no studies on other types of dystonia.
Regarding measuring the impact of treatment, generic measures may be limited, as they may be unable to address important aspects of outcome that are affected by a particular disease, and are generally not sensitive enough to detect changes in outcome which occur in response to treatment or over time. This is highlighted by significant floor and ceiling effects found on a number of SF-36 dimensions. Thus, measures used in these studies appear, in general, not to address the pertinent areas of health impact of dystonia. In addition, the majority of studies report the statistical significance of findings but not effect sizes, which may misrepresent the true changes experienced by patients. Disease-specific measures should be more appropriate to assess therapies but at present the vast majority of existing disease-specific measures have not been comprehensively evaluated from a scientific point of view. Therefore, the full impact of treatment has yet to be addressed.

CONCLUSIONS AND RECOMMENDATIONS

Dystonia has far-reaching effects on QL. Research in QL is growing but has thus far focused largely on CD patients and is largely limited to psychological outcomes. There is little consistency or comparability in the rating scales used, making meta-analysis difficult. We suggest the following areas for future research:

- Large studies are required to assess the impact of all types of dystonia on a broad range of QL measures.
- Studies should present the psychometric properties of generic scales used to show appropriateness of measures in dystonia patient groups.
- We recommend that there is conformity in the types of measures used in each of the studies, allowing for comparison. Comprehensive measurement would include generic measures used in conjunction with an appropriately validated disease-specific measure (e.g. CDIP-58).

REFERENCES

In recent years the importance of evaluating the impact of disease and treatments on health has become clear. However, health cannot be measured directly and, instead, indicators should be used to represent clinical outcomes. Increasingly, rating scales are used to score aspects of disease (e.g. symptoms) or elicit patients’ opinion about aspects of health (e.g. psychological well-being). This chapter provides information on dystonia rating scales. It has three aims:

1. To provide an introduction to the use and development of rating scales.
2. To describe existing dystonia rating scales.
3. To critically evaluate scales with the view to recommendations for future directions of research.

AN INTRODUCTION TO RATING SCALES

Background

The origins of scale development can be traced back to psychophysics in the 1800s, which claimed that people are able to make subjective judgments about physical stimuli, such as the brightness of lights of varying intensity and the loudness of different sounds, in an accurate and internally consistent manner. The next three-quarters of a century revealed that the logarithmic relationship did not fit all types of stimuli, and in the mid-1950s, the logarithmic approach was replaced by Stevens’ Power Law. This new approach recognized that the relationship between stimulus and subjective responses was not linear. This law has been since tested and has been used to argue that people can make subjective judgments in a consistent manner, even when asked to make abstract comparisons. This is particularly relevant to the health measurement field in which many rating scales incorporate such comparisons.

The use of rating scales in health research began at the beginning of the 20th century. However, it was not until the end of the 1940s that rating scales were used in neurology. At the same time, psychometricians extended the basic principles of rating scale development, and the essential scientific properties of rating scales (e.g. reliability and validity) became well established. In the 1970s, broader aspects of health began to be included in clinical research (e.g. activities of daily living) and the last two decades have witnessed increasing recognition of the importance of rating scales for all aspects of health measurement.

Science

Although scale evaluation methods (i.e. psychometrics) have been used in the social sciences for the best part of the last century, they have been slow to transfer to health research. However, it is clear that for scales to be useful they need to be rigorously evaluated. At a minimum, this should include psychometric evaluations of reliability, validity, and, when assessing treatment effects, responsiveness. Table 23.1 shows a summary of the main traditional psychometric properties.

In brief, the reliability of a measure is the degree to which it is free from random error. Reliability is an important property of a rating scale, because it is essential to establish that any changes observed in patient groups, due to a treatment, are due to the treatment and not to problems in the scale. There are two general approaches to evaluate reliability: internal consistency (a function of the number of items and their covariation within a scale) and test–retest reproducibility (whether a measure yields the same results on repeated applications). Validity is the extent to which a scale measures what it intends to measure. There are two main types of validity: content validity (how well a
measure covers important parts of the target health components) and construct validity (testing the expected relations of health dimensions to each other, both internally and externally). Finally, if a new scale is to be used in evaluating the effects of a given intervention (e.g. botulinum toxin injections), responsiveness needs to be evaluated. Responsiveness is the ability of a measure to detect significant change over time, such as a meaningful reduction in symptoms from the patient’s perspective.15

Types of rating scale
Scales can be considered either generic (i.e. applicable across patient groups or diseases) or specific (i.e. developed for a specific patient group or condition). Table 23.2 summarizes the main types of rating scale. Generic measures are useful, as they permit direct comparisons of different patient populations.16 However, they may be unable to address important aspects of outcome that are affected by a particular disease, and are generally not as sensitive as specific measures to detect clinical change.17 There are two main types of specific measure: disease-specific measures are developed for a specific disease or condition (e.g. dystonia), whereas site-specific measures assess health problems in a specific part of the body (e.g. Oxford Hip Score18). Specific measures ensure more comprehensive assessment of important outcome domains, and are generally more sensitive in detecting the effects of treatment on outcome and changes in outcome over time.19 However, they do not allow comparisons between different patient groups.13

What makes a good rating scale?
The features that determine high-quality rating scales have been widely published.12,13,20 Central to these guidelines is the tenet that as scales represent various dimensions of health, they should incorporate patients’ opinions and be tested to ensure scientific rigour. In short, current guidelines for good practice state that measures should be developed from an item pool formed from patient interviews, expert opinion, and literature review. This should be followed by field testing involving large numbers of the target patient group: first, to carry out item reduction to select the best indicators of outcome; second, to comprehensively evaluate the measurement properties of the final instrument in an independent sample.

A full evaluation of rating scales extends beyond the basic components of reliability, validity, and responsiveness.12 Scale developers also need to consider conceptual issues (e.g. conceptual and empirical bases for content) as well as practical concerns (e.g. time taken to complete the scale). The current gold standard for evaluating rating scales has been set out by the Scientific Advisory Committee of the Medical Outcomes Trust (SAC).12 These criteria form a defined set of eight key attributes for rating scales: conceptual and measurement model; reliability; validity; responsiveness; interpretability; respondent and administrative burden; alternate forms; and cultural and language adaptations. Each criterion has a number of requirements (e.g. validity is divided into content-, construct-, and criterion-related). A general rule of thumb is that the more
criteria evaluated and fulfilled, the better the quality of scales. The next section describes dystonia rating scales. This is followed by a critical appraisal of these scales using the SAC guidelines.

DISEASE-SPECIFIC RATING SCALES FOR DYSTONIA

This chapter focuses on disease-specific ratings developed for patients with dystonia. The preceding chapter in this book (Dystonia and Quality of Life) describes further types of measure used in dystonia research. Ten rating scales have been developed for generalized dystonia, cervical dystonia (CD), and craniocervical dystonia. In this section, each scale is presented, including its purpose, a description of its content, and psychometric evaluation described in the associated development/validation paper(s). Table 23.3 summarizes the content and evaluation of each of the scales and Table 23.4 summarizes psychometric data where reported. First, clinician-rated scales are presented, followed by patient-rated scales.

**Clinician-rated scales**

Four clinical rating scales have been developed to assess the impact of dystonia.

**Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)**

Purpose The TWSTRS measures symptom severity, disability, and pain in patients with CD. It has mainly been used in treatment trials.

Content Three main scales: clinician-rated symptom severity, patient-rated disability (including activities of daily living), and pain scales. The symptom scale rates severity of head movements on 2-, 4-, and 5-point scales. In addition, duration of symptoms, sensory tricks, shoulder elevation, and range of motion are rated on 3-, 4-, 5-, and 6-point scales. The disability scale (on 6-point scales) comprises six areas, including daily activities, work, reading, and driving. The pain scale rates severity, duration, and degree on 6-point scales.

Psychometric data Reliability and validity have been presented: the TWSTRS scales have been shown to have acceptable inter-rater reliability (ICC >0.71–0.85); evidence for validity is shown by moderate within-scale correlations ($r >0.61–0.68$).

**Unified Dystonia Rating Scale (UDRS) and Global Dystonia Rating Scale (GDS)**

Purpose The UDRS and GDS measure the severity of the symptoms of dystonia. These measures focus on individual body areas.
Table 23.3 Dystonia rating scales – description and psychometric data

<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
<th>Reported psychometrics</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinician-rated scales</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Three main scales:</td>
<td>Reliability</td>
</tr>
<tr>
<td></td>
<td>• symptom severity scale – neurologist-rated</td>
<td>Inter-rater reliability ($\alpha$):</td>
</tr>
<tr>
<td></td>
<td>• disability scale – patient-rated (including work, daily activities)</td>
<td>• 0.71–0.85 (range)</td>
</tr>
<tr>
<td></td>
<td>• pain scale – patient-rated (presence, severity)</td>
<td>Validity ($r$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 0.61–0.68 (range)</td>
</tr>
<tr>
<td>Unified Dystonia Rating Scale (UDRS) and Global Dystonia Rating Scale (GDS)&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Two main scales:</td>
<td>Reliability</td>
</tr>
<tr>
<td></td>
<td>• Two symptom scales – neurologist-rated</td>
<td>Internal consistency:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• $\alpha &gt; 0.91$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• inter-rater reliability ICC $&gt; 0.71$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• weighted $\kappa = 0.52–0.90$</td>
</tr>
<tr>
<td>Burke–Fahn–Marsden Scale&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Two main scales:</td>
<td>Reliability</td>
</tr>
<tr>
<td></td>
<td>• movement scale – neurologist-rated</td>
<td>Movement scale:</td>
</tr>
<tr>
<td></td>
<td>• disability scale – patient-rated (includes speech, hygiene, daily activities)</td>
<td>• inter-rater ($&gt; 0.85$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• intra-rater ($&gt; 0.98$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Construct validity ($r$)</td>
</tr>
<tr>
<td></td>
<td>Three scores:</td>
<td>Movement scale:</td>
</tr>
<tr>
<td></td>
<td>• Movement (clinician-rated)</td>
<td>• with global severity ($&gt; 0.69$)</td>
</tr>
<tr>
<td></td>
<td>• Tremor (clinician-rated)</td>
<td>• with disability scale (0.70)</td>
</tr>
<tr>
<td>Tsui Scale&lt;sup&gt;25,40&lt;/sup&gt;</td>
<td></td>
<td>Reliability</td>
</tr>
<tr>
<td></td>
<td>Three scores:</td>
<td>Inter-rater ($r &gt; 0.85$)</td>
</tr>
<tr>
<td></td>
<td>• Movement (clinician-rated)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Tremor (clinician-rated)</td>
<td></td>
</tr>
<tr>
<td><strong>Patient-rated scales</strong></td>
<td>Eight 5-point scales made up of:</td>
<td>Rasch</td>
</tr>
<tr>
<td>Cervical Dystonia Impact Scale (CDIP-58)&lt;sup&gt;26-28&lt;/sup&gt;</td>
<td>three symptom scales (i.e. head and neck, pain and discomfort, sleep); two activity scales (i.e. upper limb activities, walking); three psychosocial scales (i.e. annoyance, mood, psychosocial functioning)</td>
<td>• MNSQ infit &lt; 1.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• even spread of item calibrations</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• hierarchical structure</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reliability</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• $\alpha &gt; 0.92$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• item-total correlation $&gt; 0.64$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• test–retest $&gt; 0.83$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Validity</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• within-scale analyses and comparisons with external measures (e.g. SF-36 ($r = 0.48–0.66$), GHQ ($r = 0.30–0.66$) and HADS ($r = 0.31–0.80$))</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Responsiveness effect sizes (0.23–0.66)</td>
</tr>
</tbody>
</table>

(Continued)
<table>
<thead>
<tr>
<th>Measure</th>
<th>Description</th>
<th>Reported psychometrics</th>
</tr>
</thead>
</table>
| Body Concept Scale (BCS)³⁰ | One scale (four factors)  
Body concept scale – patient-rated (22 items) | Reliability  
• α = 0.95  
• test–retest (1 month) = 0.87
Construct validity  
• BCS and total = 0.44
• BCS and Beck Depression Inventory = 0.41
• PCA produce four-factor structure |
| Functional Questionnaire for disability³⁰ | One scale (four factors)  
Functional disability scale – patient-rated (27 items) | Reliability  
• α = 0.92 (27 items)
• Test–retest (1 month) = 0.93
Validity  
• PCA produce four-factor structure |
| Ways of Coping Checklist³¹ | Patient-rated  
64 items (six factors: wish-fulfilling fantasy; threat-minimization; negative reappraisal/coping; cognitive restructuring; religious faith; instrumental coping) | Reliability  
α >0.70 (64 items) |
| Freiberg Questionnaire for dystonia (torticollis version)³⁴ | Patient-rated (including medical history, course of disease, previous treatment, current neurologic, and psychosocial changes)  
Psychosocial changes section includes 23 items covering five areas (profession, everyday life, social life, family, psychological well-being) | Reliability  
α >0.87 (two factors)
Validity  
Two-factor model ‘psychological distress’:  
• (loadings 0.56–0.83) and  
‘functional disability’  
• (loadings 0.55–0.81), explaining 59.4% of the variance |
| Craniocervical Dystonia Questionnaire-24²⁹ | Patient-rated  
24 items (five scales: stigma; emotional well-being; pain; ADL; social/family life) | Reliability  
α >0.77 (all scales)
Validity  
CDQ-24 correlated with SF-36 subscales measuring similar aspects  
(Pearson’s correlation r = 0.50–0.73; p < 0.001)
Responsiveness  
Statistical significant change  
(p < 0.001) |

For abbreviations, please see text.
Table 23.4 Dystonia rating scales – description and psychometric data

<table>
<thead>
<tr>
<th>Scale</th>
<th>Conceptual and measurement model</th>
<th>Reliability</th>
<th>Validity</th>
<th>Responsiveness</th>
<th>Interpretability</th>
<th>Burden</th>
<th>Alternative modes of administration</th>
<th>Cultural and language adaptations or translations</th>
</tr>
</thead>
<tbody>
<tr>
<td>TWSTRS^22</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Burke–Fahn–Marsden Scale^24</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UDRS and GDS^23</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tsui Score^25,40</td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDIP-5^26–29</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Concept Scale^30</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional Disability Questionnaire^30</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ways of Coping Checklist^31</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Freiberg questionnaire for dystonia^34</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Craniocervical Dystonia Questionnaire-24^29</td>
<td></td>
<td>✓</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

✓ = evaluation reported.
No tick = no evaluation reported.
For abbreviations, please see text.
Content There are two clinician-rated symptom scales. The UDRS has ratings for 14 body areas, including head, trunk, and limbs. For each area, there is a 5-point severity scale (ranging from no dystonia to extreme) and a 5-point duration rating (ranging from at rest to with action). The GDS provides a global severity rating in each body area on a 0–10 scale (ranging from 0 = no dystonia to 10 = severe dystonia). The total score is the sum of the scores for all body areas.

Psychometric data Only reliability has been presented. The UDRS and GDS scales have been shown to have acceptable internal consistency (\( \alpha > 0.91 \)), and acceptable inter-rater reliability for total scores (ICC >0.71). However, more variable inter-rater reliability was found when examining body area scores (weighted \( k = 0.52–0.90 \)).

Burke–Fahn–Marsden Dystonia Scale\(^{24} \)

Purpose The Burke–Fahn–Marsden Dystonia Scale\(^{24} \) measures movement and disability for primary torsion dystonias. It has mainly been used in treatment trials.

Content There are two main scales: a clinician-rated movement scale and a patient-rated disability scale. The movement scale rates severity of movement affecting different body parts on a 5-point scale. Body areas include the head, trunk, and limbs. Trunk and limb movements are assigned a weight of 1, and scores from eyes, mouth, and neck are ‘down-weighted’ (0.5) on the premise that they cause less disability. The disability scale (also on 5 points) comprises seven areas of daily activities, including writing, dressing, and walking.

Psychometric data Reliability and validity have been presented. The movement scale has been shown to have acceptable inter- and intra-rater reliability (\( r > 0.85, r > 0.98, \) respectively). Evidence for construct validity has been found in the form of correlations with global severity and disability scale (\( r > 0.69 \)).

Tsui Scale\(^{25} \)

Purpose The Tsui Scale measures movement and tremor in CD. It has mainly been used in botulinum toxin trials.

Content There are three main scores: clinician-rated movement and tremor. Amplitude of head movement and position are scored on 4-point scales: these scores are added (maximum score = 9) and multiplied by a value that is assigned on the basis of the type of head movement (1 = intermittent or 2 = constant movements). Tremor is rated on a 3-point scale, ranging from absent to severe and multiplied by 1 (intermittent movement) or 2 (constant movement). Thirdly, shoulder elevation is rated on a 4-point scale.

Psychometric data Only reliability has been presented. The scale has been shown to have acceptable inter-rater reliability (\( r > 0.85 \)).

Patient-report scales

Six patient-reported rating scales have been developed to assess the impact of dystonia.

Cervical Dystonia Impact Scale (CDIP-58)\(^{26–28} \)

Purpose The CDIP-58 measures eight areas of health impacted upon by CD and was developed for use in clinical research, audit, and treatment trials.

Content Fifty-eight items made up of eight 5-point scales, ranging from 4 to 10 items in length: three symptom scales (i.e. head and neck, pain and discomfort, sleep); two activity scales (i.e. upper limb activities, walking); and three psychosocial scales (i.e. annoyance, mood, psychosocial functioning). Eight summary scale scores are generated by summing items and then transformed to a 0–100 scale. High scores indicate worse health.

Psychometric data Development strategy and traditional and new psychometric data techniques are presented. CDIP-58 was developed in three phases following standard guidelines.\(^{12} \) New psychometric techniques (Rasch analyses) revealed that the CDIP-58 performed well (e.g. good mean square infit (MNSQ) <1.5, even spread of item calibrations and hierarchical structure). In addition, traditional psychometric properties have been supported (e.g. Cronbach’s \( \alpha = 0.92–0.97 \), item-total correlation = 0.64–0.91, test-retest = 0.83–0.96). Within-scale analyses and comparisons with external measures (e.g. Medical Outcomes Study Short Form-36 (SF-36) (\( r = 0.48–0.66 \)), General Health Questionnaire (GHD) (\( r = 0.30–0.66 \)), and Hospital Anxiety and Depression Scale (HAD) (\( r = 0.31–0.80 \))). Moderate to high effect sizes reveal the CDIP-58 is good at detecting the impact of botulinum toxin on all eight health dimensions.\(^{28} \)

Craniocervical Dystonia Questionnaire-24 (CDQ-24)\(^{29} \)

Purpose The CDQ-24 measures the impact of craniocervical dystonia on five health-related quality of life domains. It was developed for use in clinical research.
Content Twenty-four items, forming five scales: stigma, emotional well-being, pain, activities of daily living, and social/family life. Items are rated on a 5-point scale (18 items based on frequency – never to always; 6 items based on severity – not at all to very severely). High scores indicate worse health.

Psychometric data A 29-item pool was developed based on semi-structured interviews of patients with cervical dystonia (CD) and blepharospasm (BSP). This questionnaire was sent to 203 patients with CD and BSP, resulting in the 24-item version (CDQ-24). Validity and reliability data were assessed in 231 patients with CD and BSP. Internal consistency and reliability: Cronbach’s α value range from 0.77 to 0.89. CDQ-24 subscales showed moderate to high correlations with those SF-36 subscales measuring similar aspects (Pearson’s correlation r = 0.50–0.73; p <0.001, each). Statistical sensitivity to change supported significant improvements of all CDQ-24 subscores in the de novo patients from baseline to 4-week follow-up.

Functional Disability Questionnaire

Purpose The Functional Disability Questionnaire measures disability due to CD. Four areas are included: social, physical activity, self-care, and leisure activities.

Content There are 27 items, forming four factors: social disability, physical activity, self-care, and leisure activities. Each item is rated on a 4-point scale, ranging from 1 (not affected) to 4 (severely affected). Subscores for each factor are derived by summation of raw scores. High scores indicate worse health.

Psychometric data Reliability and validity have been presented. The scale has been shown to have acceptable internal consistency (Cronbach’s α = 0.92) and test–retest reliability (ICC = 0.93). Construct validity is supported by principal components analysis (PCA).

Body Concept Scale

Purpose The Body Concept Scale measures the impact of CD on body concept.

Content There are 22 semantic differential scales, forming four factors: speed/strength, postural/movement-related, evaluative/esthetic, and tension. Each item is rated on a 7-interval semantic scale. Subscores for each factor are derived by summation of raw scores. High scores indicate a more negative body concept.

Psychometric data Reliability and validity have been presented. The scale has been shown to have acceptable internal consistency (Cronbach’s α = 0.95), and test–retest reliability (ICC = 0.87). Construct validity is supported by moderate correlations of the scale and disfigurement ratings and the Beck Depression Inventory (0.44 and 0.41, respectively).

Ways of Coping Checklist

Purpose The Ways of Coping Checklist measures coping in CD and was adapted from an original scale devised by Folkman and Lazarus and revised by Felton et al.

Content There are 64 items, forming six factors: wish-fulfilling fantasy, threat-minimization, negative reappraisal/coping, cognitive restructuring, religious faith, and instrumental coping. Subscores for each factor are derived by summation of raw scores. High scores indicate poorer coping.

Psychometric evaluation Reliability and validity have been presented. The scale has been shown to have acceptable internal consistency (Cronbach’s α = 0.70). Construct validity supported by principal components analysis.

Freiberg Questionnaire for dystonia (torticollis version)

Purpose The Freiberg Questionnaire measures behavioral aspects of CD.

Content This multi-item questionnaire consists of open-ended, dichotomous, and 5-point response options. Items include medical history, course of disease, previous treatment, current neurologic, and psychosocial changes. The psychosocial changes section includes 23 items, covering five areas (profession, everyday life, social life, family, and psychological well-being).

Psychometric data Reliability and validity have been presented on the psychosocial changes subscale. This scale is shown to have acceptable internal consistency (Cronbach’s α = 0.87). Construct validity was supported by principal components analysis.

CRITICAL EVALUATION OF DYSTONIA RATING SCALES

Researchers have a number of options when selecting a measure for outcome studies. In order to make recommendations for dystonia scale selection for future studies, current measures were examined to determine how they have been developed and evaluated.
Strengths

Existing dystonia scales cover a wide range of important outcomes, including symptoms, activities of daily living, and aspects of psychosocial functioning, which provide researchers with a good range of alternative measures for different research aims. Measures are either clinician-rated, patient-rated, or a combination of both, which also provides choice in the mode of administration and allows the combination and comparison of clinician and patient ratings. Finally, some psychometric data are presented for each of the scales, providing further useful information for instrument selection.

Weaknesses

There are a number of drawbacks to the majority of existing scales. The main limitations of clinician-rated scales are that they are predominantly observer-dependent and do not incorporate the patient’s perspective of physical, psychological, and social health impact of the disorder. Therefore, additional patient-report rating scales must be used to overcome this. However, the majority of the patient scales focus on a narrow range of outcomes, primarily on psychological dimensions. Only one disease-specific scale (CDIP-58) has been developed following standard guidelines (i.e. patient-generated item pool, item reduction, and psychometric evaluation) and fulfils many of the SAC scale evaluation criteria. For the remainder of the measures, the psychometric properties were limited. For example, reliability and validity analyses of the Burke–Fahn–Marsden Scale and TWSTRS were confined to inter-rater reliability and some construct validity.

The lack of appropriately evaluated scales has implications for clinical research. For example, in CD research a number of studies have investigated the treatment effects of botulinum toxin type A (BTX-A), botulinum toxin type B (BTX-B), and drug treatment, and surgery. Most studies report improvement, but have either been unable to discriminate between patients, or have described small changes post-treatment. However, as none of the CD scales used in these studies had been developed appropriately or been evaluated for responsiveness, it is difficult to disentangle treatment and measurement effects. This poses serious questions about the validity of the findings.

New developments in rating scale assessment

Rating scale use and development in dystonia research is still in its infancy, and only recently have studies been carried out using rigorous methodologies. Despite this, the health measurement field is moving quickly, and techniques applicable to dystonia studies are being developed and advanced. The methods described in this chapter are termed traditional psychometric methods and are currently the most commonly used methods of rating scale development and validation. It is important that neurologists be familiar with these methods of rating scale evaluation but also be aware of their limitations which restrict the impact of their use in research and routine clinical practice.

From a research perspective, the first limitation of these traditional methods is that raw scores are non-linear counts and not interval measures. This potentially biases the interpretation of scores and score changes, and may result in treatment effectiveness being underestimated. A second limitation is that raw scores are scale-dependent. Therefore, different scales purporting to measure the same health construct cannot be accurately equated, or their results combined for systematic reviews and meta-analyses. A third limitation is that the traditional psychometric properties of scales are sample-dependent and, therefore, not necessarily stable across different samples. This means that before using a rating scale in different patient populations, new validation data must first be collected and analyzed. A fourth limitation is that rating scales tend to cover a limited spectrum of quality of life. Samples in clinical studies often extend outside of the range of the scale, resulting in floor and ceiling effects. These represent subsamples of patients for whom health changes will not be detected, or be underestimated by scales.

From a clinical perspective, rating scales developed using traditional psychometric techniques provide raw scores that are not precise enough for individual patient clinical decision-making. Importantly for neurologists, this means that scales developed using such methods are valid for population-based research, but are not necessarily valid as clinical measurement tools for individual patients. Such rating scales cannot be used in routine clinical practice.

These limitations of summed rating scales were recognized some time ago in education and psychology. Research led to the development of Rasch item analysis and Item Response Theory (IRT) models. These new psychometric methods convert raw scores into interval measures using a log odds-ratio transformation. Recently, Rasch methodology has been used in questionnaire development as a means of increasing the clinical utility of new questionnaires for individual patients. There are two clinically relevant issues. First, as a consequence of the mathematics of the model, it is legitimate to sum items to produce total scores and, in
turn, the total scores produce interval-level measures from ordinal level rating scale data. Thus, when items (data) fit the model, we can be confident that items can be summed to produce valid total scores, and that we are able to measure consistently across the whole range of disease impact. This improves the accuracy with which clinical change can be measured. Secondly, Rasch analysis provides estimates for patients (and items) that are independent of the sampling distribution of items (and patients). Among other benefits, this allows for accurate estimates suitable for individual person measurement. This can help directly inform upon patient monitoring, management, and treatment.

The latent advantages of this new approach to rating scale development are significant. If neurologists perceive that a ‘research questionnaire’ also provides useful clinical information regarding an individual patient’s outcome, they may be more likely to offer the questionnaire to their patients in the context of prospective studies and clinical trials. Patients, as well, may be more likely to complete questionnaires if they perceive that they are deriving some direct benefit by providing the information. This can improve communication with the patient, allowing the physician to be more effective in addressing the specific issues of a patient. Thus, the clinical utility of a questionnaire that is able to measure health-related quality of life in clinical settings is the potential to improve clinical outcomes for individual patients with dystonia.

Another exciting prospect of these new methods is that by providing information about item performance, not available using traditional psychometric methods, these new techniques can be used to create banks of items with known characteristics. These calibrated item banks lay the foundation for rapid and efficient individual patient measurement using computer algorithms, which in turn opens the door to computer-adaptive testing. In this technique, rather than giving the same set of items to each individual, the items are selected based on the ability level or other characteristics.

CONCLUSIONS AND RECOMMENDATIONS

There is little consistency or comparability in dystonia rating scales used in current research, making meta-analysis difficult. Much of the emphasis is on observer (clinician)-rated scales, which do not often take account of the patient’s perspective of the health impact of dystonia. Much of the research into patient-reported outcomes of dystonia is limited, focusing primarily on psychological dimensions of patient well-being. The majority of the dystonia rating scales do not meet the rigorous scientific standards required (i.e., reliability, validity, and responsiveness). Therefore, for future research, the following recommendations can be made:

- Clinician-rated scales: the TWSTRS and the Burke–Fahn–Marsden Dystonia Scale are the most popular measures for dystonia studies, the UDRS and GDS are new scales for general dystonia, but there is a need for new measures to be developed and evaluated following standard guidelines.
- Patient-rated scales: for CD research, the CDIP-58 should be used, as it is the only existing measure to have followed recommended guidelines and have extensive testing using both traditional and new psychometric methods.
- There is a need for more dystonia-specific validated measures to assess the health impact beyond CD, including the effectiveness of treatment.

It is appropriate when designing trials to use both clinician-rated and patient-rated scales to assess new treatments. In the long term, the use of appropriate dystonia rating scales is vital as policy and patient decisions based on outcome studies depend on scientific quality.

REFERENCES


Index

Page references to figures, tables and boxes are shown in italics. Genes and genetic loci have been grouped in the index.

abductor spasmodic dysphonia (ABSD) 111–15
   treatment 116, 116
acute drug-induced dystonia see acute dystonic reactions (ADRs)
acute dystonic reactions (ADRs)
   anesthetic agents 149
   causative drugs 149–50, 150
   clinical features 149
   cranial dystonia 92–3
   definition 149
   pathophysiology 150
   risk factors 150
   treatment 150–1
   see also tardive dystonia
adductor breathing dystonia 112
   treatment 116, 117
adductor spasmodic dysphonia (ADSD) 111–15
adult-onset focal PTD (DTY7) 29
age at onset 3
   cervical dystonia (CD) 75–6, 76
   primary dystonia 16–17, 18
   psychogenic movement disorder 174–5
   secondary dystonia 20, 21, 138
age, gender, and type of dystonia 18
AIDS (acquired immunodeficiency syndrome) 150
Alzheimer's disease 85
amino and organic acidurias 134, 141–2
anatomic distribution 2–3
anesthetic agents, ADR causation 149
anticholinergic agents 77, 100, 150, 155, 184
anticonvulsants 149, 166
antidepressants 149
antidopaminergic agents 185–6
apraxia of eyelid opening 87
aromatic amino acid decarboxylase (AADC) deficiency 141
Ashkenazi Jews 3, 17, 27, 53–4
   see also DYT1 dystonia
ataxia with vitamin E deficiency 144
ataxia-telangiectasia 143
Auctioneer's jaw 94
autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) 162, 165, 167
autosomal recessive PTD (DTY2) 29
baclofen 184–5
basal ganglia, abnormality 40–1, 41, 131, 139
Batten disease 140–1
benign paroxysmal torticollis in infancy 162–3
benzodiazepines 185
   ADR causation 149
   TDT treatment 155
benztropine 150
Bereitschaftspotential 40
biopterin levels 123
blepharospasm 2, 83–4, 85–8
   with additional perioral involvement 86
apraxia of eyelid opening 87
botulinum toxin 87–8, 194–5
   clinical features 85–6
   dark glasses 86
   disease course 86
   drug treatment 87, 87
   etiology 87
   eyelid lifting operations 88
   Meige syndrome 83, 86, 86
   prevalence 85
   surgical treatment 87, 219
botulinum toxin (BTX) 189–203
   antibody development 199–200, 201–3
   Auctioneer's jaw 94
biochemistry and pharmacology 191–3
blepharospasm and hemifacial spasm 87–8, 194–5
cervical dystonia (CD) 77, 197–200
Clostridium botulinum (CB) 189–91
cranial dystonia 77
formulations
   commercially available 189–91, 190
   dose equivalence 194
   history 189–91
   laryngeal dystonia 115–17, 116, 196–7
   mechanism in dystonia 193
botulinum toxin (BTX) (Continued)

NBAI 94
oromandibular dystonia 91–2, 196
physiotherapy 226–7
possible target muscles in blepharospasm 88
preparation 191
presynaptic terminal 191–3
quality of life issues 245–6, 246
resistance 199–200, 201–3
SNARE complex 191
structured treatment plan 235
tardive dystonia 155
task-specific dystonia 105
therapeutic trials 194–201
toxin types 189–91, 194
trismus 94
upper limb muscles 103
writer’s cramp 100–1, 101, 200–1
botulinum toxin treatment, writer’s cramp 102
brachial dystonia 2–3
bromocriptine 183–4
Brueghel’s syndrome 83–4, 84
bruxism 92
calcium antagonists, ADR causation 149
carbamazepine 186
carbidepia 183
cervical dystonia (CD) 2, 73, 73–7
age related causes 75–6, 76
botulinum toxin 77, 197–200
Cervical Dystonia Severity Scale (CDSS) 74
Craniocervical Dystonia Questionnaire (CDQ-24) 74–5
deep brain stimulation 216–17
functional stereotactic surgery 214–18
head positions 2, 73, 73–4
neck pain 2, 73, 74
‘null point’ 2
peripheral surgery 209–14
physiotherapy 223–7
role of trauma 74
secondary nature of CD 75, 75
tardive CD 76
Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) 74, 199
treatment 77
children and adolescents, drug therapy treatment algorithm 185
chorea-acanthocytosis 143
clonazepam 166, 186
Clostridium botulinum (CB) 189–91
cocaine, ADR causation 149
Cochrane Database Review 2005, blepharospasm 195
complex regional pain syndrome (CRPS) 176
cortical motor dysfunction 40–1
corticobasal degeneration (CBD) 106
cranial dystonia 81–94
acute dystonic reactions 92–3
Auctioneer’s jaw 94
bruxism 92
cranial muscles 81–3, 82, 83
definitions 83–4
differential diagnosis 84–5
etiology 85
familial nocturnal faciomandibular myoclonus 94
neuroacanthocytosis 94
neurodegeneration with brain accumulation of iron (NBAI) 93, 93–4
trismus 94
see also blepharospasm
deep brain stimulation (DBS) 32, 48–9, 77, 126
cervical dystonia 216–17
efficacy and outcomes 215–16
generalized dystonia 217
secondary dystonia 218
segmental and focal dystonia 217–18
tardive dystonia 156
degenerative neurologic disorders 6–8
degenerative processes, heredodegenerative dystonia 135
diagnosis 1–11
diagnostic evaluation 8–11
primary dystonia 9
secondary dystonia 9–11
disinhibition, disorders 37–8
intracortical inhibition 38
surround inhibition 38–40, 39
L-dopa/decarboxylase inhibitor 122, 123
dopamine metabolism
[18F]-dopa PET analysis 49
in DRD 49–50
dopamine receptor blocking drugs (DRBs)
ADR and TDT effects 149, 153, 154–5
exposure vs. TDT% 153
in TDT 155
therapy 90, 92, 92–3
dopamine receptor hypersensitivity 154
dopamine-responsive dystonia (DRD) 5–6, 9–10, 30, 30–2, 49–50, 107
clinical presentation 121–2
diagnosis 123–4
dopamine metabolism 49–50
genetic and molecular basis 122
glucose metabolism 50
limb dystonia 106
molecular pathogenesis 122–3
pterin synthesis defects 124
tyrosine hydroxylase (TH) deficiency 124
dopaminergic agents 183–4
drug therapy 183–7
children and adolescents, treatment algorithm 185
drug-induced dystonia see acute dystonic reactions (ADRs)
dyskinesias 159–66
dystonia
causes 28
classification 2, 2–8
definitions 1, 27, 83–4
history of study 53
dystonia specialist nurse (DSN)
  background 233–4
  botulinum toxin, structured treatment plan 235
  dystonia care team, organization of 234
  qualities needed 234–7
  referral process 235
  role and responsibilities 234, 237
  service development 237–9
  dystonia-plus syndromes 5–6, 29–32, 30, 31, 121–8
  definition 121
  DYT1 dystonia 27–8, 53–61, 65–6
  DYT endophenotypes 59–60
  DYT1 phenotype 58–60
  future research 61
  GAG deletion, 9, 27–8, 54, 58
  genetic counseling and testing 60, 60
  H allele 57
  invertebrates models 56
  mouse models 56–7
  neuropathology 55
  role in focal dystonia 56
  variants 57
  in vitro studies 55–7
  writer’s cramp 99
  see also limb dystonia; primary torsion dystonia (PTD)

early-onset parkinsonism (EOPD) 123–4
early-onset PTD see DYT1 dystonia
Ecstasy (3,4-methylenedioxymethamphetamine),
  ADR causation 149
EEG potential variations
  Bereitschaftspotential 40
  contingent negative variation (CNV) 40
  electromyographic (EMG) activity 35
Epidemiological Study on Dystonia in Europe (ESDE) 17, 74
epidemiology
  concepts 15–16
  primary torsion dystonia (PTD) 16–19, 65
  secondary dystonia 19–22
  epidemiology of the primary dystonias in the north
  of England 17
ethnicity factors
  primary dystonia 3, 16, 17, 27
  secondary dystonia 20
etiology
  primary dystonia 3
  secondary dystonia 5–8, 6–7
exercise-induced dystonia 161, 163–4
‘eye of the tiger’ 131, 139
eyelid closure, movement sequence 84
‘face of the giant panda’ 131
Fahr’s disease 131, 139
familial nocturnal faciomandibular myoclonus 94
familial striatal necrosis 143
[18F]-fluorodeoxyglucose (FDG) 45–6, 99
focal dystonia 2
  DYT1 effects 57
  see also specific dystonias
focal hand dystonia 46, 48
fucosidosis 141
functional imaging
  primary torsion dystonia (PTD) 45–50
  functional magnetic resonance imaging (fMRI) 46
  abnormal sensory activation patterns 48
  psychogenic dystonia 177
  vs. PET 46–7
functional stereotactic surgery, cervical dystonia 214–18
GAG deletion, DYT1 9, 27–8, 54, 58
  gangliosidosis, GM1 & GM2 140
  gastric reflux 115
gender-specific
  factors, secondary dystonia 20, 21
  prevalence rates primary dystonia 17, 18
  generalized dystonia 2
genes
  ASA/ARSA 140
  ATP1A3 127–8
  ATP7B 132–8
  ATXN3 8
  CHRN group 165
  CLN group 141, 163
  CSE 165
  CYP2D6 22
  DDP group 142
  DJ1 143
  DYT group 3, 27, 29
  DYT1 3, 17–18, 27–8, 38, 45–7, 49, 53–61, 65–6, 99, 107, 126, 152, 175
  DYT2 28, 67
  DYT4 67
  DYT6 28, 45–6, 66
  DYT7 29, 30, 66, 75, 106
  DYT12 6, 126
  DYT13 28, 66–7, 106
  EKD2 164
  FPD1 163
  FUCA1 141
  GALC 140
  GCH1 5, 9–10, 122–3, 124
  GLRA1 166
  HAGH 163
  HE1 139
  IBGC1 139
  LRRK2 143
  MR-1 163
  NPC1 139
  PANK2 94, 139
  parkin mutation 5, 106
  pml1 143
  SGCE 6, 124–6, 125
  SURF1 142
  TOR1A (see DYT1)
  UCH-L1 143
  see also genetic dystonia; specific form of dystonia
genetic counseling and testing
  DYT1 dystonia 60, 60

see also dystonia specialist nurse; dystonia care team; genetic dystonia
INDEX

generic dystonia 3, 27–32, 106

classification 4, 29, 31
see also genes; genetic loci; specific forms of dystonia

 genetic loci
1p21 165
1p35 143
2q31–q36 163
2q33–q35 163
4p14 143
4q21 143
6q25–27 143
7q21-31 124–6
9q32-34 3, 27, 53–4
13q14 132–8
14q13 124
14q22.1-q22.2 5
14q24.3-q31 5, 139
14q31 140
16p12-q12 165
18p deletion 127
18q11 139
19q13.2 6, 126
20p13 139
20q13.2 165
22q13 140

geste antagoniste 1, 36, 73–4
glucose metabolism in DRD 50
glutaric acidemia type I 141
glyceropyrrolate 77

H allele, DYT1 57
Hallervorden–Spatz syndrome see neurodegeneration with brain iron accumulation type 1; pantothenate kinase-associated neurodegeneration

hemidystonia 2, 131
hemifacial spasm see blepharospasm
heredodegenerative dystonia
causes 133–5
HIV (human immunodeficiency virus) 150
homocystinuria 142
human deafness-dystonia syndrome 142
Huntington's disease (HD) 22, 81, 85, 107, 142

identifying dystonia 1–2
idiopathic basal ganglia calcification (IBGC) 131, 139
idiopathic torsion dystonia see primary torsion dystonia
imaging 45–50
treatment effects on brain activation 48–9
infantile bilateral striatal necrosis 143
infantile convulsions and choreoathetosis (ICCA) syndrome 161, 163–4
intracortical inhibition 38
intrathecal baclofen (ITB) 218–19
invertebrates models DYT1 dystonia 56

Krabbe’s disease 140

laryngeal dystonia
assessment of symptoms 112, 112–13

botulinum toxin 115–17, 116, 196–7
diagnosis 111–12
forms 111, 112
nasolaryngoscopy 114
pathophysiology and pathogenesis 117
treatment 115–17, 116, 196–7
Leber’s hereditary optic neuropathy 142
Leigh disease 142
Lesch–Nyhan syndrome 141
leukodystrophies 140
levodopa 183
limb dystonia
clinical features 105–6
course and prognosis 106
gene testing 106–7
treatment 107
lisuride 183–4
lysosomal storage disorders 133, 139–41

Machado–Joseph disease see spinocerebellar ataxia
Meige syndrome 83, 86
metabolic errors, congenital 133–5, 141
metachromatic leukodystrophy (MLD) 140
metal and mineral metabolism disorders 133
metallic disorders 133
metformin, ADR causation 149
microvascular decompression (MVD), cervical dystonia 213–14
mitochondrial disorders 134, 142
Mohr–Tranebjaerg syndrome 142
motor control
abnormal FDG PET patterns 46–8
features of impairment 35
plasticity 41–2
repetitive activity 41
silent period (SP) 37
motor evoked potentials (MEPs) 37–40
mouse models, DYT1 dystonia 56–7
musician’s cramp 99, 101–5
clinical features 102–3
pain management 228–9
physiotherapy 228–9
poor posture correction 229
myasthenia gravis 85
myectomy
blepharospasm 219
cervical dystonia 212–13
myoclonus-dystonia (M-D) 5–6, 30, 30–2, 121, 124
clinical signs and symptoms 126
gene mapping and cloning 124–6
genetic heterogeneity 126–7
myotomy, cervical dystonia 212–13

nasolaryngoscopy, laryngeal dystonia 114
neuroacanthocytosis 94
neurodegeneration
with brain accumulation of iron (NBAI) 9, 93, 93–4, 139
limb dystonia in 106
neuroferritinopathy 139
neuroleptic agents
acutedystonicroactions20
tardivedystonia20
neuronalceroid-lipofuscinosis(NCL)140–1
neuronalintrannuclearinclusiondisease143–4
Niemann–PickdiseasetypeC11,133,139–40
non-dystoniclaryngealmovementdisorder114–15
nursingseedy dystonia special nurse(DSN)

Oppenheim’sdystonia seedy DYT1 dystonia
orbicularisioculismuscle,fiberarchitecture84
organicacidurias134,141–2
orobuccolingualdystonia83
overflow(excessmuscleactivation)1,35

painmanagement
musician’scramp228–9
physiotherapyfor224
primarytorsiondystonia229–30
panthothenikinase-associatedneurodegeneration
(PKAN) seeyenneurodegeneration with brain
accumulation of iron
paradoxicalvocalfolddysfunction(PVFD)112,115
Parkinson syndromes 30,30–2,127,135,143
Parkinson’s disease 5,8,143
dystonia in PD 22,123,127
Parkinson’s-plus syndromes 8
paroxysmal dystinesias 105
classification 159–60,160
definition 159
history 159
pathophysiology165–6
secondary(‘symptomatic’)163
treatment 166
seeyalso specifidystinias
paroxysmal dystonia 31,32
paroxysmal dystonic choreoathetosis(PDC) seeyeparoxysmal
non-kinesigenic dystinesia(PNKD)
paroxysmal exercise-induced dystinesia(PED)159
clinical features 161
genetics 165
PEDplus syndrome 161
paroxysmal hypnogenic dystinesia(PHD) 160
clinical features 162
paroxysmal kinesigenic choreoathetosis(PKC) seeyeparoxysmal
kinesigenic dystinesia; paroxysmal
non-kinesigenic dystinesia(PNKD)
paroxysmal kinesigenic dystinesia(PKD)159
association with epilepsy 161
clinical features 160–1,161

paroxysmal non-kinesigenic dystinesia (PNKD) 159
association with spasticity 162
biochemical pathways 164
clinical features 161–2
genetics163,164
pathophysiology35–42
Pelizaeus–Merzbacher disease 140
persistent dystonia see tardive dystonia
phenol 77
physiotherapy
botulinum toxin 226–7
development of rehabilitation programs 223–7
dynamic correction, right cervical dystonia 226
generalized dystonias 229–30
pain management 224
patient involvement 226
primary torsion dystonia (PTD) 229–30
Report Form 225
task-specific dystonias 227–9
post-traumatic movement disorder 176
seeyalsopsychogenic dystonia
post-traumatic painful torticollis 176,177
pre-supplementary motor area (Pre-SMA) 46
primary generalized dystonia see primary torsion
dystonia (PTD)
primary somatosensory cortex (S1) 36
primary torsion dystonia (PTD)
adult-onset focal PTD (DTY7) 29
autosomal recessive PTD (DTY2) 29
clinical features 65–7,68
diagnostic evaluation 9
DYT2 67
DYT4 67
DYT6 66
DYT7 66
DYT13 66–7
epidemiology 16–19,65
etiology 3
familial pedigrees 67
functional imaging 45–50
genetics27–30
incidence 16
late-onset PTD 28–30
non-DYT1 PTD 28,67–70
pain management 229–30
physiotherapy 229–30
prevalence 16–17,17
risk factors 17–19
sensitivity and specificity predictions, ROC curve 69
survival curves 70
seeyalso DYT1 dystonia
INDEX

prochlorperazine, ADR causation 149
propionic acidemia 142
psychogenic dystonia 1–2
classification 174
clinical features and diagnosis 172–6
epidemiology 171–2, 172
features 175
history 171
neuroimaging 177–8
neurophysiologic studies 178
psychopathology 177
treatment and prognosis 179–80
see also post-traumatic movement disorder
pterin synthesis defects 124
quality of life (QL)
appraisal of research 246–7
background 241
categorical scheme 245
evaluation 241–2
measurement studies 242–6, 243, 244
recommendations 247
treatment effects 245–6, 246
rapid-onset dystonia-parkinsonism (RDP) 30, 30–2, 127, 143
biochemical and imaging studies 127
clinical presentation 127
genetic studies and molecular pathogenesis 127–8
rating scale assessment
background 249
clinician-rated scales 251–5, 252
new developments 257–8
patient-report scales 252–3, 255
psychometric data 254
scientific basis 249–51
evaluation 256–8
recommendations 258
reliability, validity, and responsiveness 250
types 250, 250, 251, 254
rating scales
Body Concept Scale 256
Burke–Fahn–Marsden Dystonia Scale 255, 257
Cervical Dystonia Impact Scale (CDIP-58) 255, 257
Cervical Dystonia Severity Scale (CDSS) 74
Craniocervical Dystonia Questionnaire-24
(CDQ-24) 255–6
Freiberg Questionnaire for dystonia
(torticollis version) 256
Functional Disability Questionnaire 256
Global Dystonia Rating Scale (GDS) 251–5
Toronto Western Spasmodic Torticollis Rating Scale
(TWSTRS) 74, 199, 251, 257
Tsui Scale 255
Unified Dystonia Rating Scale (UDRS) 251–5
Ways of Coping Checklist 256
writer’s cramp rating scale (WCRS) 101
reciprocal inhibition 35
reflex sympathetic dystrophy (RSD) 176
reserpine 135
risk factors
acute dystonic reactions 150
anecdotal illness 18
cigarette smoking 19
gene factors 22
hypertension 19
neuroleptic agents 20, 22
occupation 19
primary dystonia 17–19
secondary dystonia 22
tardive dystonia 153–4
thyroid disorders 19
trauma 18–19, 74
vestibular changes 19
rolandic epilepsy, paroxysmal exercise-induced dystonia, and
writers’ cramp (RE-PED-WC syndrome) 161, 163–4
secondary dystonia
age at onset 20, 21, 138
basal ganglia involvement 40–1, 41, 131
causes 132
deep brain stimulation (DBS) 218
diagnostic investigation 131–2, 136–7
epidemiology 19–22
genetics 30–2, 31
segmental and focal dystonia
deep brain stimulation (DBS) 217–18
segmental dystonia 3
selective peripheral denervation 210, 210–12, 211, 212
sensory dysfunction
abnormal sensory discrimination 36
activation patterns, MRI abnormalities 48
sensory input 36–7
sensory tricks 1, 36, 73–4
‘shortening reaction’ 223
sigma receptors 150
SNARE complex 191
spasmodic dysphonia (SD) treatment 115, 116
spasmodic torticollis 1, 36
physiotherapy 223–7
spinocerebellar ataxia (SCA) 8, 142–3
surgical treatment
blepharospasm surgery 219
functional stereotactic surgery 214–18
deep brain stimulation 215–18
pallidotomy 214–15
thalamotomy 214
history 209
intrathecal baclofen (ITB) 218–19
peripheral surgery, cervical dystonia 209–14
intradural rhizotomy and nerve sectioning 213
microvascular decompression (MVD) 213–14
myotomy and myectomy 212–13
selective peripheral denervation 210, 210–12, 211, 212
surround inhibition 38–40, 39
symptomatic limb dystonia 106
tardive dyskinesia (TDK) 151

tardive dystonia (TDT)
  botulinum toxin treatment 155
  clinical features 151–2
  deep brain stimulation (DBS) 156
  definition 151
  differential diagnosis 152, 153
  DRB exposure vs. TDT% 153
  incidence and prevalence 21, 152
  neuroleptic agents 20
  outcome and remission 154, 154
  pathophysiology 154–5
  risk factors 153–4
  treatment 155–6
  types 151

  see also acute dystonic reactions (ADRs)

  task-specific dystonia 97–107
  behavioral therapies 104–5
  botulinum toxin treatment 105
  clinical features 102–3
  course and prognosis 103–4
  electromyography (EMG) investigations 104, 104
  physiotherapy 227–9

  see also musician’s cramp; writer’s cramp

tetrahexyphenidyl 184

tetrahexyphenidyl 184

trihexyphenidyl 184

trihexyphenidyl 184

trinucleotide repeat disorders 134–5, 142–3

triose-phosphate isomerase deficiency 141

triptans, ADR causation 149

tyrosine hydroxylase (TH) 122–3, 124

voice tremor 112

  treatment 116, 116–17

Westphal’s phenomenon 223

Wilson’s disease 6–8, 9, 10–11, 93, 94, 131–9

writer’s cramp

  behavioral therapies 99–100
  botulinum toxin treatment 100–1, 101, 200–1
  efficacy and outcomes 101, 200–1
  studies 102
  techniques 101, 200
  classification 100
  clinical features 97–8, 98
  corrective handwriting exercise 228
  course and prognosis 98
  electromyography (EMG) studies 98–9, 99
  etiology 100
  forearm muscles involved 97
  functional imaging studies 99
  physiotherapy 227–8
  prevalence 97
  RE-PED-WC syndrome 161, 163–4
  surgery 101
  systemic drug treatment 100
  transcranial magnetic stimulation (TMS) 99
  writer’s cramp rating scale (WCRS) 101

  see also task-specific dystonia

X-linked dystonia-parkinsonism (Lubag) 127, 143
Clinical Diagnosis and Management of Dystonia

Almost 100 years have passed since the first clinical descriptions were made of cases of dystonia. In the ensuing century, the study of this protean movement disorder has undergone a turbulent evolution, with dramatic shifts in the views regarding its causation and phenomenology. For a considerable period of time dystonia was considered a psychological or a psychiatric disorder, yet today, the dystonias are now recognized as, in the majority of cases, an organic neurological disorder.

The time, therefore, is fitting to take stock of the knowledge of the various conditions that are recognized as dystonias. Warner and Bressman have drawn together a series of monographs from world leaders in the field of dystonia. *Clinical Diagnosis and Management of Dystonia* will lead the reader through the phenomenology and etiology of dystonia, to then describe specific forms. The final chapters summarize various medical and surgical treatment strategies for dystonia, including paramedical input, and conclude with how the physician can measure dystonia and its effects on quality of life.

**With contributions from:**

Fereshte Adib Saberi
Alberto Albanese
Friedrich Asmus
Anna Rita Bentivoglio
Kallash P Bhatta
Jean-Pierre Breton
Yvette M Bordeau
Susan B Bressman
Stefan J Cano
Maren Carbon
Anabel R Chade
Martin Clouter
Cynthia L Comella
Dirk Dresler
Mark J Edwards
David Eidelberg
Antonio E Elia
Steven J Frucht
Thomas Gasser
Howard L Geyer
Paul Greene
Mark Hallett
Joseph Jankovic
Christoph Kamm
Su Kanchana
Meike Kasten
Marianne King
Joachim K Krauss
Anthony E Lang
Thomas J Loher
Christy L Ludlow
Jorg Muller
Laurie J Ozelius
Werner Poeewe
Tamara Pringsheim
Caroline M Tanner
Ronald Tintner
Enza Maria Valente
Thomas T Warner

**Thomas T Warner PhD FRCP** is Reader in Clinical Neurosciences, Department of Neurosciences, Institute of Neurology, University College London, London, UK, and Honorary Consultant Neurologist at the Royal Free Hospital and National Hospital for Neurology and Neurosurgery, London.

**Susan B Bressman MD** is Chair, Department of Neurology, Beth Israel Medical Center, and Professor, Department of Neurology, Albert Einstein College of Medicine, New York, NY, USA.

informa healthcare

[QR Code]

www.informahealthcare.com