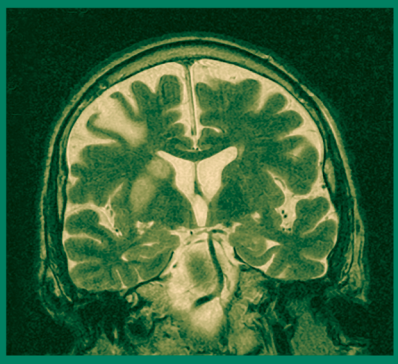
Movement Disorder Emergencies

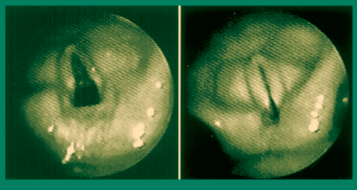
Diagnosis and Treatment

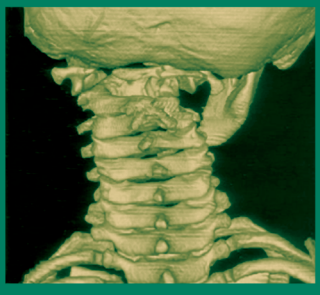
Edited by

Steven J. Frucht, MD

Stanley Fahn, MD







HUMANA PRESS

Movement Disorder Emergencies

CURRENT CLINICAL NEUROLOGY

Daniel Tarsy, MD, SERIES EDITOR

Movement Disorder Emergencies: *Diagnosis and Treatment,* edited by ***Steven J. Frucht and Stanley Fahn,*** *2005*

Psychiatry for Neurologists, edited by ***Dilip V. Jeste and Joseph H. Friedman,*** *2005*

Status Epilepticus: *A Clinical Perspective,* edited by ***Frank W. Drislane,*** *2005*

Thrombolytic Therapy for Acute Stroke, Second Edition, edited by ***Patrick D. Lyden,*** *2005*

Inflammatory Disorders of the Nervous System: *Pathogenesis, Immunology, and Clinical Management,* edited by ***Alireza Minagar and J. Steven Alexander,*** *2005*

Neurological and Psychiatric Disorders: *From Bench to Bedside,* edited by ***Frank I. Tarazi and John A. Schetz,*** *2005*

Multiple Sclerosis: *Etiology, Diagnosis, and New Treatment Strategies,* edited by ***Michael J. Olek,*** *2005*

Parkinson's Disease and Nonmotor Dysfunction, edited by ***Ronald F. Pfeiffer and Ivan Bodis-Wollner,*** *2005*

Seizures in Critical Care: *A Guide to Diagnosis and Therapeutics,* edited by ***Panayiotis N. Varelas,*** *2005*

Vascular Dementia: *Cerebrovascular Mechanisms and Clinical Management,* edited by ***Robert H. Paul, Ronald Cohen, Brian R. Ott, Stephen Salloway,*** *2005*

Atypical Parkinsonian Disorders: *Clinical and Research Aspects*, edited by ***Irene Litvan,*** *2005*

Handbook of Neurocritical Care, edited by ***Anish Bhardwaj, Marek A. Mirski, and John A. Ulatowski,*** *2004*

Handbook of Stroke Prevention in Clinical Practice, edited by ***Karen L. Furie and Peter J. Kelly,*** *2004*

Clinical Handbook of Insomnia, edited by ***Hrayr P. Attarian,*** *2004*

Critical Care Neurology and Neurosurgery, edited by ***Jose I. Suarez,*** *2004*

Alzheimer's Disease: *A Physician's Guide to Practical Management,* edited by ***Ralph W. Richter and Brigitte Zoeller Richter,*** *2004*

The Visual Field: *A Perimetric Atlas,* edited by ***Jason J. S. Barton and Michael Benatar,*** *2003*

Surgical Treatment of Parkinson's Disease and Other Movement Disorders, edited by ***Daniel Tarsy, Jerrold L. Vitek, and Andres M. Lozano,*** *2003*

Myasthenia Gravis and Related Disorders, edited by ***Henry J. Kaminski,*** *2003*

Seizures: Medical Causes and Management, edited by ***Norman Delanty,*** *2002*

Clinical Evaluation and Management of Spasticity, edited by ***David A. Gelber and Douglas R. Jeffery,*** *2002*

Movement Disorder Emergencies

Diagnosis and Treatment

Edited by

Steven J. Frucht, *MD*
Stanley Fahn, *MD*
Department of Neurology
Columbia University Medical Center
New York, NY

HUMANA PRESS TOTOWA, NEW JERSEY

999 Riverview Drive, Suite 208
Totowa, New Jersey 07512

humanapress.com

This publication is printed on acid-free paper. ∞
ANSI Z39.48-1984 (American Standards Institute) Permanence of Paper for Printed Library Materials.

Cover illustration: (Left) From Fig. 1B, Chapter 11, "Hemiballism–Hemichorea," by Ronald B. Postuma and Anthony E. Lang; (top right) from Fig. 2, Chapter 6, "Abductor Paresis in Shy-Drager Disease," by Eiji Isozaki; and (bottom right) from Fig. 1A, Chapter 9, "Pseudodystonic Emergencies," by Beom S. Jeon and Jong-Min Kim.

Production Editor: Robin B. Weisberg

Cover design by Patricia F. Cleary

For additional copies, pricing for bulk purchases, and/or information about other Humana titles, contact Humana at the above address or at any of the following numbers: Tel.: 973-256-1699; Fax: 973-256-8341; E-mail: orders@humanapr.com; or visit our Website: www.humanapress.com

Printed in the United States of America. 10 9 8 7 6 5 4 3 2 1

eISBN: 1-59259-902-8

Library of Congress Cataloging-in-Publication Data
Movement disorder emergencies : diagnosis and treatment / edited by Steven J. Frucht, Stanley Fahn.
p. ; cm. -- (Current clinical neurology)
Includes bibliographical references and index.
ISBN 1-58829-305-X (alk. paper)
1. Movement disorders--Case studies. 2. Neurological emergencies--Case studies. [DNLM: 1. Movement Disorders--diagnosis--Case Reports. 2. Emergencies--Case Reports. 3. Movement Disorders--therapy--Case Reports. WL 390 M93543 2005] I. Frucht, Steven J. II. Fahn, Stanley, 1933- III. Series.
RC376.5.M677 2005
616.8'0425--dc22

2004017845

Series Editor's Introduction

Movement Disorder Emergencies: Diagnosis and Treatment provides a fresh and unique approach to what is already a high-profile subspecialty area in clinical neurology. The disorders covered in this volume are standard fare in the field but emphasize the urgencies and emergencies that can occur. One of the very attractive features of the field of movement disorders is that diagnosis is often based on unique visible and sometimes audible phenomenological symptoms and signs. Therefore, in this era of highly sophisticated laboratory and radiological diagnostic tools, the diagnosis of many movement disorders is still largely made in the clinic where pattern recognition is key. Crucial to astute clinical diagnosis is broad clinical experience. In short, you have to have seen one to recognize one! Patients with movement disorders nearly always present as outpatients but, as aptly recognized by Drs. Frucht and Fahn, this may include acute manifestations leading to emergency presentations, often in an emergency room setting, where they are very likely to be unrecognized and therefore poorly managed.

The authors define an "emergency" movement disorder as one in which failure to promptly diagnose and treat may result in significant morbidity or mortality. However, they also stress the importance of certain "can't miss" diagnoses such as Wilson's disease, dopa-responsive dystonia, and Whipple's disease in which delayed diagnosis in less emergent situations can lead to slowly evolving and often irreversible neurological damage with tragic consequences. Particularly useful are patient vignettes at the beginning of each chapter, which serve to focus the reader's attention and highlight the urgency of the problem being discussed. The chapters are very practical in emphasizing keys to diagnosis and treatment but do not skimp on the underlying science, thereby providing in one reference source most of what is necessary to know about these disorders.

Especially useful are chapters devoted to specific disorders that often fail to get sufficient attention of their own in movement disorder texts. For example, consistent with the well-known emergency medicine axiom to first assure an adequate airway, there are chapters devoted to vocal cord abductor paresis in multiple system atrophy and emergencies of the upper aerodigestive tract. Malignant catatonia gets its own chapter and the parkinsonism-hyperpyrexia syndrome is presented separately from neuroleptic malignant syndrome. The remaining chapters comprehensively cover the broad range of movement disorders in a manner the readership will find very satisfying.

Daniel Tarsy, *MD*
Parkinson's Disease and Movement Disorders Center
Beth Israel Deaconess Medical Center
Harvard Medical School, Boston, MA

Preface

The neurologist's standard questions when approaching a patient are: "Where is the lesion? What is the lesion? What can I do about it?" When perusing *Movement Disorder Emergencies: Diagnosis and Treatment*, we expect the interested reader to pose a similar set of questions: "Why another book about movement disorders? What is a movement disorder emergency?"; and most importantly, "Is this book worth the money?"

Commonly thought of as a pure outpatient specialty, movement disorders may present urgently within the hospital or to the emergency room. The response to a course on the topic that we delivered from 2001 to 2004 at the American Academy of Neurology annual meeting convinced us that the time was right for a small volume devoted to the subject. We hope that the interested reader will agree that the disorders and clinical problems presented in the text are important, well within the purview of neurology residents, general neurologists, movement disorder fellows and movement disorder neurologists. We would be delighted if neurointensivists or those interested in emergency medicine also were interested.

In answer to the final (and most important) question facing those who must decide whether or not to read *Movement Disorder Emergencies: Diagnosis and Treatment*, consider this. We are grateful to our many contributors, drawn from an international roster, for the time and effort they expended in producing these carefully written, comprehensive chapters. We think you will agree that they represent some of the leading experts in the discipline. If you don't care for the format or presentation, blame the editors, not the contributors. The accompanying CD illustrates virtually all of the movement disorder emergencies described in the text, a necessary and in our view indispensable resource for learning about these conditions.

We wish to thank our colleagues and families for their help and support. This book is dedicated to the patients depicted within, who often endure these disorders with grace and stoicism.

Steven J. Frucht, *MD*
Stanley Fahn, *MD*

Contents

Contributors

EVA ANDERMANN, MD, PHD, FCCMG • Montreal Neurological Hospital and Institute, Montreal, Quebec, Canada

FREDERICK ANDERMANN, MD, FRCP(C) • Montreal Neurological Hospital and Institute, Montreal, Quebec, Canada

BORIS BENTSIANOV, MD • Division of Laryngology, Voice and Swallowing, Department of Otolaryngology, State University of New York, Downstate Medical Center, Brooklyn, New York

HENRY R. BLEIER, MD • Department of Psychiatry, University of Pennsylvania School of Medicine and the Department of Veterans Affairs Medical Center, Philadelphia, PA

ANDREW BLITZER, MD, DDS • New York Center for Voice and Swallowing Disorders, St. Luke's/Roosevelt Hospital Center, New York, NY

GEORGE J. BREWER, MD • Departments of Human Genetics and Internal Medicine, University of Michigan Medical School, Ann Arbor, MI

E. CABRINA CAMPBELL, MD • Department of Psychiatry, University of Pennsylvania School of Medicine and the Department of Veterans Affairs Medical Center, Philadelphia, PA

STANLEY N. CAROFF, MD • Department of Psychiatry, University of Pennsylvania School of Medicine and the Department of Veterans Affairs Medical Center, Philadelphia, PA

AJAY CHITKARA, MD • New York Center for Voice and Swallowing Disorders, St. Luke's/Roosevelt Hospital Center, New York, NY

ANTHONY CULTRARA, MD • New York Center for Voice and Swallowing Disorders, St. Luke's/Roosevelt Hospital Center, New York, NY

STEWART A. FACTOR, DO • Movement Disorders Program, Department of Neurology, Emory University, Atlanta, GA

STANLEY FAHN, MD • Department of Neurology, Columbia University Medical Center, New York, NY

HUBERT H. FERNANDEZ, MD • Department of Clinical Neurosciences, Brown University School of Medicine, Providence, RI

BLAIR FORD, MD • Department of Neurology, Columbia University Medical Center, New York, NY

JOSEPH H. FRIEDMAN, MD • Department of Clinical Neurosciences, Brown University School of Medicine, Providence, RI

STEVEN J. FRUCHT, MD • Department of Neurology, Columbia University Medical Center, New York, NY

YOSHIAKI FURUKAWA, MD • Movement Disorders Research Laboratory, Centre for Addiction and Mental Health-Clarke Division, Toronto, Ontario, Canada

CHRISTOPHER G. GOETZ, MD • Department of Neurological Sciences, Rush University Medical Center, Chicago, IL
MARK FORREST GORDON, MD • Department of Neurology, Long Island Jewish Medical Center, New Hyde Park, NY
PAUL E. GREENE, MD • Department of Neurology, Columbia University Medical Center, New York, NY
ROBERT A. GREENSTEIN, MD • Department of Psychiatry, University of Pennsylvania School of Medicine and the Department of Veterans Affairs Medical Center, Philadelphia, PA
MARK GUTTMAN, MD • Human Neurochemical Pathology Laboratory, Centre for Addiction and Mental Health-Clarke Division, Toronto, Ontario, Canada
VANESSA K. HINSON, MD, PhD • Department of Neurosciences, Medical University of South Carolina, Charleston, SC
EIJI ISOZAKI, MD • Department of Neurology, Tokyo Metropolitan Neurological Hospital, Tokyo, Japan
JOSEPH JANKOVIC, MD • Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, TX
BEOM S. JEON, MD, PhD • Department of Neurology, Seoul National University Hospital, Seoul, South Korea
JONG-MIN KIM, MD • Department of Neurology, Seoul National University Hospital, Seoul, South Korea
STEPHEN J. KISH, PhD • Human Neurochemical Pathology Laboratory, Centre for Addiction and Mental Health-Clarke Division, Toronto, Ontario, Canada
CAROLYN KWAK, MS, PA-C • Parkinson's Disease Center and Movement Disorders Clinic, Department of Neurology, Baylor College of Medicine, Houston, TX
ANTHONY E. LANG, MD, FRCP(C) • Morton and Gloria Shulman Movement Disorders Center, Toronto Western Hospital, Toronto, Ontario, Canada
ADENA LEDER, DO • Department of Neurology, Long Island Jewish Medical Center, New Hyde Park, NY
JOHN LYNCH, MD, MRCPI • Beaumont Hospital, Ireland
TIM LYNCH, MD, MRCPI, BSc, FRCPI • The Mater Misericordiae Hospital, Dublin, Ireland
STEPHAN C. MANN, MD • Department of Psychiatry, University of Pennsylvania School of Medicine and the Department of Veterans Affairs Medical Center, Philadelphia, PA
MELISSA J. NIRENBERG, MD, PhD • Department of Neurology, Columbia University Medical Center, New York, NY

JOSE OBESO, MD • Department of Neurology, Clinica Universitaria and Medical School, University of Navarra, Pamplona, Spain
ROSER PONS, MD • Department of Neurology, Columbia University Medical Center, New York, NY
RONALD B. POSTUMA, MD, FRCP(C) • Morton and Gloria Shulman Movement Disorder Center, Toronto Western Hospital, Toronto, Ontario, Canada
ANTHONY SANTIAGO, MD • Rockwood Clinic, PS, Spokane, WA
KENNETH A. SULLIVAN, PhD • Department of Psychiatry, University of Pennsylvania School of Medicine and the Department of Veterans Affairs Medical Center, Philadelphia, PA
P. D. THOMPSON, MD, PhD • The Royal Adelaide Hospital, The University Department of Medicine, Adelaide, Australia

Companion CD

The companion CD-ROM included with this volume contains video content provided by the editors. Humana Press has provided a custom viewer on the CD for your convenience in viewing and navigating the content, which is indexed to the corresponding chapter in the book. The following index lists the chapters for which video content is provided. Please note that not all chapters in the book have corresponding video content.

Minimum System Requirements for the Companion CD-ROM:

- For Microsoft Windows: An Intel Pentium II with 64 MB of available RAM running Windows 98, or an Intel Pentium III with 128 MB of available RAM running Windows 2000 or Windows XP.
- For Macintosh OS X: A Power Macintosh G3 with 128 MB of available RAM running Mac OS X 10.1.5, 10.2.6, or 10.3.
- For Macintosh Classic: A Power Macintosh G3 with 64 MB of available RAM running System 9.2.

1

A Brief Introduction to Movement Disorders

Steven J. Frucht and Stanley Fahn

INTRODUCTION

Movement disorders is a subspecialty field of neurology concerned with patients who either move too much or not enough. This text and its accompanying CD are *not* designed to serve as a basic textbook of movement disorders. Several excellent texts are already available to satisfy this need. Rather, this book focuses on an interesting and, we think, underrepresented area within movement disorders: movement disorder emergencies.

We define a *movement disorder emergency* as any neurological disorder, evolving acutely or subacutely, in which the clinical presentation is dominated by a primary movement disorder, and in which failure to accurately diagnose and manage the patient may result in significant morbidity or even mortality. Movement disorder emergencies include such diverse entities as acute forms of parkinsonism, chorea, and tics; disease-specific emergencies such as abductor paresis in multiple system atrophy; and conditions like Wilson's disease and dopa-responsive dystonia where failure to properly diagnose and treat the patient leads to unacceptable morbidity.

This short chapter will begin with a clinical review of our approach to a patient with a movement disorder. We also review the major categories of movement disorders as a prelude to the chapters that follow. Videotaped examples of the primary movement disorders are presented in the accompanying CD. In addition, each chapter begins with one or more patient vignettes, and wherever possible videotaped examples of the various movement disorder emergencies have been included in the CD.

THE APPROACH TO THE PATIENT WITH A MOVEMENT DISORDER

Like all areas of neurology, the approach to the patient with a movement disorder begins with the patient's history. Certain elements of the history are particularly important in patients with movement disorders. Patients presenting with an acute movement disorder emergency may be unable to provide a history; however,

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

most patients referred for evaluation to an outpatient center can provide key elements of their stories. Patients and their spouses or companions should be asked to describe the time course in which symptoms developed (hours vs days vs months), whether the condition is getting worse, whether involuntary movements are suppressible, what factors trigger or ameliorate their symptoms, and whether movements are present only while awake or also while asleep. A complete review of past and present medications, including those purchased without a prescription, is critical. Exposure to environmental chemicals, occupational toxins, or illicit drugs, and family history of neurological disabilities are other important queries.

Examination of a patient with a movement disorder depends on careful observation. We often simply watch patients for several minutes in order to define the phenomenology of the movements. Unlike classical neurology's emphasis on localization, it is far more important to define the phenomenology of the movements than to determine their origin. Patients can be classified into two main groups—those who move too little (hypokinetic or parkinsonian) and those who move too much (hyperkinetic). Hyperkinetic disorders are further classified by the speed of the movements, their frequency and amplitude, whether they are regular or irregular, and their stimulus-sensitivity. Dystonia, chorea, tics, myoclonus, and tremor are the major forms of hyperkinetic movement disorders. Sometimes more than one movement disorder is present, such as in a patient with generalized parkinsonism and dystonia of the hand, or in a patient with myoclonus and dystonia.

All patients referred for evaluation of a movement disorder should also receive a general neurological examination, including a Mini-Mental Status Exam. Laboratory and imaging studies are of secondary importance in the movement disorder evaluation, and are best used to confirm or refute possible diagnoses suggested by history and examination. If needed, magnetic resonance imaging (MRI) is the preferred imaging modality in most patients.

HYPOKINETIC DISORDERS

Akinesia, hypokinesia, and bradykinesia are terms used to describe patients with an absence or paucity of movement. The latter term is most commonly used, and refers to patients with parkinsonism. Parkinsonism is a neurological syndrome characterized by a combination of one of six cardinal features: rest tremor, bradykinesia, rigidity, flexed posture, freezing, and loss of postural reflexes. At least two of the six cardinal features must be present before the diagnosis of parkinsonism can be made, with one of them being rest tremor or bradykinesia.

Patients with parkinsonism can be classified by etiology into four groups. Primary parkinsonism (i.e., Parkinson's disease) is a neurodegenerative disorder characterized by loss of dopaminergic neurons within the substantia nigra and accumulation of Lewy bodies within remaining neurons. Secondary parkinsonism includes drug-induced forms (i.e., neuroleptic-induced), toxin-induced parkinsonism (MPTP), postencephalitic parkinsonism, and vascular parkinsonism. Parkinson-plus syndromes encompass a group of disorders that mimic Parkinson's

disease, with the burden of additional neurological deficits. This group includes multiple system atrophy (an umbrella term including three conditions that share similar pathology: olivopontocerebellar atrophy, Shy–Drager syndrome, and striatonigral degeneration), progressive supranuclear palsy, and corticobasal ganglionic degeneration. Heredodegenerative parkinsonism includes a wide variety of disorders that are progressive, typically with other neurological deficits accompanying parkinsonism. Examples include Wilson's disease, X-linked dystonia parkinsonism (also known as Lubag), frontotemporal dementia, juvenile Huntington's disease, and neuroacanthocytosis, among others.

A variety of medications are available to treat parkinsonism. Levodopa is typically administered with carbidopa in the form of Sinemet (carbidopa/levodopa), in strengths 25/100, 25/250, and in controlled-release preparations (25/100, 50/200). A variety of dopamine agonists are available as well, including the ergot agonists bromocriptine and pergolide, and the nonergots pramipexole and ropinirole. Amantadine, selegiline, entacapone, and anticholinergics are often used as well. In general, patients with Parkinson's disease enjoy the best response to these drugs, and patients with Parkinson-plus disorders and heredodegenerative forms of parkinsonism benefit either incompletely or not at all. Since its introduction moe than 30 years ago, no drug has supplanted levodopa as the most effective and best tolerated antiparkinson agent.

Acute parkinsonism and the parkinsonism–hyperpyrexia syndrome will be discussed in Chapters 2 and 3. Parkinsonism is the dominant clinical phenotype of the neuroleptic malignant syndrome and malignant catatonia (Chapters 4 and 5). Respiratory compromise resulting from abductor paresis is a treatable and life-threatening problem in patients with multiple system atrophy, and is considered in Chapter 6.

HYPERKINETIC DISORDERS

Once the examiner has determined that a patient has a hyperkinetic movement disorder, the next question is: which one is it? The major categories of hyperkinetic disorders include five conditions: dystonia, chorea, tics, myoclonus, and tremor. Rarer hyperkinetic movement disorders include entities such as paroxysmal dyskinesias, stereotypies, episodic ataxia, restless leg syndrome, periodic limb movements of sleep, myokymia, myorhythmia, hemifacial spasm, and hyperekplexia. Of these, only hyperekplexia (exaggerated startle syndrome) qualifies as a movement disorder emergency.

Dystonia

Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. The relatively long duration of movements, simultaneous contraction of agonist and antagonist groups, and sustained contractions in discrete muscle groups in an affected body part help distinguish dystonia from other hyperkinetic disorders. A *geste*

antagoniste or sensory trick is a unique feature of dystonia; gently touching the chin in a patient with cervical dystonia, or changing the grip of the pen in a patient with writer's cramp results in immediate improvement in dystonic contractions. Dystonia may be focal, affecting one body part: eyes (blepharospasm), neck (torticollis), vocal cord (spasmodic dysphonia), hand, foot or trunk; segmental (affecting two continuous body parts); hemidystonic (affecting an ipsilateral hand and foot); or generalized.

Similar to parkinsonism, dystonia is classified into four etiologic groups. Patients with primary dystonia have pure dystonia in isolation, often the result of a genetic mutation. The most common form of primary dystonia is DYT-1 dystonia, first described by Oppenheim in 1911. The classic presentation begins in childhood, affecting a hand or a foot, sometimes spreading to involve other body areas. Dystonia-plus syndromes refer to conditions in which dystonia is accompanied by another movement disorder. The two major forms are dopa-responsive dystonia and myoclonus-dystonia. Secondary dystonias include dystonic disorders caused by external factors, such as encephalitis, trauma, stroke, tumor, toxins, and drug exposure (e.g., neuroleptic-induced acute and tardive dystonia). The clinical picture of heredodegenerative dystonia is dominated by other neurologic deficits; this group includes such disparate conditions as X-linked dystonia-parkinsonism (Lubag), Huntington's disease, Wilson's disease, glutaric acidemia, neuronal intranuclear hyaline inclusion disease, and Leigh's disease.

Anticholinergics, baclofen, and clonazepam are most commonly used in patients with generalized dystonia, but side effects often limit their use in adults. Focal dystonia affecting the eyes, jaw, neck, vocal cords, or limbs is best treated with local injection of botulinum toxin, which directly chemodenervates the body part involved. Injections are effective, safe, and virtually free of significant side effects except for the possibility of excess weakness in the muscles injected. They may be uncomfortable and thus difficult to use in children, and they must be repeated every 3 to 6 months. Recent experience suggests that deep brain stimulation of the globus pallidus is an effective treatment for patients with severe, generalized dystonia who fail medical treatment, particularly patients with DYT-1 dystonia.

Dystonia affecting the vocal cords may contribute to airway embarrassment; this is discussed in Chapter 7. Dystonic storm refers to uncontrolled, violent dystonic spasms that often require treatment in an intensive care unit (Chapter 8). Several conditions may mimic dystonia, such as tetanus and atlanto-axial rotatory subluxation; their management is reviewed in Chapter 9.

Chorea

Chorea refers to involuntary movements that are rapid, brief, unsustained, continuous, often flowing in quality, and typically moving from one part of the body to another. Chorea may occur in hereditary disorders such as Huntington's disease, neuroacanthocytosis, ataxia-telangiectasia, and benign hereditary chorea. It is more commonly encountered in the setting of metabolic derangements (hyperglycemia),

as a para-infectious disorder (poststreptococcal chorea), or after exposure to drugs such as neuroleptics (tardive dyskinesia), anticonvulsants, or noradrenergic stimulants.

Most neuroleptics will help to control chorea regardless of etiology; however, their side effects include depression, parkinsonism, and QT prolongation. These drugs carry a small but real risk of engendering tardive disorders, even with brief use. Valproic acid is another agent that has been used to control chorea, typically in poststreptococcal cases. Tetrabenazine is a dopamine depletor and blocker that does not induce tardive disorders, suggesting a unique position within this group. Severe chorea is an important movement disorder emergency, discussed in Chapters 10 (tardive disorders) and 11 (hemiballism-hemichorea). The management of Sydenham's chorea and other poststreptococcal movement disorders is discussed in Chapter 12.

Tics

Tics are relatively brief movements (motor tics) or sounds (vocal tics) performed in response to an internal urge, and which are often repetitive and gestural (stereotypic). Unlike dystonia, myoclonus, chorea, and tremor, tics can often be completely suppressed. Performance of the tic generally reduces the uncomfortable urge. Simple tics involve one muscle group (blinking, shoulder shrug), whereas complex tics are sequenced activities that may replicate normal movements, save for their need to be repeated or their inappropriate content or context.

Although tics may occur after infection or medication exposure, most patients evaluated for tics have a primary tic disorder which, in its fully expressed state, is best known as Tourette's syndrome. Obsessive-compulsive symptomatology and attention deficit hyperactivity disorder are common comorbidities in this population. Clonazepam, clonidine, guanfacine, serotonin-specific reuptake inhibitors, neuroleptics, and tetrabenazine have been used to treat tics. When tics are severe and persistent, interfering with school performance or social life, they represent a tic emergency (Chapter 14). Vocal tics are especially disturbing to young children or working professionals, and they represent another movement disorder emergency (Chapter 15).

Myoclonus

Myoclonus refers to shock-like, involuntary movements arising from the central or peripheral nervous system. True myoclonus is easily distinguished from other hyperkinetic disorders by its speed, lack of suppressibility, and frequent stimulus sensitivity (to light touch, reflex, or pin prick). Myoclonus may be focal (affecting one body part), multifocal (typically affecting hands and feet simultaneously), or generalized (whole-body jerks). It may be positive, reflecting active contraction of a muscle group, or negative, reflecting loss of postural tone in a limb or in the trunk. Myoclonus may originate within the cortex, from subcortical structures, within the brainstem (palatal myoclonus, reticular reflex myoclonus, and startle), from the spinal cord (spinal segmental myoclonus, and propriospinal myoclonus),

or from peripheral nerve root irritation. Determining the origin of myoclonus is critical in the selection of appropriate treatment.

Physiological myoclonus refers to normal myoclonic jerks that everyone has experienced, such as hypnogenic jerks on falling asleep, and hiccups (diaphragmatic myoclonus). Essential myoclonus, also known as myoclonus-dystonia, is a rare genetic disorder in which individuals develop myoclonus in isolation in their second decade. Exquisite response to alcohol, normal life span, and frequent anxiety and obsessive-compulsive disorder are characteristics of this condition. Epileptic forms of myoclonus include juvenile myoclonic epilepsy, infantile spasms, and other serious epilepsy conditions. The final and largest category includes symptomatic myoclonus, either with or without prominent seizures. Progressive myoclonic epilepsy forms the first group, including disorders such as myoclonic epilepsy with ragged red fibers, ceroid lipofuscinosis, lafora body disease, sialidosis, and GM1 gangliosidosis. Symptomatic myoclonus without prominent seizures occurs as the result of drug exposure, after trauma or anoxia (posthypoxic myoclonus), and in a variety of progressive neurodegenerative conditions.

Although no drugs are approved for the treatment of myoclonus, several antiepileptic agents have been borrowed to treat myoclonic disorders; these agents include valproic acid, clonazepam, levetiracetam and zonisamide. Often, several drugs are required in combination to obtain adequate control. Myoclonus is commonly seen in patients with serotonin syndrome (Chapter 16), principally affecting the legs. Exaggerated startle, a brainstem form of myoclonus, defines hyperekplexia, an inherited startle syndrome that is discussed in Chapter 17.

Tremor

Tremor is a rhythmic, oscillatory movement disorder most commonly affecting the head, voice, hands, or feet. Tremor may be present at rest, with posture, or with action (kinetic tremor). Rest tremor is common in Parkinson's disease, typically affecting the hand at 3 to 4 Hz frequency. The postural tremor of essential tremor, the most common form of kinetic tremor, is faster, typically affects the head, voice, and hands, and often improves with alcohol. Propranolol and primidone help ameliorate the symptoms of essential tremor, but rarely completely relieve tremor. As the most common involuntary movement disorder, tremor is rarely a prominent feature in patients with movement disorder emergencies.

"DON'T MISS" DIAGNOSES

Included in this text are three disorders that might not, at first glance, appear to be true emergencies. Wilson's disease (Chapter 18), dopa-responsive dystonia (Chapter 19), and Whipple's disease (Chapter 20) typically present to the outpatient clinic arena, and the time frame in which neurologic symptoms develop is typically months or even years. However, we have chosen to classify these three disorders as emergencies for the following reasons: they are treatable, with the potential of return to baseline status; they are rare, with protean clinical presenta-

tions that make diagnosis difficult; and the consequences of a missed or delayed diagnosis can be severe. Because of these reasons, we thought that these "don't miss" diagnoses deserved to be included in a book on movement disorder emergencies.

2

Acute Parkinsonism

Hubert H. Fernandez and Joseph H. Friedman

PATIENT VIGNETTES

Patient 1: A 75-year-old woman with a history of bipolar affective illness dating back to her 20s was admitted to the hospital after falling and breaking her hip while walking her dog. She had been living alone. She underwent a total hip replacement without incident and was at her mental and physical baseline in the recovery room and then on the postsurgical floor. Two days after surgery she suddenly became mute, stiff, and unresponsive. In addition to her usual regimen of 600 mg lithium, 20 mg fluoxetine, and 4 mg trifluoperazine daily, she had received five doses of meperidine (50 mg/bolus intravenously) for pain control. She kept her eyes open and responded to visual threat and deep pain but not voice. She had markedly increased tone and was akinetic. When her arms were elevated, she slowly lowered them. Deep tendon reflexes were normal. Physical examination, vital signs, laboratory tests, including lithium levels and head computed tomography (CT) were unremarkable. She remained in this state for 3 days before a movement disorder consultation was requested.

Patient 2: A 15-year-old girl developed a febrile illness with diffuse erythematous, maculopapular rash, conjunctivitis, and headache for 4 days. On the fifth day, as her fever and rash resolved, she became increasingly drowsy and difficult to arouse. When awake, she followed commands very slowly. Her visual fields and eye movements were normal. No ptosis was noted, and her face was expressionless and her mouth held partly open. A mild, intermittent resting tremor was noted in the left hand. No other adventitious movements were noted. She was diffusely rigid with asymmetry. Deep tendon reflexes were normal and plantar responses were equivocal. The remainder of her neurological examination was unremarkable. Medical and family history was noncontributory. Immunizations were complete apart from measles. Her white cell count was 14.0×10^9/L with 45% neutrophils and 48% lymphocytes. Cerebrospinal fluid (CSF) analysis showed 20 white blood cells/mm (all lymphocytes), no red blood cells, and normal protein and glucose. Serum measles antibody titers (by complement fixation) 10 days after the rash were 1:160; 3 weeks later, the titer was 1:80. Electroencephalogram (EEG) and CT of the head were unremarkable. She was started on 25/100 mg of carbidopa/levodopa at one-half tablets three times

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

per day with significant improvement. Over the next 3 months, her tremor, bradykinesia, and rigidity slowly resolved.

INTRODUCTION

Secondary parkinsonism as a result of an identifiable, nondegenerative disorder is common, primarily occurring following exposure to medications that block dopamine D2 receptors *(1)*. Primary parkinsonism *(2)* is caused by a variety of slowly progressive disorders, and the date of symptom onset is usually hard to pinpoint. Most secondary forms of parkinsonism, including the drug-induced forms, evolve over weeks, but may develop over hours to days. It is often difficult to recognize akinetic rigid syndromes at their early stages, especially in patients who may be systemically ill.

The broad categories for etiologies of acute parkinsonism are found in Table 1. Parkinsonism may be a relatively minor aspect of a life-threatening disorder, or may be the presenting and most obvious feature. In the latter case, establishing the onset may be problematic, as patients and families often note the symptoms only when the patient is brought to medical attention after a fall or a spell of incontinence. With diligent questioning, one can usually determine that the process began much earlier than originally reported.

Acute parkinsonism in psychiatric disorders occurs in two settings—catatonia and conversion. Although parkinsonism may be seen with severe depression *(3)*, particularly in the elderly as well as in persons with severe obsessive-compulsive disorder *(4)*, the onset is not usually acute.

NONINFECTIOUS ACUTE PARKINSONISM

Structural Lesions

Obstructive hydrocephalus is a well-known cause of parkinsonism *(5)*. Normal pressure hydrocephalus often mimics parkinsonism, but the onset is insidious. Acute parkinsonism from hydrocephalus may occur in both adults and children, either as a result of shunt obstruction or at presentation. One 16-year-old patient had parkinsonism noted on awakening from repair of a shunt malfunction; the shunt was blocked although hydrocephalus was not present. Another case developed immediately after shunt revision. Some cases of obstructive parkinsonism are responsive to levodopa. Obstructive hydrocephalus following meningitis or subarachnoid hemorrhage may also cause parkinsonism.

Vascular parkinsonism, previously called atherosclerotic parkinsonism, usually results from tiny lacunes in the basal ganglia *(6)*. This is generally insidious in onset and slowly progressive, although sudden worsening may occur with new strokes. Acute parkinsonism following a single stroke is rare *(7–14)*. Kim described six patients who developed hemi-parkinsonism, three with rest tremor and cogwheeling rigidity *(10)*. Tremor and other signs of parkinsonism developed after weakness improved. Imaging studies revealed large infarcts involving the supple-

Table 1
Etiologies for Acute Parkinsonism

Infectious
Postinfectious
Autoimmune
systemic lupus erythematosus
Medication
"typical" side effects of dopamine receptor blocker
idiosyncratic effects
neuroleptic malignant syndrome
serotonin syndrome
chemotherapeutic drugs
Toxic
carbon monoxide
cadmium
MPTP
ethanol withdrawal
ethylene oxide
methanol
disulfiram
bone marrow transplantation
Structural
stroke
subdural hematoma
central and extra-pontine myelinolysis
tumor
hydrocephalus
Psychiatric
catatonia
conversion
obsessive-compulsive disorder
malingering

mentary motor area or cingulate gyrus. Other frontal strokes have also caused acute parkinsonism *(11,12)*. As one might expect, strokes in the substantia nigra may cause parkinsonism *(7–9)*, but these are exceedingly rare. Interestingly, strokes in the lenticular nuclei do not cause parkinsonism *(13)*. Acute hemorrhage is a less common cause of acute parkinsonism *(14)*.

Toxic/Metabolic

A number of poisons may induce parkinsonism. Some, like manganese, develop subacutely *(15)* or over long periods of time *(16)*. Parkinsonism may follow carbon monoxide poisoning after an acute, life-threatening poisoning during recovery from coma *(17,18)*. Carbon monoxide poisoning is a persistent problem in some coun-

tries, notably Korea, where faulty oil-burning heaters are used. The globus pallidus is typically involved, but recent data suggests that white matter deterioration must also be present for parkinsonism to develop. Cadmium *(19)* and ethylene oxide *(20)*, disulfiram (used to prevent alcoholics from imbibing) *(21)*, and cyanide poisoning are other uncommon causes *(22,23)*.

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has a special place in the history of movement disorders *(24)*. After its identification by Langston and colleagues as the source of a mini-epidemic of severe, acute parkinsonism in intravenous drug abusers in the San Francisco Bay area, MPTP was exploited as a tool for research into Parkinson's disease (PD). The drug is taken up by glial cells and converted to MPP+, which is secreted and taken up by dopaminergic cells in the pars compacta of the substantia nigra. This was the first systemically administered drug that selectively targets these cells, and because it has a similar effects in other primates, it has been widely used to create animal models of PD. These models are superb for testing symptomatic treatments for motor dysfunction but do not simulate the disease itself. The onset of parkinsonism occurs after the first few doses.

Acute parkinsonism is a rare complication of insect stings *(25,26)*. Acute parkinsonism developed within 3 days of a wasp sting *(25)* associated with pallidal necrosis, followed by acute deterioration 6 months later with degeneration of the nigrostriatal pathway. Bee stings have not been implicated.

Parkinsonism resulting from alcohol withdrawal has been reported rarely *(27–29)*. A follow-up of some of these patients 1 or more years later proved that this withdrawal phenomenon was not a premature unmasking of subclinical PD. Parkinsonism occurred early in withdrawal, and sometimes resolved within 1 week *(27)*. The mechanism is postulated to be a metabolic effect of ethanol on striatal dopamine or dopamine receptors.

Twelve days after overly rapid correction of hyponatremia, a 66-year-old woman became confused and developed parkinsonism. Magnetic resonance imaging (MRI) revealed central pontine myelinolysis. She was responsive to very low doses of levodopa, and her parkinsonism gradually resolved *(30)*. Another similar case was also accompanied by pyramidal features *(31)*. Parkinsonism is not typical for central pontine myelinosis *(32)*. Hypoxic insult to the basal ganglia may cause parkinsonism or dystonia *(33–35)*. This is uncommon and typically occurs after a major brain insult. The syndrome has occurred in children *(34)* as well as adults, and damage to the lenticular nuclei is clearly visible on MRI. Onset is usually delayed, but symptoms may develop rapidly.

Neuroleptic malignant syndrome (NMS) is variably defined but generally requires fever, alteration of mental status, and rigidity (*see* Chapter 11 for a complete discussion of NMS) *(36,37)*. Many patients have extreme elevations of creatine phosphokinase (CPK) as a result of rhabdomyolysis, but this is not required for diagnosis. Elevations in the CPK to the 1000 to 2000 range are sometimes seen in otherwise normal, treated psychotic patients, even in the absence of signs or symptoms of muscle or tone abnormalities. The major differential diagnosis is with in-

fection. Infections frequently cause exacerbations of neurological syndromes, including parkinsonism, in people on neuroleptics. NMS may occur at any point once a patient is treated with neuroleptics, but it usually occurs relatively shortly after drug initiation or dose increase. Although there is a general sentiment that the newer atypical neuroleptics are less likely to cause NMS, there is as yet little data to support this. The onset of NMS may be fulminant, progressing to coma over hours, but it usually develops over days. Patients develop fever, stiffness, and mental impairment with delirium and obtundation. The impaired mental state may initially be overlooked. Rigidity may be so severe that the limbs cannot be moved. The muscle contractions may mimic a tonic seizure. Management of NMS requires excluding infection, stopping the suspected offending drug, close monitoring of autonomic and respiratory parameters, and treatment with dopaminergic replacement (either levodopa or dopamine agonists).

Dopamine D2 receptor-blocking drugs routinely cause parkinsonism *(1)*. This may also occur with lithium or valproic acid. The syndrome usually develops over the course of weeks, but may occasionally develop over days. In patients who have a primary parkinsonian syndrome, a low-potency neuroleptic or even an atypical antipsychotic can induce acute parkinsonism. This is not uncommon when a patient with PD is treated with an antiemetic such as prochlorperazine or metoclopramide.

A handful of children who underwent bone marrow transplantation (BMT) and chemotherapy developed an acute parkinsonian syndrome, sometimes evolving over hours, 2 to 3 months after transplant *(38,39)*. In addition to parkinsonism, cognitive and mental changes also occurred. No particular medication could be implicated, and one patient had had an autologous transplant eliminating the possibility of a graft-vs-host reaction. MRI revealed demyelination, and brain biopsies revealed regions of variably active inflammatory demyelinating lesions. Severe and persistent neurologic sequelae were seen. Several reports in the literature describe an acute parkinsonian syndrome occurring with a variety of anticancer drugs *(40)*. Some of these were extremely responsive to levodopa, and the parkinsonism was not permanent.

A handful of teenagers with systemic lupus involving the nervous system developed acute onset parkinsonism in the setting of active central nervous system (CNS) involvement *(41,42)*. Chorea is the more common movement disorder, associated both with systemic lupus and with the lupus anticoagulant antibody.

Psychiatric

Catatonia is an important diagnosic possibility to consider in acute parkinsonism *(43,44)*. Catatonia should be strongly considered in any patient with acute-onset akinesia and no obvious cause, such as toxin exposure, hypoxic ischemia, CNS infection, or hydrocephalus. Concurrent use of neuroleptic drugs that may cause parkinsonism may complicate the diagnosis. Although for many decades catatonia was considered a variant of schizophrenia, Diagnostic and Statistical Manual (DSM) criteria have been revised to recognize it as a manifestation of manic-de-

pressive disorder as well. It is actually more common in the affective disorders. The patient may have had previous spells that may not have been recognized, and therefore resolved, over long periods of time. The patient may have been functioning quite well until recently when behavioral problems began to recur. Catatonia may punctuate a manic spell or follow a bout of catatonic excitement, suggesting a burnt-out excitatory process like encephalitis. A catatonic, unlike someone with parkinsonism, will not attempt to move. The patient will not appear to be uncomfortable or get hungry. All studies will be normal. If there is no organic disorder, then an EEG, if the eyes are closed, will be normal.

Most physicians incorrectly think of catalepsy as the defining characteristic of the syndrome. Not all patients have waxy flexibility or maintain postures that are externally imposed. The hallmark features of catatonia are negativism, a refusal to cooperate generally manifest as mutism or minimal interaction, and lack of movement. Patients may be stiff or, in contrast, exhibit "mit-gehen," in which they move with the imposed movement, "helping" the movement. Thus, one sees a patient who is not moving but may not be in the typical flexed posture of parkinsonism. There is no tremor, and despite an alert status, little interaction with the environment. Patients will not follow commands and may not respond to pain. Because the patient may keep his or her eyes closed, coma and encephalopathy must be excluded. If the patient's eyes are open, then coma is not a consideration. However, if the eyes are closed and the patient is stiff and unresponsive to deep pain, then the possibility of coma needs to be considered. If a patient is catatonic, there may be no response to deep pain but cranial nerve reflexes will remain intact. It is unlikely that a catatonic will respond to suggestion, but it is certainly worth trying; "If he is truly comatose/unable to move/stiff/etc., then he will keep his hand above his face when I drop it." If the patient is simply severely parkinsonian from neuroleptics, then he or she should be able to comply with some requests, such as moving the eyes, raising a finger, and so on.

Psychogenic parkinsonism is not common but should always be considered in acute-onset cases, especially in young patients. In studies of new referrals to movement disorders specialists, about 2–5% have presumed psychogenic diagnoses *(45)*. Acute-onset parkinsonism without a demonstrable cause is not likely organic. The behavioral causes are catatonia, conversion, and malingering. Conversion disorder is a type of somatoform disorder, in which patients express mental stress as physical disability *(46)*. One characteristic that helps distinguish it from organic disorders *(47,48)* is the acute onset. In idiopathic PD, tremor tends to vary throughout the day, often prominent in time of stress and absent during periods of relaxation. These variations usually occur over minutes, whereas in conversion the symptoms tend to resolve for hours or even days at a time. Factors that typically worsen tremor in PD—cold, heavy lifting, and excitement—don't necessarily affect conversion tremor. On exam, tremor resolves with distraction and varies in frequency, whereas tremor of PD is usually no faster than 4 Hz. The slowness of conversion has a more deliberate character, especially during handwriting. Balance impairment is usually

Table 2
Classification of Infectious Causes of Parkinsonism

A.	von Economo's disease (ED)/encephalitis lethargica
B.	Postencephalitic parkinsonism (PEP) of von Economo
C.	Sporadic, postpandemic ED-like and PEP-like cases
D.	Parkinsonism associated with known viral encephalitis
E.	Parkinsonism associated with nonviral encephalitis
F.	Parkinsonism associated with nonencephalitic infectious
G.	Postvaccinal parkinsonism

not present. The presence of a "belle indifference" attitude is often but not always present in conversion. Some patients with bona fide PD will mask their concern, either because they don't understand the implications of the diagnosis or as a denial mechanism. Often patients with conversion have experience with the disorder or a background in medicine, including employment as a nurse, medical secretary, or lab technician. The single most common stressor in women with conversion is a history of childhood sexual or physical abuse.

INFECTIOUS PARKINSONISM

Classification and Clinical Features

Since von Economo first described acute parkinsonism, similar illnesses have been reported with a myriad of infectious agents. In this section, we have divided the infectious causes of parkinsonism into seven categories (*see* Table 2).

von Economo's disease (ED) was probably seen prior to his initial description of 13 cases with onset between February and April 1917 in Vienna *(49)*. Urechia *(50)* probably described the first recorded credible case series of ED with onsets in April and May 1915 in Bucharest. Somewhat later (1915 or 1916), cases were described in the French army *(51,52)*. On the other side of the globe, a massive encephalitic outbreak affecting 65,000 Chinese in the province of Yunnanfou caused devastation from 1917 to 1927 *(53)*. By 1919, cases had been reported throughout the world. The peak incidence in the United States was in 1923, with about 2000 reported deaths. No major outbreaks of epidemic encephalitis occurred after 1926, and by 1935 the disease had virtually disappeared.

von Economo was the first to recognize and classify three distinct forms of the acute illness, which he called "encephalitis lethargica." He described the *somnolent-ophthalmoplegic form* as a "prodromal phenomena consisting of general discomfort, shivering, headache and slight pharyngitis. The temperature is generally only a little raised. Within the next few days, somnolence begins to predominate. The patients, when left to themselves, fall asleep in the act of sitting and standing, and even while walking, or during meals with food in the mouth. If aroused, they wake up quickly and completely, are oriented and fully conscious, but soon drop back to sleep. Sleepiness in this form may last for weeks or even months but fre-

quently deepens to a state of most intense stupor. Generally, during the first days of illness cranial nerve palsies appear. Ptosis is one of the first and most frequent symptoms. Rarely observed are supranuclear paralyses, paresis of convergence, nystagmus, optic neuritis, papilledema, pupillary disturbances and even Argyll Robertson's sign" *(54)*.

In the *hyperkinetic form*, "chorea and hemichorea as well as myoclonic twitches were observed which might degenerate into wild jactations. On the other hand, it may find its mental expression in a general, curious restlessness of an anxious or hypomanic type. In most of these cases, there is a very distinct sleep disturbance and generally the condition is one of troublesome sleeplessness" *(54)*.

von Economo termed the least frequent form *amyostatic-akinetic.* He described it as "a rigidity, without a real palsy and without symptoms arising from the pyramidal tract. This form of encephalitis lethargica is particularly common in the chronic cases, dominating the clinical picture of parkinsonism. I reserve the name 'parkinsonism,' though symptomatically identical with the amyostatic-akinetic form, rather for the chronic cases. To look at these patients one would suppose them to be in a state of profound secondary dementia. Emotions are scarsely noticeable in the face, but they are mentally intact" *(54)*.

ED was a serious, often lethal disease. "The prognosis of clinically well-documented cases of encephalitis lethargica is 40% mortality, 14% complete recovery, 26% recovery with defect, but able to work, and 20% chronic invalidity" *(54)*.

It is estimated that more than 60% of ED patients who survived developed postencephalitic parkinsonism (PEP). The sequelae occurred more often in adults than in children. The latency period was less than 5 years in 50% of cases and less than 10 years in 85% *(55)*. The average age of onset of PEP was approx 27 years. Resting tremor was the presenting symptom in two-thirds of cases while akinetic-rigid features occurred alone in about one-third *(56)*. Symptoms were occasionally unilateral and often asymmetrical *(57)*. Other neurological abnormalities besides parkinsonism were present in most patients. One of the most notable features was the presence of oculogyric crises: "they consist of tonic visual convulsions, occurring in fits and generally lasting only a few minutes, during which the patients as a rule look upwards and sideways" *(54)*. Other features included dystonia (such as blepharospasm, torticollis, cranial and torsional dystonia), myoclonus (focal or generalized), facial and respiratory tics, choreoathetosis, obsessive-compulsive behavior, pyramidal signs *(57,58)*, supranuclear gaze palsy, and eyelid apraxia *(59)*.

One study assessing the accuracy of diagnosis of PEP in pathologically proven cases showed a high reliability and sensitivity in diagnosis. The best predictors for the diagnosis included onset below middle age, symptoms lasting more than 10 years, oculogyric crisis, and history of ED *(60)*.

The course of PEP is unclear. Duvoisin and Yahr *(55)* followed 49 patients with probable PEP and observed a stable course or very slow deterioration. On the other hand, Duncan *(61)*, who studied 136 PEP inpatients in London, was impressed with the progressive nature of parkinsonian disabilities. Calne and Lees *(62)* and

Viereggel *(63)* both reported deterioration in motor function, generally late in life. The relatively uniform nature of the deterioration exceeded changes in motor function seen in normal elderly subjects and occurred without comparable age-related changes in intellect. In one report, the mean survival from the onset of symptoms was 23.2 years, with the mean age of death at 74.3 years *(56)*.

Although there appears to be general agreement that ED and PEP share a viral etiology, no causative agent was ever identified. Its occurrence around 1918 and 1919 have led some to link ED/PEP to the influenza pandemic that occurred at that time *(64)*. However, von Economo himself rejected this hypothesis on several grounds: (1) ED appeared prior to the influenza pandemic; (2) ED/PEP was not contagious, whereas influenza was highly so; (3) their clinical presentations were different; and (4) the pathology was different, with typical midbrain lesions in ED/PEP contrasting with diffuse brain congestion in cases of postinfluenzal encephalopathy *(54)*. Since the influenza pandemic affected at least 500 million persons *(65)* more than one-fourth of the world's population at that time, it is very possible that many individuals with ED may also have had influenza *(66)*.

Recent studies using immunocytochemistry and immunofluorescence to detect *in situ* antigens failed to consistently isolate influenza or any other virus in the remaining brain or CSF samples of neuropathologically confirmed ED and PEP *(66–70)*. Similarly, the search for autoantibodies did not support an autoimmune mechanism in PEP *(71)*. Finally, studies on genetic susceptibility of ED/PEP have been inconclusive. Although Elizan *(72)* saw a highly significant increase in the frequency of HLA-B14 antigen in PEP cases, Lees *(73)* could not confirm this in their samples.

ED cases considered to be associated with the 1917–1927 pandemic occurred until the early 1930s, after which the disease disappeared. Thus assuming up to a 20-year latency, no PEP cases would be expected to appear after the middle 1950s. Several sporadic ED-like and PEP-like cases, unrelated to the pandemic, have been reported with onset after 1959 *(74–80)*. Aside from one report of positive influenza A antibody titer (1:>160) *(79)* and another report of CSF cultures yielding coxsackie B4 enterovirus *(80)*, attempts to identify the viral agent in ED-like cases have failed. Nonetheless, clinical presentation, laboratory studies, imaging, and pathological findings are reminiscent of, if not identical to, ED/PEP. To distinguish these cases from parkinsonism associated with viral encephalitides, Howard and Lees *(78)* proposed major criteria for the diagnosis of ED. The illness should comprise an acute or subacute encephalitic illness with at least three out of seven features: (1) signs of basal ganglia involvement; (2) oculogyric crises; (3) ophthalmoplegia; (4) obsessive-compulsive behavior; (5) akinetic mutism; (6) central respiratory irregularities; and (7) somnolence and/or sleep inversion.

Parkinsonism may occasionally accompany viral encephalitides. Table 3 lists the viruses known to cause encephalitis with or without associated parkinsonism. In most instances, parkinsonism associated with viral infection occurs during the acute encephalitic phase or shortly thereafter. If the patient survives, the parkin-

Table 3
Causes of Viral Encephalitis

Virus	Parkinsonism	Author (*reference*)
California encephalitis (LaCrosse virus)	Not reported	
Coxackie virus	Acute	Walters *(117)*
	Acute, transient	Posner et al. *(118)*
Cytomegalovirus	Not reported	
Eastern equine encephalitis (EEE)	Not reported	
Herpes virus	Not reported	
Human immunodeficiency virus	Secondary to opportunistic infection	Nath et al. *(81)*; Carrazana et al. *(82)*; Navia et al. *(83)*; Noel et al. *(84)*; Maggi et al. *(85)*; De la Fuente et al. *(96)*; Singer et al. *(97)*; Werring and Chaudhuri *(98)*
	Part/feature of HIV encephalopathy	De Mattos et al. *(86)*; Mirsattari et al. *(87)*
Eptein–Barr virus	Acute, transient	Hsieh et al. *(119)*
Influenza virus	Acute, transient	Isgreen et al. *(120)*
Japanese B encephalitis	Followed acute phase without interval	Shiraki et al. *(121)*
	Chronic phase with interval	Ishii et al. *(122)*
	Acute, persistent	Shoji et al. *(123)*
	Acute, transient	Pradhan et al. *(124)*
Lymphocytic choriomeningitis	Acute, transient	Scheid et al. *(125)*
	Chronic, persistent	Adair et al. *(126)*
Mumps	Not reported	
Murray valley encephalitis	Reported	Bennett et al. *(127)*
Papovavirus	Not reported	
Poliovirus	Acute, transient	Bickerstaff and Clarke *(128)*; Thieffrey *(129)*
	Acute	Barrett et al. *(130)*; Duvoisin and Yahr *(55)*
	Parkinsonism in late life with history of polio as a child/young adult	Vincent and Myers *(131)*
Rubella	Not reported	
Rubeola, measles	Postmeasles, transient	Mellon et al. *(132)*; Meyer *(133)*
Russian spring–summer	Acute, transient	Henner and Hantal *(134,135)*
Encephalitis, european tick-borne encephalitis	Tremor only	Radsel-Medvescek et al. *(136)*

(continued)

Table 3 (Continued)

Virus	Parkinsonism	Author (*reference*)
St. Louis encephalitis	Tremors	Cerna et al. *(137)*; Wasay et al. *(138)*
	Dystonia with tremor as sequelae	Finley *(139)*; Finley and Rigs *(140)*
Varicella-zoster virus	Not reported	
Venezuelan equine encephalitis	Not reported	
Western equine encephalitis	Reported	Fulton and Burton *(141)*
	Chronic persistent	Mulder et al. *(142)*

sonism is usually transient, although it can take several months to resolve. Unlike EP or PEP, oculogyric crises, ophthalmoplegia, cranial neuropathies, or psychiatric/behavioral disturbances are rare.

In human immunodeficiency virus (HIV)-infected patients, parkinsonism may develop from exposure to dopamine blockers (such as prolonged use of metoclopramide); secondary to opportunistic infections (toxoplasmosis, progressive multifocal leukoencephalopathy, tuberculosis) affecting the basal ganglia *(81–85)*; or as part of HIV encephalopathy in the absence of opportunistic infections *(86,87)*. The parkinsonian syndrome is often unresponsive to levodopa *(88)*.

Rarely, parkinsonism is associated with nonviral infectious agents: spirochetes (neurosyphilis and lyme disease), mycoplasma pneumoniae, and opportunistic infections accompanying HIV. Most reported cases of parkinsonism from spirochetal *(89,90)* and mycoplasma *(91–95)* infections present with acute onset and improve markedly with appropriate treatment, despite the severity of the initial clinical presentation. Of five reported cases with mycoplasma, the presenting extrapyramidal features were parkinsonism and/or dystonia, accompanied by seizures in three cases. All patients were children or young adults, and in all cases, MRI revealed selective involvement of the corpus striatum except for one case with concomitant involvement of the substantia nigra and pallidum *(92)*. One case *(91)* had severe dyskinesias and dystonia with levodopa therapy, but experienced gradual resolution of symptoms.

In patients with acquired immunodeficiency syndrome (AIDS), parkinsonism, hemichorea-athetosis, and ballismus have been described with opportunistic infection. Parkinsonism, in particular, has been reported with cerebral toxoplasmosis *(82,84)*, progressive multifocal leukoencephalopathy *(96,97)*, and cerebral tuberculosis *(98)*. All but one case presented with bilateral lesions in the basal ganglia. One patient with mycobacterium tuberculosis involving the left lentiform nucleus only developed parkinsonism when the right lentiform nucleus was superinfected with toxoplasma *(85)*. There is only one reported case of parkinsonism following herpes ophthalmicus *(99)*.

A 5-year-old boy developed isolated fever 15 days after a measles vaccine shot and then developed persistent parkinsonism. MRI showed hyperintense signals affecting the substantia nigra bilaterally. He responded to levodopa but dyskinesias

appeared even at low doses *(100)*. The only other similar case was that of a 38-year-old man who experienced fever, sweats, palpitations, diplopia, and leg tremor within hours of receiving the last of three tetanus vaccinations. Within 1 week, he developed severe parkinsonism with resting tremor, generalized rigidity and bradykinesia, which responded well to levodopa and a dopamine agonist. Unlike the previous case, parkinsonism was transient *(101)*.

Neuropathology and Imaging

The pathological features of ED differ from that of other viral encephalitides (usually characterized by diffuse brain congestion and edema). In ED, pathology typically consists of nonhemorrhagic involvement of the gray matter, preferentially in the midbrain. Although the brainstem and basal ganglia bear the brunt of the burden, the cerebral cortex and spinal cord can be affected as well. The pathological hallmark of the disease is cytoplasmic inclusions of neurofibrillary tangles (NFT) within the substantia nigra (SN), associated with severe neuronal loss *(60,102,103)*. Lewy bodies are not present. In the chronic state (PEP), inflammation is often replaced with degeneration of neurons and gliosis throughout the CNS, particularly the midbrain *(104)*. NFTs occur in the absence of senile plaques *(56,105)*. Unlike Alzheimer's disease, they do not stain for α synuclein or amyloid *(106)*, but similar to progressive supranuclear palsy, they are ubiquinated and τ-positive on immunohistochemistry *(107,108)*.

MRI findings from cases of parkinsonism associated with viral encephalitis as well as ED/PEP-like cases usually reveal bilateral, symmetrical basal ganglia involvement, predominantly with signal hyperintensities in the SN but these may also involve the striatum and lenticular nucleus *(80,109)*. When symptoms resolve, these MRI lesions can be transient as well. On flourodopa positron emission tomography, PEP differs from idiopathic PD. Uptake in the putamen of PEP patients is homogenously reduced, without the anterior–posterior gradient typically seen in PD *(79,110)*. This may be a result of the more diffuse involvement of the SN pars compacta in PEP compared with the ventrolateral predominance in PD.

Evaluation

A young patient with acute or subacute onset of parkinsonism associated with a febrile illness should have a full blood count and blood chemistries including liver, renal, and thyroid function tests, tests for antinuclear antibodies and erythrocyte sedimentation rate, chest radiography, electrocardiogram, and blood and urine cultures. CSF should be sent for cell count, glucose, and protein, and extra tubes for CSF gram and acid-fast bacilli stain, Venereal Disease Research Laboratory slide test (VDRL), lyme titers, and serologies (for herpes simplex virus, herpes zoster, mumps, measles, adenovirus, enterovirus, cytomegalovirus, Epstein–Barr virus, toxoplasmosis, etc.). Serum ceruloplasmin, 24-hour urine copper and heavy metals, toxicology, HIV test, tuberculin purified protein derivatives test, and serum VDRL may be necessary. An EEG may define seizure activity and helps grade the

level of encephalopathy. Brain imaging with contrast can define ring-enhancing or granulomatous lesions. Rarely, duodenal biopsy (to rule out Whipple's disease), blood smear (for malaria), and CSF 14-3-3 protein (for prion disease) may be of value.

TREATMENT

Comments on Patient 1

This patient had been taking trifluoperazine and lithium, both of which may cause parkinsonism, but she had been taking both for many years, had not had an increase recently, and her lithium level was not elevated. Because her symptoms occurred 2 days after surgery, it was unlikely a direct result of the surgery. Meperidine may trigger severe reactions with monoamine oxidase inhibitors, but this has not been reported with the drugs she was taking. The absence of any fever argued strongly against serotonin syndrome or NMS. The fact that she was awake, blinked to threat, moved in response to pain, and had a nonfocal exam and a normal brain CT pointed to a probable psychiatric cause. Given the history of bipolar disease requiring an antipsychotic, catatonia was considered, and in fact she met criteria for this syndrome. After a baseline EEG was obtained, which was normal, an infusion of lorazepam was given. Two minutes later she awoke and was manic. This confirmed the diagnosis of catatonia and pointed to the need for more aggressive psychiatric treatment. When the effects of the lorazepam wore off within a few hours, she became catatonic again.

Diagnosis of the etiology of acute parkinsonism is of paramount importance. NMS is treatable, usually with levodopa or dopamine agonists. In cases of profound rigidity and fever the patient may be paralyzed or treated with dantrolene sodium. Unlike malignant hyperthermia, the muscles in NMS are normal, hence responsive to depolarizing drugs. Catatonia often responds to intravenous lorazepam *(44)*, however patients may require prolonged treatment to prevent recurrence. Patients who do not respond to lorazepam should be considered for electroconvulsive therapy which has been reported as successful in treating this disorder as well as NMS.

Toxic, metabolic, infectious, postinfectious and structural akinetic rigid syndromes are usually not responsive to symptomatic therapies. Levodopa requires conversion to dopamine by intact nigral cells, suggesting that dopamine agonists may be more effective when the nigra is fully depleted. Unfortunately, because the general experience with dopaminergic agents in akinetic rigid syndromes is that levodopa works faster and has fewer side effects, we therefore advocate trials of levodopa for all parkinsonian syndromes except NMS, in which case a dopamine agonist is our drug of choice. When levodopa is not helpful, we advocate a trial of 200–400 mg of amantadine per day in patients with normal renal function. Although amantadine has anti-influenza properties, there is no reason to believe it is useful for other viral syndromes. Dopamine agonists should be initiated at low doses

and slowly titrated. Because patients with acute parkinsonism may improve on their own, it may be difficult to gage the response to a slowly increasing dose of dopamine agonists. Once a patient has improved, our general approach is to slowly taper the medicines, as many patients improve spontaneously.

Comments on Patient 2

This 15-year-old girl developed acute parkinsonism immediately following presumed viral encephalitis. Measles antibody titers suggested a resolving measles infection. Her parkinsonism gradually resolved over 3 months and was not associated with oculogyric crisis, ophthalmoplegia, myoclonus, or other movement disorders. The presentation is therefore not consistent with ED or PEP. In addition to supportive measures during the acute encephalopathic phase, delivery of the appropriate antibiotic/antiviral agent may suffice to resolve parkinsonism associated with known viral or bacterial encephalitis. When symptoms persist, levodopa alone or in combination with other adjunctive anti-PD agents may be used. Anticholinergic drugs *(111)*, amantadine *(112)*, bromocriptine, and deprenyl *(113)* have all been reported to augment levodopa response.

ED and PEP patients are extremely sensitive to anti-PD drugs, with dyskinesias and motor and psychic fluctuations occurring even at very low doses. Calne et al. *(114)* reported a 6-week double-blind, placebo-controlled trial of levodopa in 40 PEP patients, with frequent adverse events among those who received levodopa. Patients experienced chorea, tics, respiratory crises, excess sweating, and psychiatric disturbances. Only a minority gained useful and enduring benefit of levodopa throughout the study. Sacks *(114)* reported an enormous range of levodopa-induced behavioral and motor abnormalities where patients alternated between a severe "off" state and an emotionally labile "on" state. Unlike in PD, where patients often chose to be "on" with dyskinesias, PEP patients preferred to be "off" to avoid emotional lability. Similarly, Duvoisin *(116)* reported 63% of patients with increased involuntary movements and 33% with psychic manifestations among 26 PEP patients treated with levodopa. Slower titration enabled some patients to enjoy a sustained response. There is one report of PEP in which oculogyric crises resolved and tremor and rigidity improved with unilateral thalamotomy *(58)*. Because parkinsonism in PEP is probably progressive or, at the very least, persistent, and patients experience extreme motor fluctuations on low-dose levodopa, stimulation of the subthalamic nucleus might also be an option.

CONCLUSION

Acute parkinsonism is a frightening and serious movement disorder emergency, with a variety of causes. Identification of the cause and institution of appropriate treatment can not only improve patients' outcome, but may even be life-saving.

REFERENCES

1. Friedman JH. Drug induced parkinsonism. In: Lang AE, Weiner WJ, eds. Drug Induced Movement Disorders. Futura, Mt Kisco, NY: 1992;41–84.
2. Fahn S, Przedborski S. Parkinsonism. In: Rowland LP, ed. Merritt's Textbook of Neurology, 10th ed. Lippincott, Williams and Wilkins, Philadelphia: 679–693.
3. Caligiuri MP, Ellwanger J. Motor and cognitive aspects of motor retardation in depression. J Affect Disord 2000;47:83–93
4. Hymas N, Lees A, Bolton D, et al. The neurology of obsessional slowness. Brain 1991;114:2203–2233.
5. Curran T, Lang AE. Parkinsonian syndromes associated with hydrocephalus: case reports, a review of the literature and pathophysiological hypotheses. Mov Disord 1994;9:508–520
6. Riley D. Secondary parkinsonism. In: Jankovic JJ, Tolosa E, eds. Parkinson's Disease and Movement Disorders, 4th ed. Lippincott, Williams and Wilkins, Philadelphia: 2002;199–211.
7. Boecker H, Weindl A, Leenders K, et al. Secondary Parkinsonism due to focal substantia nigra lesions: a PET study with (^{18}F)FDG and (^{18}F)Fluorodopa. Acta Neurol Scan 1996;93:387–392.
8. Stern G. The effects of lesions in the substantia nigra. Brain 1966;89:449–478.
9. Hunter R, Smith J, Thomson T, Dayan AD. Hemiparkinsonism with infarction of the ilpsilateral substantia nigra. Neuropathol Appl Neurobiol 1978;4:297–301.
10. Kim JS. Involuntary movements after anterior cerebral artery territory infarction. Stroke 2001;32:258–261.
11. Nagaratnam N, Davies D, Chen E. Clinical effects of anterior cerebral artery infarction. J Stroke Cerebrovasc Dis 1998;7:391–397.
12. Dick JP, Benecke R, Rothwell JC, et al. Simple and complex movements in a patient with infarction of the right supplementary motor area. Mov Disord 1986;1:255–266.
13. Russmann H, Vingerhoets F, Ghika J, et al. Acute infarction limited to the lenticular nucleus: clinical, etiologic and topographic features. Arch Neurol 2003;60:351–358
14. Turjanski N, Pentland B, Lees AJ, Brooks DJ. Parkinsonism associated with acute intracranial hematomas: an (^{18}F)Dopa positron-emission tomography study. Mov Disord 1997;12:1035–1038.
15. Wang JD, Huang CC, Hwang YH, et al. Manganese induced parkinsonism: an outbreak due to an unrepaired ventilation control system in a ferromanganese smelter. Br J Ind Med 1989;46:856–859.
16. Feldman RG. Manganese. In: Occupational and Environmental Medicine. Lippincott Raven, Philadelphia: 168–188.
17. Sohn YH, Jeong Y, Kim HS, Im JH, Kim JS. The brain lesion responsible for parkinsonism after carbon monoxide poisoning. Arch Neurol 2000;57:1214–1218.
18. Perry GF. Occupational medicine forum. What are the potential delayed health effects of high level carbon monoxide exposure? J Occup Med 1994;36:595–597.
19. Okuda B, Iwamoto Y, Tachibana H, Sugita M. Parkinsonism after acute cadmium poisoning. Clin Neurol Neurosurg 1997;99:263–265.
20. Barbosa ER, Comerlatti LR, Haddad MS, Scaff M. Parkinsonism secondary to ethylene oxide exposure: case report. Arq Neurosiquiatr 1992;50:531–533.
21. Laplane D, Attal N, Sauron B, et al. Lesions of the basal ganglia due to disulfiram neurotoxicity. J Neurol Neurosurg Psychiatry 1992;44:925–929.
22. Messing B. Extrapyramidal disturbance after cyanide poisoning. J Neural Transm Suppl 1991;33:141–147.
23. Pentore R, Venneri A, Nichelli P. Accidental choke-cherry poisoning: early symptoms and neurological sequelae of an unusual case of cyanide intoxication. Ital J Neurol Sci 1996;17:233–233.
24. Langston JW, Ballard P, Tetrud JW, Irwin I. Chronic parkinsonism in humans due to a product of meperidine analogue synthesis. Science 1983;219(4587):979–980.
25. Leopold NA, Bara-Jimenez W, Hallett M. Parkinsonism after a wasp sting. Mov Disord 1999;14:122–127.

26. Bogolepov NK, Luzhetskaya TA, Fedin AI, et al. Allergic encephalomyelopolyradiculoneuritis from a wasp sting (clinico-patholo report). Zh Nevropatol Psikhiatr Im SS Korsakova 1978;78:187–191.
27. Shandling M, Carlen PL, Lang AE. Parkinsonism in alcohol withdrawal: a follow up study. Mov Disord 1990;4:36–39.
28. Carlen PL, Lee MA, Jacob M, Livishitz O. Parkinsonism provoked by alcoholism. Ann Neurol 1981;9:84–86.
29. Lang AE, Marsden CD, Obeso JA, Parkes JD. Alcohol and parkinson disease. Ann Neurol 1982;12:254–256.
30. Tinker R, Anderson MG, Anand P, et al. Pontine myelinolysis presenting with acute parkinsonism as a sequel of corrected hyponatremia. J Neurol Neurosurg Psychiatry 1990;53:87–89.
31. Dickoff DJ, Rapps M, Yahr MD. Striatal syndrome following hyponatremia and its rapid correction. Arch Neurol 1988;45:112–114.
32. Victor M, Ropper AH. Adam's and Victor's Principles of Neurology. 7th ed. McGraw Hill, New York: 2001;1193–1195.
33. Hawker K, Lang AE. Hypoxic-ischemic damage of the basal ganglia. Case reports and a review of the literature. Mov Disord 1990;5:219–224.
34. Straussberg R, Shahar E, Gat R, Brand N. Delayed parkinsonism associated with hypotension in a child undergoing open-heart surgery. Dev Med Child Neurol 1993;35:1007–1014.
35. Li JY, Lai PH, Chen CY, et al. Postanoxic parkinsonism: clinical radiologic and pathologic correlation. Neurology 2000;55:591–593.
36. Carbone JR. The neuroleptic malignant syndrome and serotonin syndromes. Emerg Clin No America 2000;18:317–325.
37. Susman VL. Clin Management of neuroleptic malignant syndrome. Psychiatr Wkly 2001;72:325–326.
38. Lockman LA, Sung JH, Krivit W. Acute parkinsonian syndrome with demyelinating leukoencephalopathy in bone marrrow transplant recipients. Pediatr Neurol 1991;7:457–463.
39. Devinsky O, Lemann W, Evans AC, et al. Akinetic mutism in a bone marrow transplant recipient following total-body irradiation and amphotericin B chemoprophylaxis. A positron emission tomographic and neuropathologic study. Arch Neurol 1987;44:414–417.
40. Chuang C, Constantino A, Balmaceda C, et al. Chemotherapy-induced parkinsonism responsive to levodopa: an underrrecognized entity. Mov Disord 2003;18:328–331.
41. Shahar E, Goshen E, Tauber Z, Lahat E. Parkinsonian syndrome complicating systemic lupus erythematosus. Pediatr Neurol 1998;18:456–458.
42. Yancey CL, Doughty RA, Athreya BH. Central nervous system involvement in childhood system lupus erythematosis. Arthritis Rheum 1981;24:1389–1395.
43. Friedman JH. Stereotypy and Catatonia. In: Jankovic JJ, Tolosa E, eds. Parkinson's Disease and Movement Disorders. Third Edition. Williams and Wilkins, Baltimore, MD: 1998;709–729.
44. Bush G, Fink M, Petrides G, et al. Catatonia: 2. Treatment with lorazepam and electroconvulsive therapy. Acta Psychiatr Scand 1996;93:137–143.
45. Factor SA, Podskalny GD, Molho ES. Psychogenic movement disorders: frequency, clinical profile and characteristics. J Neurol Neurosurg Psychiatry 1994;59:406–412.
46. Trimble MR. Clinical Presentations in neuropsychiatry. Semin Clin Neuropsychiatry 2002;7:11–17.
47. Lang AE, Koller WC, Fahn S. Psychogenic parkinsonism. Arch Neurol 1995;52:802–810.
48. Koller WC, Findley LI. Psychogenic tremors. Adv Neurol 1990;53:271–275.
49. Von Economo C. Encephalitis lethargica. Wien Klin Wochenschr 1917;30:581–585.
50. Urechia CL. Dix cas d'encephalite epidemique avec autopsie. Arch Inter Neurol 1921;2:65–78.
51. Cruchet R, Moutier F, Calmette A. Quarante cas d'encephalo-myelite subaigue. Bull Mem Soc Med d'Hop 1917;41:614–616.
52. Etienne G. Myelities aigues epidemiques. Deux epdiemies militares. Rev Neurol 1917;24:375–376.
53. Watson AJ. Origin of encephalitis lethargica. China Med J 1928;42:427–432.

54. Von Economo C. Encephalitis lethargica: its sequelae and treatment (translated by K.O. Newman) Oxford University Press, London: 1931;I–XIV, 1–200.
55. Duvoisin RC, Yahr MD. Encephalitis and parkinsonism. Arch Neurol 1965;12:227–239.
56. Geddes JF, Hughes AJ, Lees AJ, Daniel SE. Pathological overlap in cases of parkinsonism associated with neurofibrillary tangles. Brain 1993;116:281–282.
57. Wilson SAK. Epidemic encephalitis. In: Neurology, Vol 1. Williams and Wilkins, Baltimore: 1940;118–165.
58. Morrison PJ, Patterson VH. Cranial dystonia (Meige syndrome) in postencephalitic parkinsonism. Mov Disord 1992;7:90–91.
59. Wenning GK, Jellinger K, Litvan I. Supranuclear gaze palsy and eyelid apraxia in postencephalitic parkinsonism. J Neurol Transm 1997;104:845–865.
60. Litvan I, Jankovic J, Goetz CG. Accuracy of the clinical diagnosis of postencephalitic parkinsonism: a clinicopathologic study. Eur J Neurol 1998;5:451–457.
61. Duncan AG. The sequelae of encephalitis lethargica. Brain 1924;47:76–108.
62. Calne DB, Lees AJ. Late progression of post-encephalitic parkinson syndrome. Can J Neurol Sci 1988;15:135–138.
63. Vieregge P, Reinhardt V, Hoft B. Is progression in postencephalitic Parkinson's disease late and age-related? J Neurol 1991;238:299–303.
64. Ravenholt RT, Foege WH. 1918 Influenza, encephalitis lethargica, parkinsonism. Lancet 1982;2:860–862.
65. Laidlaw PP. Epidemic influenza: a virus disease. Lancet 1935;1:1118–1124.
66. Casals J, Elizan TS, Yahr MD. Postencephalitic parkinsonism—a review. J Neural Transm 1998;105:645–676.
67. Gamboa ET, Wolf A, Yahr MD, et al. Influenza virus antigen in postencephalitic parkinsonism brain. Arch Neurol 1974;31:228–232.
68. Martilla RJ, Halomen P, Rinne UK. Influenza virus antibodies in parkinsonism. Comparison of postencephalitic and idiopathic parkinson patients and matched controls. Arch Neurol 1977;34:99–100.
69. Elizan T, Schwartz J, Yahr MD, Casals J. Antibodies against arboviruses in postencephalitic and idiopathic Parkinson's disease. Arch Neurol 1978;35:257–260.
70. Takahashi M, Yamada T, Nakajima S, et al. The substantia nigra is a major target for neurovirulent influenza A virus. J Exp Med 1995;181:2161–2169.
71. Elizan TS, Casals J, Yahr MD. Antineurofilament antibodies in postencephalitic and idiopathic Parkinson's disease. J Neurol Sci 1983;59:341–347.
72. Elizan TS, Yahr MD. Histocompatibility antigens and postencephalitic parkinsonism. J Neurol Neurosurg Psychiatry 1983;46:688–693.
73. Lees AJ, Stern GM, Compston DAS. Histocompatibility antigens and post-encephalitic parkinsonism. J Neurol Neurosurg Psychiatry 1982;45:1060–1061.
74. Williams A, Houff S, Lees A, Calne DB. Oligoclonal banding in the cerebrospinal fluid of patients with postencephalitic parkinsonism. J Neurol Neurosurg Psychiatry 1979;42:790–792.
75. Rail D, Scholtz C, Swash M. Postencephalitic parkinsonism: current experience. J Neurol Neurosurg Psychiatry 1981;44:670–676.
76. Clough CG, Plaitakis A, Yahr MD. Oculogyric crises and parkinsonism: a case of recent onset. Arch Neurol 1983;40:36–37
77. Johnson J, Lucey PA. Encephalitis lethargica, a contemporary cause of catatonic stupor: a report of two cases. Br J Psychiatry 1987;151:550–552.
78. Howard RS, Lees AJ. Encephalitis lethargica. A report of four recent cases. Brain 1987;110:19–33.
79. Ghaemi M, Rudolf S, Schmulling S, Bamborschke S, Heiss WD. FDG-and-Dopa-PET in postencephalitic parkinsonism. J Neural Transm 2000;1289–1295.
80. Cree BC, Bernardini GL, Hays AP. Lowe G. A fatal case of coxackievirus B4 meningoencephalitis. Arch Neurol 2003;60:107–108.

81. Nath A, Jankovic J, Pettigrew LC. Movement disorders and AIDS. Neurology 1987;37:37–41.
82. Carranzana EJ, Rossitch E, Samuels MA. Parkinsonian symptoms in a patient with AIDS and cerebral toxoplasmosis. J Neurol Neurosurg Psychiatry 12:1445–1447
83. Navia BA, Petito CK, Gold JWM et al. Cerebral toxoplasmosis complicating the acquired immunodeficiency syndrome: clinical and neuropathological findings in 27 patients. Ann Neurol 1986;19:224–238.
84. Noel S, Gaillaume MP, Telerman-Toppet N et al. Movement disorders due to cerebral Toxoplasma gondii infection in patients with the acquired immunodeficiency syndrome (AIDS). Acta Neurol Belg 1992;92:148–156.
85. Maggi P, de Mari M, Moramarco A, Fiorentino P, Lamberti P, Angarano G. Parkinsonism in a patient with AIDS and cerebral opportunistic granulomatous lesions. Neurol Sci 2002;21:173–176.
86. De Mattos JP, Rosso AL, Correa RD, et al. Involuntary movements and AIDS: report of seven cases and review of the literature. Arq Neuropsiquiatr 1993;51:491–497.
87. Misattari SM, Power C, Nath A. Parkinsonism with HIV INFECTION. Mov Disord 1998;13: 684–689.
88. Cardoso F. HIV-related movement disorders. Epidemiology, pathogenesis and management. CNS Drugs 2002;16:663–668.
89. Sandyk R. Parkinsonism secondary to neurosyphilis. A case report. S Afr Med J 1983;23:665–656.
90. Garcia-Moreno JM, Izquierdo G, Chacon J, Angulo S, Borobio MV. Neuroborreliosis in a patient with progressive supranuclear paralysis. An association or a cause? Rev Neurol 1997;25:1919–1921.
91. Zambrino CA, Zorzi G, Lanzi G, Uggetti C, Egitto MC. Bilateral striatal necrosis associated with mycoplasma pnuemoniae infection in an adolescent: clinical and neurodiagnostic follow up. Mov Disord 2000;15:1023–1026.
92. Al-Mateen M, Gibbs M, Dietrch R, Mitchell WG, Menkes JH. Encephalitis lethargica-like illness in a girl with mycoplasma infection. Neurology 1988;38:1155–1158.
93. Saitoh S. Wada T. Narita M, et al. Mycoplasma pneumoniae infection may cause striatal lesions leading to acute neurological dysfunction. Neurology 1993;43:2150–2151.
94. Kim JS, Choi IS, Lee MC. Reversible parkinsonism and dystonia following probable mycoplasma pneumoniae infection. Mov Disord 1995;10:510–512.
95. Brandel J, Noseda G, Agid Y. Mycoplasma pneumoniae postinfectious encephalomyelitis with bilateral striatal necrosis. Mov Disord 1996;11:333–335.
96. Singer C, Berger JR, Bowen BC, Bruce JH, Weiner WJ. Akinetic-rigid syndrome in a 13-year old girl with HIV-related progressive multifocal leukoencephalopathy. Mov Disord 1993;8:113–116.
97. Werring DJ, Chaudhuri KR. HIV-related progressive multifocal leukoencephalopathy presenting with an akinetic-rigid syndrome. Mov Disord 1996;11:758–761.
98. De la Fuente J, Bordon J, Moreno JA, et al. Parkinsonism in an HIV-infected patient with hypodense cerebral lesion. Tuber Lung Dis 1996;77:191–192.
99. Strong G. Parkinson's syndrome following herpes ophthalmicus. Br Med J 1952;1:533.
100. Fenichel GM. Postvaccinal parkinsonism. Mov Disord 1993;8:253.
101. Reijneveld JC, Taphoorn MJB, Hoogenraad TU, Van Gijn J. Severe but transient parkinsonism after tetanus vaccination. J Neurol Neurosurg Psychiatry 1997;63:258–259.
102. McCall S, Henry JM, Reid AH, Taubenberger JK. Influenza RNA not detected in archival brain tissues from acute encephalitis lethargica cases or in postencephalitic parkinson cases. J Neuropathol Exp Neurol 2001;60:696–704.
103. Krusz JC, Koller WC, Ziegler DK. Historical Review: abnormal movements associated with epidemic encephalitis lethargica. Mov Disord 1987;2:137–141.
104. Elizan TS, Casals J. Astrogliosis in von Economo's and postencephalitic Parkinson's diseases supports probable viral etiology. J Neurol Sci 1991;105:131–134.
105. Hof PR, Charpiot A, Delacourte A, et al. Distribution of neurofibrillary tangles and senile plaques in the cerebral cortex in postencephalitic parkinsonism. Neurosci Lett 1992;139:10–14.

106. Josephs KA, Parisi JE, Dickson DW. Alpha-synuclein studies are negative in postencephalitic parkinsonism of von Economo. Neurology 2002;59:645–646.
107. Ikeda K, Akiyama H, Kondo H, Ikeda K. Anti-tau-positive glial fibrillary tangles in the brain of postencephalitic parkinsonism of Economo type. Neurosci Lett 1993;162:176–178.
108. Wong KT, Allen IV, McQuaid S, McConnell R. An immunohistochemical study of neurofibrillary tangle formation in post-encephalitic parkinsonism. Clin Neuropathol 1996;15:22–25.
109. Shen WC, Ho YJ, Lee SK, Lee KR. MRI of Transient post-encephalitic parkinsonism. J Comp Assist Tomo 1994;18:155–159.
110. Caparros-Lefebvre D, Cabaret M, Godefroy O, et al. PET study and neuropsychological assessment of a long-lasting post-encephalitic parkinsonism. J Neural Transm 1998;105:489–495.
111. Solbrig MV, Nashef L. Acute parkinsonism in suspected herpes simplex encephalitis. Mov Disord 1993;8:233–234.
112. Savant CS, Singhal BS, Jankovic J, Khan MAK, Virani A. Substantia nigra lesions in viral encephalitis. Mov Disord 2003;18:213–227.
113. Alves RSC, Barbosa ER, Scaff M. Postvaccinal parkinsonism. Mov Disord 1992;7:178–180.
114. Calne DB, Stern GM, Laurence DR. L-dopa in postencephalitic parkinsonism. Lancet 1969;1:744–746.
115. Sacks O. Awakenings. Harper Perennial, New York: 1990.
116. Duvoisin RC, Lobo-Antunes J, Yahr MD. Response of patients with post-encephalitic parkinsonism to levodopa. J Neurol Neurosurg Psychiatry 1972;35:487–495.
117. Walters JH. Postencephalitic parkinson syndrome after meningoencephalitis due to coxackie virus group B, type 2. N Engl J Med 1960;263:744–747.
118. Posner CM, Huntley CJ, Poland JD. Para-encephalitic parkinsonism. Acta Neurol Scand 1969;45:199–215.
119. Hsieh JC, Lue KH, Lee YL. Parkinson-like syndrome as the major presenting symptom of Epstein-Barr virus encephalitis. Arch Dis Child 2002;87:358–359.
120. Isgreen WP, Chutarian AM, Fahn S. Sequential parkinsonism and chorea following "mild" influenza. Trans Am Neurol Assoc 1976;101:56–59.
121. Shiraki H. Goto A, Narabayashi H. Etat passe et present de l'encephalite Japonnaise au Japon. Rev Neurol (Paris) 1963;108:633–696.
122. Ishii T, Marsushita M, Hamada S. Characteristic residual neuropathological features of Japanese B encephalitis. Acta Neuropathol (Berl) 1977;38:181–186.
123. Shoji H, Watanabe M, Itoh S, Kuwahara H, Hattori F. Japanese encephalitis and parkinsonism. J Neurol 1993;240:59–60.
124. Pradham S, Pandey N, Shashank S, et al. Parkinsonism due to predominant involvement of the substantia nigra in Japanese encephalitis. Neurology 1999;53:1781–1786.
125. Scheid W, Ackerman R, Felgenhauer K. Lymphozytare Choriomeningitis unter dem bild der Encephalitis lethargica. Dtsch Med Wochenschr 1968;93:940–943.
126. Adair CV, Gould RL, Smadel JE. Aseptic meningitis, a disease of diverse etiology. Clinical and etiological studies of 854 cases. Ann Intern Med 1953;39:675–704.
127. Bennett NMcK. Murray Valley encephalitis, 1947: clinical features. Med J Aust 1976;2:446–450.
128. Bickerstaff ER, Cloake PCP. Mesencephalitis and rhombencephalitis. Br Med J 1951;2:77–81.
129. Thieffrey S. Enterovirus et maladies du systeme nerveux. Revisiou critique et experience personnelle. Rev Neurol (Paris) 1963;108:753–776.
130. Barrett AM, Gairdner D, McFarlan AM. An outbreak of encephalitis possibly due to poliomyelitis virus. Br Med J 1952;1:1317–1322.
131. Vincent FM, Myers WG. Poliomyelitis and parkinsonism. N Engl J Med 1978;298:688–689.
132. Mellon AF, Appleton RE, Gardner-Medwin D, Aynsley-Green A. Encephalitis lethargica-like illness in a 5 year old. Dev Med Child Neurol 1991;33:153–56.
133. Meyer B. Encephalitis after measles with severe parkinsonian rigidity: recovery. Br Med J 1943;1:508.

134. Henner K, Hanzal F. Encephalite tchecoslavaque a tiques. Rev Neurol (Paris) 1957;96:384–408.
135. Henner K, Hanzal F. Les encephalities europeenes a tiques. Rev Neurol (Paris) 1963;108:697–752.
136. Rasdel-Medvescek A, Marolt-Gomiscek M, Pouse-Trojar M, Gajsek-Zima M. Late sequelae after tick-borne meningoencephalitis in patients treated at the hospital for infectious diseases at University Medical Centre of Ljubljana during the period 1974–1975. Zentralbl Bakteriol 1980;9:281–284.
137. Cerna F, Mehrad B, Luby JP, et al. St. Louis encephalitis and the substantia nigra: M R imaging evaluation. Am J Neuroradiol 1999;20:114–118.
138. Wasay M, Diaz-Arastia R, Suss R, et al. St. Louis encephalitis : a review of 11 cases in a 1995 Dallas, Texas epidemic. Arch Neurol 2000;57:114–118.
139. Finley KH. Postencephalitic manifestations of viral encephalitides. In: Fields WS, Blattner RJ, eds. Viral Encephalitis. CC Thomas, Springfield, IL: 1958;69–94.
140. Finley KH, Riggs N. Convalescence and sequelae. In: Monath TP, ed. St. Louis Encephalitis. American Public Health Association, Washington, DC: 1980;535–550.
141. Fulton JC, Burton AN. After effects of WEE infection in man. Canad MAJ 1953;69:268–272.
142. Mulder DW, Parrot M, Thaler M. Sequelae of western equine encephalitis. Neurology 1951;1:318–327.

3

Parkinsonism-Hyperpyrexia Syndrome in Parkinson's Disease

Stewart A. Factor and Anthony Santiago

PATIENT VIGNETTE

A 44-year-old right-handed man with a 14-year history of Parkinson's disease (PD) presented to the emergency department with an acute onset of fever, confusion, rapidly progressive difficulty with ambulation, and dysphagia. He presented initially in 1987 with left upper limb tremor and slowness. Work-up for secondary parkinsonism was unrevealing, and treatment was initiated first with anticholinergic agents and then levodopa. By 1991, he had developed bilateral symptoms and signs. Motor fluctuations and complications emerged within 5 years of onset, with considerable anxiety and behavioral problems as well. He required high doses of dopaminergic agents for the last 8 years.

He had been fully able to communicate, perform activities of daily living, and ambulate 48 hours prior to presentation. He had recently been incarcerated, and during his confinement his medications were abruptly stopped for unclear reasons. His usual dosing schedule included 25/100 of carbidopa/levodopa (C/L), one tablet every 2 hours starting at 6 AM to 8 PM, with two tablets at 10 PM, midnight, and 2 AM. In addition, he was also prescribed 1 mg pergolide, three times per day, and quetiapine 25 mg five and one-half tablets each day in divided doses. In July 2000, he underwent deep brain stimulation (DBS) surgery, with bilateral leads placed in the subthalamic nuclei. They were operational as of the last office visit. DBS surgery lead to improved off times and less dyskinesias, but allowed only minimal changes in levodopa dose.

In the emergency department, the patient appeared acutely ill. He was febrile, with a temperature of 38.3°C, heart rate of 100, blood pressure of 140/90, and respiratory rate of 24. He was awake but confused and unable to follow commands or intelligibly communicate. His mucus membranes were dry. He appeared diffusely stiff, with severe rigidity of the neck and limbs. A coarse tremor was present in both upper extremities, but no other involuntary movements were seen. No signs of trauma were found. Pupils were symmetrical and reactive to light, and fundoscopic exam was normal. Reflexes were present and symmetric, with no pathologic reflexes.

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

Laboratory studies revealed a white blood cell count of 16,000 cells/mm^3, blood urea nitrogen of 39 mg/dL, and normal red blood cell indices. No iron indices were measured. Creatine kinase was over 4000. Cranial computed tomography scan revealed bilateral DBS leads without acute pathology. A lumbar puncture with cerebrospinal fluid analysis was normal. The diagnosis of parkinsonism-hyperpyrexia syndrome was reached: a nasogastric tube was placed and levodopa and pergolide were reinstituted, with intravenous fluids. Despite treatment, his condition worsened, with medically refractory hypertension, respiratory distress, seizures, and ultimately renal failure. He died 3 days after presentation. Postmortem exam revealed bilateral pulmonary emboli with infarction. Examination of the brain revealed marked depigmentation of the substantia nigra and the locus ceruleus, with Lewy bodies confirming the diagnosis of PD.

INTRODUCTION

Neuroleptic malignant syndrome (NMS) is a potentially fatal drug-induced movement disorder that was first described by Delay and associates in 1960 *(1,2)*. These authors reported NMS as the "most serious but also rarest and least known of complications of neuroleptic chemotherapy" *(2)*. Since the 1980s, NMS has been a more focused concern in the treatment of psychiatric patients because of its potentially high mortality rate of 5 to 20% *(3,4)*. The characteristic clinical features include hyperthermia, muscle rigidity, dysautonomia, and mental status changes. Hyperthermia is present in nearly all cases of NMS, and muscle rigidity is reported in more than 90% of patients *(3–7)*. Alterations in mental status can range from fluctuating alertness to agitation and delirium and eventually to frank stupor or coma *(6,8)*. Muteness is also seen, although less commonly than catatonia. Unstable blood pressure, cardiac arrhythmia, dyspnea, pulmonary edema, and bladder incontinence are common signs of dysautonomia, with diastolic hypertension possibly being a specific feature *(3)*. Several laboratory abnormalities support the diagnosis including elevated creatine kinase (CK), elevated white blood cell (WBC) count, and diminished serum iron *(3)*.

It was initially believed that NMS only occurred in psychiatric patients, particularly those with schizophrenia and affective disorders, who were treated with neuroleptics. Although particular risk factors in this patient population have been delineated, it has become clear that any patient exposed to these agents is at risk for NMS *(3)*. This constellation of symptoms has since been recognized in patients exposed to other agents such as dopamine depleters (tetrabenazine) *(9)*, a related syndrome (serotonin syndrome) associated with exposure to serotonin-specific reuptake inhibitors *(10)*, and cocaine *(11)*.

In 1981, a similar disorder was described in a patient with Parkinson's disease (PD) triggered by sudden withdrawal of dopaminergic medications, specifically levodopa, amantadine, and biperiden. Several dozen other cases have since been reported. The syndrome seen in PD has been reported under a variety of different names, including NMS, neuroleptic malignant-like syndrome (NMLS) *(12,13)*, levodopa-withdrawal hyperthermia, parkinsonism-hyperpyrexia syndrome (PHS) *(14)*, lethal hyperthermia *(15)*, dopaminergic malignant syndrome *(16)*, and acute

dopamine depletion syndrome *(17)*. PHS is the most specific and clinically descriptive term. As we show here, levodopa withdrawal is not the only cause of this entity, and the term "dopaminergic" pertains to any NMS-like syndrome. It is important to draw a distinction between true NMS and PHS. From this point forward, when discussing this syndrome in parkinsonian patients, we use the term PHS. This chapter reviews the clinical entity PHS and discusses its management.

CLINICAL FEATURES

Although PHS is rare, several situations are notable triggers. The scenario most commonly reported is the "levodopa holiday" *(13,18–20)*. These cases were all reported in the 1980s when drug holidays were still utilized for therapeutic purposes. They were recommended in patients with intractable "off" periods and psychosis, although their utility was controversial *(21,22)*. Drug holidays often involved rapid reduction and complete cessation of dopaminergic medication. Patients would remain off for up to 14 days, despite well-known risks associated with immobility, such as aspiration pneumonia and pulmonary embolism. Drug holidays are no longer used; however, there are other situations when dopaminergic medications are discontinued posing an equal risk. In several reports, the medications were stopped by the patients themselves because of side effects, misunderstanding of medication instructions, or a desire to try alternative medications *(12,16,17)*. In one case, the medications were stopped because physicians thought the patient had psychogenic parkinsonism *(17)*. PHS has also been seen in PD patients with partial withdrawal of dopaminergic therapy, or when medication regimens were changed. Iwuagwa et al. *(23)* described a case with onset linked to discontinuing tolcapone. When the patient became confused, the treating physician thought this was exacerbated by levodopa; after that was also stopped, PHS escalated. Cunningham et al. *(24)* described a patient who developed hyperthermia, rigidity, and dysautonomia when immediate-release levodopa was switched to controlled-release, and bromocriptine was tapered off from 40 mg per day to zero in a few days. Peak serum levodopa levels are notably lower with controlled-release formulations than with immediate-release. Keyster et al. *(17)* reported a similar case where PHS occurred when a patient was switched from levodopa to bromocriptine.

Another situation where PHS has been reported is in PD patients treated for a coexisting psychiatric disorder with neuroleptics. One such patient with schizophrenia and PD treated with neuroleptics for his primary psychotic disorder became gravely ill after cessation of anti-parkinsonian medications *(25)*. In another case, a patient admitted to the hospital for drug-induced psychosis had his levodopa stopped and haloperidol started at the same time. Severe "off" periods associated with motor fluctuations can also trigger such events. Pfeiffer and Sucha *(15)* reported a single patient developing repeated PHS features with "off" episodes. Events occurred for years, lasting 1 or 2 hours and improved when he turned "on." He ultimately died during a severe episode associated with a fever of 41.7°C.

Two other situations have been reported in single cases that occurred without change in medication regimen. One involved perimenstrual "off" times with symptoms of PHS *(26)*. In this case, it is believed that elevated estrogen and progesterone levels may have decreased central nervous system (CNS) dopaminergic stimulation in a manner similar to cutting medication doses. The other case involved metabolic alteration, particularly hypernatremia *(27)*—the mechanism by which this caused PHS is unclear.

The patient vignette presented here suggests a new potential risk for PHS in PD patients. Deep brain stimulation (DBS) of the subthalamic nucleus is a relatively new treatment for advanced PD. When performed properly, DBS leads to a substantial decrease in "off" time and severity. This improvement can in turn lead to a decrease in levodopa requirements by about 30% *(28)*. Some authors advocate discontinuing levodopa altogether *(29)*, but others have voiced concern regarding this objective *(30)*. Our patient had subthalamic DBS implanted and abruptly stopped medications, although not as part of the programming plan. He developed PHS and pulmonary embolism, which was ultimately fatal.

The frequency of PHS in PD has not been studied formally, but the disorder appears to be rare. We identified 79 cases reported in the literature. The details of the cases were varied. One paper was a therapeutic trial that included 40 cases *(31)*, two papers reported 11 cases each *(16,32)*, two reports described 3 cases each *(13,17)*, and the rest were single-case reports. Serrano-Duenas *(16)*, with one of the larger cohorts, reported that 11 cases accounted for 3.6% of his PD patient population and 0.04% of total patient consultations for PD. In the study by Sato et al. *(31)*, 40 cases were seen over a 3-year period. These findings may suggest that PHS may be more prevalent than previously recognized.

Patients developing PHS were more likely to be male (44 of 79 reported), with duration of PD ranging from 2 to 16 years and baseline levodopa dose at time of onset ranged from 200 to 2100 mg per day. Not all patients have advanced PD with motor fluctuations. In the report by Ueda et al. *(32)*, only 4 of 11 cases was experiencing this problem at the onset of PHS.

The clinical features of PHS are nearly identical to NMS, and the clinical presentation seems fairly stereotyped. The time of onset of symptoms after change in dopaminergic therapy ranged from 18 hours to 7 days. The initial feature in most patients is severe rigidity along with tremor, with progression to an immobile state *(16,17,32)*. Within 72 to 96 hours, most patients are febrile with altered mental status ranging from agitation and confusion to stupor and coma. Autonomic signs such as tachycardia, tachypnea, labile blood pressure, urinary incontinence, pallor, and diaphoresis often accompany this. In some cases fever, mental status changes, and autonomic dysfunction may occur from the outset along with worsening of parkinsonism *(32)*. Temperatures as high as 41.7°C have been reported *(13,15)*. Laboratory findings usually reveal leukocytosis (as high as 26,000) and elevated CK (ranging from 260 to 50,000 in reported cases). There have been no reports where iron levels were examined. Respiratory distress is not uncommon, and mechanical ventilation may be necessary *(18,25)*. Mutism, as part of the mental status

derangement, was reported by several authors *(12,24,27)*. Other neurological features include seizures *(19)* and myoclonus *(14)*.

Although this description seems very similar to NMS, there appear to be some differences. Serrano-Duenos *(16)* performed the only available comparison, looking at 11 PHS patients and 21 NMS patients. They found that the latency to onset of symptoms after the inciting event was twice as long (93 h vs 49 hours) for PHS as for NMS. In addition, in PHS the elevation of CK and WBC was significantly less robust. The duration of hospitalization was also shorter (8.4 vs 12.2 days). As expected, PHS patients were older than those in the NMS group. These findings suggest that NMS is a more aggressive disorder than PHS, and caries a poorer prognosis.

As with NMS, PHS may carry serious sequelae. Some patients only partially recover from the event, left with significantly worse PD *(16,17)*. In one case, a patient at Hoehn and Yahr stage II prior to the incident became wheelchair-bound afterwards *(16)*. Medical complications are also a concern. Deep venous thrombosis is a serious complication, and may ultimately result in pulmonary emboli. Several patients have developed aspiration pneumonia during a bout of PHS, and two cases developed renal failure *(13,17)*, complications well described in NMS. Finally, four of the reported cases (including ours) were fatal *(13,15,18)*. Two died in hyperthermic coma with no other explanation, one died with aspiration pneumonia and renal failure, and one from pulmonary embolism.

ILLUSTRATIVE CASES FROM THE LITERATURE

The following four cases from the literature illustrate this disorder. In addition, Table 1 summarizes the time frame involved in development of PHS after dopaminergic drug withdrawal, and recovery after therapy in six representative cases from two recent papers *(16,17)*.

Case 1 (17)

A 75-year-old man with a diagnosis of PD was treated with immediate-release carbidopa/levodopa (C/L) 25/100, one tablet three times a day for 1 year. When 100 mg of amantadine was added for symptomatic benefit, the patient mistakenly discontinued his C/L. Within 5 days he became tremulous, weak, pale, diaphoretic, and dyspneic. Amantadine was increased without clinical benefit. It was discovered that C/L had been discontinued and it was restarted, but only at twice daily dosing. Over the ensuing week, the patient became progressively confused, resulting in the cessation of C/L. Within 48 hours, he worsened considerably and because of continued confusion, 9 mg of haloperidol was given. Soon after, the patient became mute, agitated, and severely rigid with a diffuse coarse tremor. Laboratory review revealed leukocytosis, hypernatremia, and an elevated CK (452 U/L). Within 5 hours of this evaluation, the patient's temperature rose to 38.5°C. Bromocriptine (2.5 mg every 6 hours) was started, and within 72 hours, the patient's condition markedly improved. C/L was subsequently restarted, and the patient fully recovered.

Table 1
Summary of Selected Clinical Cases From Two Recent Publications *(16,17)* Illustrating the Time Frames Involved in Onset and Recovery of Parkinsonism-Hyperpyrexia Syndrome

Patient demographics	Medication discontinued	Clinical features within 24 hours	Clinical features within 96 hours	Improvement within 24 hours	Improvement within 96 hours
75-year-old man with PD for 1 year	C/L 300 mg/day	None reported	Weak, rigid, tremulous, diaphoretic	None reported	Full resolution within 5 days
67-year-old woman with PD and schizophrenia	C/L 250 mg/qid	Febrile (41.2°C); mute, tremulous, rigid	Same	Afebrile, improved sensorium	Full resolution within 48 hours
64-year-old man with PD for 7 years	C/L 250 mg/qid, benz. 2 mg/day, trihex. 4 mg/day	Tremulous, rigid	Febrile (39.4°C); mute, confused, severe tremor and rigidity	Less rigid and tremulousness, improved sensorium	Progressive improvement without return to baseline after 10 days
74-year-old woman with PD(H&Y III)	C/L 750 mg/day, seleg. 10 mg/day	Rigid, unable to ambulate or feed self	Febrile (37.9°C); stupor, severe rigidity	Afebrile, alert, much less rigid	Progressive improvement without return to baseline after 10 days
69-year-old man with PD (H&Y II)	C/L 750 mg/day, bromo. 7.5 mg/day	Severe rigidity, unable to ambulate	Febrile (38.7°C); somnolent, severe rigidity	Afebrile, alert, much less rigid	Progressive improvement without return to baseline after 10 days
69-year-old woman with PD (H&Y IV)	C/L 1125 mg/day, seleg. 10 mg/day	Febrile, severe rigidity, unable to ambulate	Febrile (39.2°C); stupor, severe rigidity	Afebrile, alert, much less rigidity	Progressive improvement without return to baseline after 10 days

C/L, carbidopa/levodopa; Ama, amantadine; Seleg., selegiline; Bromo., bromocriptine; H&Y, Hoehn and Yahr; PD, Parkinson's disease; qid, four times a day.

Case 2 (17)

A 64-year-old man was treated for 7 years for PD, most recently with C/L 25/250 four times a day, benztropine 2 mg per day and trihexiphenidyl 4 mg per day. Four days prior to presentation, his medications were abruptly changed to 2.5 mg of bromocriptine twice a day and propranolol. Within 3 days, tremor, rigidity, and impaired speech worsened, and his temperature rose to 39.4°C. His previously prescribed medications were restarted, but without benefit. On admission, he was febrile, mute, and diaphoretic, with marked rigidity and tremor. Serum CK at the time was 545 U/L. Treatment with bromocriptine and dantroline sodium was begun, but he remained febrile. Chest X-ray revealed a right lower lobe infiltrate consistent with aspiration pneumonia, and antibiotics were initiated; fever resolved within 4 days. Despite clinical improvement, his tremor and rigidity remained worse than before the event.

Case 3 (16)

A 74-year-old woman abruptly stopped taking her antiparkinsonian medication. She had advanced disease (Hoehn and Yahr stage III), and had been taking 75/750 mg of C/L per day, 10 mg per day of selegiline and 80 mg per day of propranolol. She decided to begin an alternative, natural treatment for PD and did not discuss this first with her treating physician. Within a short time, she became markedly rigid, and was unable to walk or feed herself. Within 96 hours, she was diaphoretic, somnolent, febrile (37.9°C), rigid, and stuporous, and had a serum CK of 759 U/L on presentation to a local hospital. A diagnosis of PHS as a result of abrupt medication withdrawal was made, a nasogastric tube was placed, and dopaminergic medication was restarted. Within 9 hours she became alert, and rigidity lessened within 15 hours. On discharge 9 days later, rigidity was worse than prior to the incident.

Case 4 (18)

A 51-year-old man with a 9-year history of PD was admitted to the hospital because of severe levodopa-induced dyskinesias. His medications on admission included C/L 25/250 three times a day and 50 mg of diphenhydramine four times a day. C/L was reduced by one half for 3 days and then stopped altogether (drug holiday), and diphenhydramine was cut to twice each day (BID). Two days later, the dyskinesias stopped and were replaced by rigidity, bradykinesia, and tremor. On the third day his temperature rose to 38.2°C, his heart rate to 120 beats per minute, his respiratory rate to 28 inhalations per minute, and he was diaphoretic. The temperature increased further to 40.4°C by day 10, and he remained confused and disoriented. Anti-PD medications were restarted, and intravenous fluids and low-dose heparin were begun. By day 10, CK was 260 U/L, and on day 14 WBC was 13,200/mm^3. Work-up for infection was negative, and antibiotics were initiated empirically. Despite therapy, he remained febrile and stuporous. He was intubated and placed on a ventilator, but died in hyperthermic coma on day 15 after discontinuing medications.

RISK FACTORS AND PATHOGENESIS

In practice, many PD patients have their doses of dopaminergic medications decreased or stopped and yet only a very small fraction experience PHS. On the other hand, some patients are susceptible enough to develop this syndrome without changing medications *(26,27)*. There have been attempts to evaluate potential risk factors in PD patients *(32–35)*. The most ambitious of these was a study by Ueda et al. *(32)*, which examined clinical and neurochemical features over a 3-year period in 98 consecutive hospitalized PD patients. Demographics, disease severity, and cerebrospinal fluid monoamine metabolites including homovanillac acid (HVA), 3-methoxy-4-hydroxyphenyglycol, and 5-hydroxyindole acetic acid were evaluated. Eleven of the 98 had a history of PHS (either remote or leading to the study admission). The PHS group had significantly worse parkinsonism and a greater daily levodopa dose. No difference was seen between groups with respect to gender, age, duration of disease, or maximum levodopa dose. HVA cerebrospinal fluid (CSF) levels were significantly lower in the PHS group, the only feature independently related to the occurrence of PHS. A second study by the same group *(33)* examined HVA CSF levels in 9 patients during and after an episode of PHS, and compared them to 12 PD patients with simple worsening of PD with discontinuing medications. HVA levels were significantly lower in the PHS group. The authors suggested that the lower baseline level left a "narrow safety margin," leading to an increased susceptibility to the occurrence of PHS. Other studies *(34,35)* suggest that the presence of motor fluctuations, psychosis, and dehydration prior to the event represent other possible risks.

It is generally accepted that alterations in dopaminergic transmission in the brain are the pathogenic mechanism of NMS *(3,36)*. Abnormalities in muscle membrane function, changes in peripheral and central sympathetic outflow, and alterations in central serotonin metabolism have also been implicated *(3)*. The occurrence of PHS (a clinically identical syndrome to NMS) with dopaminergic drug withdrawal in PD indicates that a hypodopaminergic state alone is sufficient to trigger both disorders.

The clinical features of PHS can be explained by central dopamine depletion. The motor features of PHS are exaggerated PD symptoms related to decreased dopaminergic activity in the nigro-striatal system. The role of dopamine in thermal regulation is also well known. These dopamine pathways within the hypothalamus include the preoptic area, the anterior hypothalamus concerned with thermal detection, and the posterior hypothalamus involved with generation of effector signals. The thermosensitive neurons respond to local changes in blood temperature as well as to afferent information from peripheral thermosensors. Dopamine and dopamine agonists modulate hypothalamic temperature regulation, whereas dopamine receptor antagonists block this ability *(3)*. Dopaminergic depletion can also explain mental status changes through modulation of mesolimbic and mesocortical pathways *(3)*.

TREATMENT

PHS is a neurological emergency. The key to treatment is early recognition of the syndrome and rapid reintroduction of withdrawn antiparkinsonian medication

Table 2
Steps in the Management of Parkinsonism-Hyperplexia Syndrome in Parkinson's Disease

Recognition of the disorder
Verification of patients' medication regimen/compliance
Reintroduction of antiparkinsonian medications
Supportive measures: antipyretics/cooling blankets
re-hydration
intensive care unit monitoring/management (*see* text)
Clinical evaluation for possible comorbid conditions
Bromocriptine 2.5 mg orally three times daily, titrated by 2.5 mg three times daily as necessary
Dantrolene sodium 10 mg/kg/day intravenously in divided doses (three or four times daily) as necessary

(*see* Table 2). If there is no history of medication schedule alteration, then other causes must be sought, including the use of neuroleptics. When discontinuation of medication is the cause, the drug most commonly responsible is levodopa, and it should be re-instituted first, via nasogastric tube if necessary. Because PHS has occurred in two patients as a result of poor absorption of levodopa relating to diet, this is an important consideration. Beyond that, the treatment is similar to that of NMS, including rehydration with intravenous fluids and treatment of hyperthermia with antipyretics and cooling blankets, as well as supportive measures such as mechanical ventilation, cardiovascular monitoring, intravenous access, nasogastric suctioning/feeding, and prevention of thrombophlebitis. Metabolic evaluation and work-up to exclude infection are necessary. Because these patients are at risk for infections such as aspiration pneumonia, it is reasonable to initiate antibiotic therapy while the work-up is underway. Additional medical therapy with bromocriptine or other dopamine agonists and dantroline should be utilized. Bromocriptine is orally administered, with an initial dose of 2.5 mg three times daily, titrated for effect in increments of 2.5 mg three times daily every 24 hours. Dantrolene, a muscle relaxant initially used to treat malignant hyperthermia, is a parental compound typically dosed as 10 mg/kg per day in three to four divided doses. With proper therapy, symptoms will reverse in 10 hours to 7 days. Most of the patients described ultimately required a fairly lengthy hospital stay (5–22 days).

One recent study examined the use of methylprednisolone pulse therapy as an added regimen for PHS in PD *(31)*. In a randomized trial, all patients received levodopa, bromocriptine, and dantrolene sodium, and patients were randomized to receive placebo or 1000 mg of methylprednisolone for 3 days. Results suggested that steroid pulse therapy might shorten the course of the illness, perhaps by as much as 10 days, although notable overlap between groups was seen. This is the only double-blind, placebo-controlled trial in PHS or NMS, and further investigation is warranted.

CONCLUSION

PHS is a neurological emergency that has the potential to end in fatality. In all likelihood, it is underrecognized and more common than the literature might suggest. The use of several terms to describe the diagnosis in the literature has contributed to the confusion. A unifying term could improve awareness, especially if the term relates specifically to those patients with underlying parkinsonism. That is why we believe that PHS, recommended by Gordon and Frucht *(14)*, fulfills that role.

There are several ways to prevent PHS. First, drug holidays are no longer considered an appropriate treatment approach in PD. If reduction in dopaminergic therapy is needed, gradual reduction is mandated and patients should be made aware of the possible occurrence of PHS. This applies to patients with multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration *(37)*. It is important to avoid the use of standard neuroleptics in these patients because they are already at risk for NMS or PHS. Even atypical antipsychotics have the potential to lead to NMS or PHS in PD. The agents best tolerated by PD patients are quetiapine and clozapine *(38)*, but they should also be prescribed with caution. Although patients with more severe disease and those taking larger daily levodopa doses are at greater risk *(32–35)*, even patients with early PD and taking low doses of levodopa can develop PHS. Once the syndrome does occur, recognition is paramount and rapid reintroduction of dopaminergic medications imperative.

REFERENCES

1. Delay J, Pichot P, Lemperiere T, et al. Un neuroleptique majeur non-phenothiazinique et non-reserpinique, l'haloperiol, dans le traitment des psychosis. Annales Medicopsychologiques 1960;118:145–142.
2. Delay J, Denicker P. Drug induced extrapyramidal syndromes. In: Vinken PJ, Bruyun GW, eds. Handbook of Clinical Neurology Amsterdam, North Holland: 1968;258–259.
3. Factor SA, Singer C. Neuroleptic malignant syndrome. In: Lang AE and Weiner WJ, eds. Drug-induced Movement Disorders. Futura, Mount Kisco, NY: 1992;199–230.
4. Caroff SN. The neuroleptic malignant syndrome. J Clin Psychiatry 1980;41:79–82.
5. Shalev A, Munitz H. The neuroleptic malignant syndrome: agent and host interaction. Acta Psychiatr Scand 1986;73:337–347.
6. Rosebush P, Stewart T. A prospective analysis of 24 episodes of neuroleptic malignant syndrome. Am J Psychiatry 1989;146:717–725.
7. Kurlan R, Hamill R, Shoulson I. Neuroleptic malignant syndrome. Clin Neuropharmacol 1984;7:109–120.
8. Mueller PS. Diagnosis and treatment of neuroleptic malignant syndrome: a review. Neuroview 1987;3:1–5.
9. Burke RE, Fahn S, Mayuex R, et al. Neuroleptic malignant syndrome caused by dopamine-depleting drugs in a patient with Huntington's disease. Neurology 1981;31:1022–1026.
10. Sternbach H. The serotonin syndrome. Am J Psychiatry 1991;148:705–713.
11. Kosten TR, Kleber HD. Rapid death during cocaine abuse: a variant of neuroleptic malignant syndrome. Am J Drug Alcohol Ab 1988;14:335–346.
12. Toro M, Matsuda O, Mikizuich K, Sugano K. Neuroleptic malignant syndrome-like state following withdrawal of antiparkinsonian drugs. J Nerv Ment Dis 1981;169:324–327.
13. Friedman JH, Feinberg SS, Feldman RG. A neuroleptic malignant like syndrome due to levodopa therapy withdrawal. JAMA 1985;254:2792–2795.

14. Gordon PH, Frucht SJ. Neuroleptic malignant syndrome in advanced Parkinson's disease. Mov Disord 2001;16:960–961.
15. Pfeiffer RF, Sucha EL. "On-off"-induced lethal hyperthermia. Mov Disord 1989;4:338–341.
16. Serrano-Duenos M. Neuroleptic malignant syndrome-like, or—dopaminergic malignant syndrome—due to levodopa therapy withdrawal, clinical features in 11 patients. Parkinsonism Relat Dis 2003;9:175–178.
17. Keyser DL, Rodnitzky RL. Neuroleptic malignant syndrome in Parkinson's disease after withdrawal of alteration of dopaminergic therapy. Arch Int Med 1991;151:794–796.
18. Sechi GP, Tanda F, Mutani R. Fatal hyperpyrexia after withdrawal of levodopa. Neurology 1984;34:249–251.
19. Figá-Talamanca L, Gualandi C, DiMeo L, et al. Hyperthermia after discontinuance of levodopa and bromocriptine therapy: impaired dopamine receptors a possible cause. Neurology 1985;35:258–261.
20. Hirschorn KA, Greenberg HS. Successful treatment of levodopa induced myoclonus and levodopa withdrawal-induced neuroleptic malignant syndrome: a case report. Clin Neuropharmacol 1988;11:278–281.
21. Mayeux R, Stern Y, Mulvey K, et al. Reappraisal of temporary levodopa withdrawal ("drug holiday") in Parkinson's disease. N Engl J Med 1985;313:724–728.
22. Factor SA, Molho ES, Podskalny GD, Brown D. Parkinson's Disease: drug-induced psychiatric states. Adv Neurol 1995;65:115–138.
23. Iwuagwa CU, Riley D, Bonomo RA. Neuroleptic malignant-like syndrome in an elderly patient caused by abrupt withdrawal of tolcapone, a catechol-*o*-methyltransferase inhibitor. Am J Med 2000;108:517–518.
24. Cunningham MA, Darby DG, Donnan GA. Controlled-release delivery of L-dopa associated with nonfatal hyperthermia, rigidity and autonomic dysfunction. Neurology 1991;41:942–943.
25. Henderson VW, Wooten GF. Neuroleptic malignant syndrome: a pathogenetic role for dopamine receptor blockage? Neurology 1981;31:132–137.
26. Mizuta E, Yamasaki S, Nakatake M, Kuno S. Neuroleptic malignant syndrome in a Parkinsonian woman during the premenstrual period. Neurology 1993;43:1048–1049.
27. Cao L, Katz RH. Acute hypernatremia and neuroleptic malignant syndrome in Parkinson disease. Am J Med Sci 1999;318:67–68.
28. The Deep Brain Stimulation For Parkinson's Disease Study Group. Deep-Brain Stimulation of the subthalamic nucleus or the pars interna of the globus pallidus in Parkinson's disease. N Engl J Med 2001;345:956–963.
29. Vingerhoets FJG, Villemure JG, Temperli P, Pollo C, Pralong E, Ghika J. Subthalamic DBS replaces levodopa in Parkinson's disease: two-year follow-up. Neurology 2002;58:396–401.
30. Kleiner-Fisman G, Saint-Cyr JA, Miyasaki J, Lozano A, Lang AE. Subthalamic DBS replaces levodopa in Parkinson's disease (letter). Neurology 2002;59:1293–1294.
31. Sato Y, Asoh T, Metoki N, Satoh K. Efficacy of methylprednisolone pulse therapy on neuroleptic malignant syndrome in Parkinson's disease. J Neurol Neurosurg Psychiatry 2003;74:574–576.
32. Ueda M, Hamamoto M, Nagayama H, et al. Susceptibility to neuroleptic malignant syndrome in Parkinson's disease. Neurology 1999;52:777–781.
33. Ueda M, Hamamoto M, Nagayama H, Okubo S, Amemiya S, Katayama Y. Biochemical alterations during medication withdrawal in Parkinson's disease with and without neuroleptic malignant-like syndrome. J Neurol Neurosurg Psychiatry 2001;71:111–113.
34. Kuno S, Komure O, Mizuta, Yamazaki S, Nishitani H. Neuroleptic malignant syndrome associated with withdrawal of antiparkinsonian drugs. In: Nagatsu T, Fisher A, Yoshida M, eds. Basic clinical and therapeutic aspects of Alzheimer's and Parkinson's disease, vol 2. Plenum, New York: 1990;245–248.
35. Yamawaki Y, Ogawa N. Successful treatment of levodopa-induced neuroleptic malignant syndrome (NMS) and disseminated intravascular coagulation (DIC) in a patient with Parkinson's disease. Intern Med 1992;31:1298–1302.

36. Genis D. Neuroleptic malignant syndrome: impaired dopaminergic systems? Neurology 1985;35:1806.
37. Konagaya M, Goto Y, Matsuoka Y. Neuroleptic malignant syndrome-like condition in multiple system atrophy. J Neurol Neurosurg Psychiatry 1997;63:120-121. Letter.
38. Friedman JH, Factor SA. Atypical antipsychotics in the treatment of drug-induced psychosis in Parkinson's disease. Mov Disord 2000;15:201–211.

4

Neuroleptic Malignant Syndrome

Stanley N. Caroff, Stephan C. Mann, E. Cabrina Campbell, Kenneth A. Sullivan, and Jose Obeso

PATIENT VIGNETTES

Patient 1: A-16-year-old woman, who lives on a farm and spends time outdoors had been well with no psychiatric history until 1 week prior to admission. At that time, she developed difficulty sleeping and bizarre behavior including assault, sobbing, undressing in public, and thoughts of suicide that prompted admission to the hospital. On examination, she is labile, agitated, and delusional and experiences tactile, visual, and auditory hallucinations. She is found to have impaired recall, dyscalculia, and right-sided sensory deficits. She is started on 2 mg of haloperidol orally twice a day, and she also receives 5 mg intramuscularly for worsening agitation. Within a few hours, she develops a temperature of 39.8°C, tachycardia, diaphoresis, and board-like rigidity with cogwheeling, tremors, and mutism. A generalized seizure is observed. Despite administration of diphenylhydantoin, steroids, diazepam, benztropine, and three electroconvulsive treatments, she remains rigid and unresponsive with temperatures up to 40.5°C.

Laboratory examination reveals elevated serum creatine phosphokinase (CPK) (44,000 IU) and peripheral leukocytosis. Serial electroencephalograms (EEGs) show diffuse generalized slowing, but a computed tomography (CT) scan of the head is normal. Lumbar puncture on three occasions reveals 30–70 white blood cells/mm^3 (98% lymphocytes) with normal pressure, glucose, and protein. Cultures, stains, serology, and polymerase chain reaction are negative. Haloperidol is discontinued, and dantrolene and amantadine are administered. Over 2 weeks, she becomes alert, verbal, and ambulatory, but shows memory deficits and dysarthria, which resolve after 6 months.

Patient 2: A 65-year-old man with a history of alcohol dependence was admitted with a complaint of abdominal pain and nausea. Observation of a mass on a magnetic resonance imaging scan of the abdomen was followed by surgery for a perforated diverticulum. Postoperatively, he appears restless, agitated, and delirious. He receives

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

2 mg of haloperidol and 2 mg of lorazepam intravenously every 2 hours. Within 24 hours, he becomes unresponsive, tachycardic, hypotensive, tremulous, rigid, and febrile with temperatures reaching 41.5°C. Laboratory examination reveals hypoxia, metabolic acidosis, elevated serum CPK (21,500 IU), and leukocytosis. An EEG shows diffuse generalized slowing and a CT scan of the head demonstrates mild cortical atrophy. Haloperidol is discontinued, but he develops sudden respiratory arrest requiring intubation. Lorazepam is continued and dantrolene and bromocriptine are administered. Subsequently, he is treated for acute renal failure and disseminated intravascular coagulation. He gradually improves over 4 weeks, but continues to exhibit persistent dysarthria and mild ataxia several months later.

INTRODUCTION

Neuroleptic malignant syndrome (NMS) was first identified by Delay et al. during early trials of haloperidol *(1)*. Although subsequently studied in France and Japan, NMS remained obscure until 1980, after which increasing recognition resulted in hundreds of published case reports, primarily in the psychiatric literature *(2–4)*. These clinical observations enabled a more precise definition of NMS, clarified risk factors and treatment strategies, renewed interest in related hyperthermic disorders, and shed light on the pathophysiology of the syndrome *(3,4)*. Increased awareness and the recent introduction of atypical antipsychotic medications with reduced liability for producing movement disorders have probably reduced the incidence of NMS in psychiatric settings *(5,6)*. Nevertheless, the evaluation and treatment of NMS remain obscure to most practicing physicians, especially outside of psychiatry. This is alarming, given that NMS remains potentially lethal if unrecognized, and underscores the need for increased awareness of the diagnosis and management of this serious drug reaction.

EPIDEMIOLOGY

Although NMS occurs infrequently, the widespread use of neuroleptics in medicine and psychiatry suggests that the absolute number of cases is significant. The incidence of NMS varies depending on the population at risk, prescribing practices, and methods of case ascertainment. Combining data from published studies of NMS in psychiatric patients treated with neuroleptics, we have estimated the incidence of NMS to be about 0.2% *(3)*. However, it is possible to reduce the incidence of NMS by using conservative doses of neuroleptics, minimizing risk factors, and recognizing incipient cases.

Several small, controlled studies have been conducted to identify reliable risk factors *(7,8)*. NMS has been reported in both sexes and in all age groups. Although elevated environmental heat and humidity have been proposed as contributing factors in a few cases, NMS occurs independent of ambient conditions. NMS is not specific to any neuropsychiatric diagnosis. It has developed in patients treated with neuroleptics for diverse psychiatric illnesses, as well as in patients who receive neuroleptics for agitation, sedation, or gastrointestinal disorders in medical settings.

Several authors have proposed an increased risk of NMS in patients with preexisting catatonia and disorders affecting the basal ganglia *(3,9,10)*. Additional evidence suggests that exhaustion, agitation, and dehydration may predispose patients to develop NMS *(3,7,8)*.

Pharmacologically, about 17% of NMS patients experienced a similar episode during prior exposure to neuroleptics, suggesting a trait susceptibility to the disorder. Virtually all classes of drugs that induce dopamine D-2 receptor blockade have been associated with NMS. This includes all typical neuroleptics used as antipsychotics. Although the newer, atypical antipsychotics have also been associated with NMS in published case reports, their liability for inducing NMS is likely lower *(6)*.

NMS cases, including some that were fatal, have also been reported in association with other neuroleptic drugs prescribed by medical and surgical practitioners *(11)*. These include prochlorperazine, metoclopramide, droperidol, and promethazine. We believe that such cases of NMS remain seriously underreported and underrecognized *(11)*.

NMS does not result from overdosage with neuroleptics; rather, it usually occurs with therapeutic use *(3)*. Within this range, however, several studies have suggested that patients who develop NMS are more likely to have received relatively higher doses, more rapid titration, and more parenteral injections of neuroleptics compared to controls *(7,8)*. Data are inconclusive as to whether use of adjunctive or concomitant medications (e.g., antiparkinsonian drugs or lithium) increase or decrease the risk of NMS.

Although evidence from small cohort studies suggests that these clinical and pharmacological variables correlate with the risk of NMS, the low incidence rate and idiosyncratic occurrence of the disorder precludes their use as reliable risk factors for risk–benefit evaluation of neuroleptic therapy when indicated in a given patient.

PATHOPHYSIOLOGY

Several lines of evidence support acute reduction in dopamine activity in the brain as the basic mechanism underlying NMS *(3,12)*. All neuroleptics implicated in NMS share the property of dopamine receptor blockade. Clinical studies indicate that the risk of NMS correlates with the dose, potency, rate, and route of administration of dopamine antagonists *(7,8)*. Dopamine agonists have been administered empirically as effective therapy for NMS. Patients with Parkinson's disease (PD) or other related disorders have developed NMS-like syndromes after abrupt withdrawal of dopamine agonists. Patients with lesions interrupting dopamine pathways have developed akinetic mutism and hyperthermia resembling NMS. Studies of neurotransmitter metabolites in cerebrospinal fluid obtained from patients with NMS reveal central dopamine hypoactivity as a possible trait marker for NMS *(13,14)*. A few preliminary and unreplicated studies have also suggested abnormalities in the dopamine D2 receptor gene of patients who recovered from NMS

episodes *(15,16)*. Studies of clinical correlates of frontal–subcortical circuits provide a framework within which individual NMS symptoms may be localized to perturbations in specific dopamine pathways *(12)*. Finally, changes in dopamine pathways in response to stress may be implicated as an additional state-related cofactor involved in the triggering of NMS *(12)*.

Although the evidence for a central role of dopamine in the pathophysiology of NMS is compelling, other mechanisms have been proposed as contributing factors. These include a relative excess of glutaminergic transmission secondary to dopamine blockade, effects of low serum iron on dopamine receptor function, and the effects of reduced activity of γ-aminobutyric acid (GABA) *(3,12,14)*. Gurrera *(17)* postulated a pivotal role for dysregulation of the sympathetic nervous system in producing the characteristic hypermetabolic manifestations of NMS.

Finally, even though NMS and malignant hyperthermia (MH) induced by anesthetics differ in their pharmacological triggers (with MH attributed to a primary pharmacogenetic defect in skeletal muscle), their similar clinical presentations culminating in a final common hypermetabolic syndrome suggests potential parallels. Clinical reports of an increased risk of NMS following administration of neuroleptics in patients with preexisting myopathies or unexplained creatine phosphokinase (CPK) elevations lends support to overlapping or convergent mechanisms between NMS and MH *(11)*. This clinical evidence, combined with the known pharmacological effects of neuroleptics on CPK levels, membrane permeability, calcium regulation, and contractility in skeletal muscle, is intriguing and merits further investigation *(11,18)*.

CLINICAL CHARACTERISTICS

In addition to the development of reliable risk factors, it is critical to identify the early signs of NMS in order to abort the progression of the syndrome. Although NMS has a variable onset and sometimes evolves rapidly, rigidity and altered mental status usually occur early, followed by autonomic changes and hyperthermia *(19)*. In more than 80% of cases in which a single presenting sign was reported, rigidity or mental status change was the initial manifestation *(19)*. Other prodromal signs may include obtundation, catatonia, tachycardia, tachypnea, labile blood pressure, dysarthria, dysphagia, diaphoresis, sialorrhea, incontinence, rigidity, myoclonus, tremors, low-grade fevers, or serum CPK elevations. Clinicians should diagnose NMS early and document the rationale for stopping neuroleptic therapy. Unfortunately, these early signs are not specific for NMS, do not necessarily progress to NMS, and do not invariably precede the syndrome *(3)*.

Clinical features of NMS are listed in Table 1. NMS may be thought of as a form of drug-induced hyperthermia, usually associated with profuse sweating. Extreme temperature elevations represent a medical emergency and may cause irreversible brain damage if not reduced immediately. Generalized rigidity, often described as "lead-pipe," is a core feature of NMS, and is usually associated with myonecrosis. Cogwheeling, spontaneous and action myoclonus of multifocal distribution, and

Table 1
The Clinical Features of Neuroleptic Malignant Syndrome

- Administration of neuroleptics, particularly high-potency conventional agents
- Signs and symptoms
  Hyperthermia (>38°C)
  Muscle rigidity with or without cogwheeling
  Tremor, myoclonus
  Mental status changes (stupor, mutism, delirium)
  Autonomic instability (tachycardia, labile blood pressure)
  Tachypnea, dyspnea
  Diaphoresis, sialorrhea, incontinence
  Dysarthria, dysphagia
- Positive laboratory findings
  Creatine phosphokinase elevation, leukocytosis, metabolic acidosis, hypoxia, low serum iron, elevated serum catecholamines, slowing on electroencephalogram
- Complications
  Cardiorespiratory arrest, acute renal failure, rhabdomyolysis, pulmonary emboli, aspiration pneumonia, disseminated intravascular coagulation, limb contractures, ischemic brain damage
- Exclusion of other central, systemic, and toxic causes of hyperthermia

postural tremors are often described along with other movement disorders. Mental status changes include clouding of consciousness ranging from stupor to coma, delirium, or the onset of catatonia. The classic NMS patient appears awake but dazed, stuporous, and mute. Autonomic activation and instability are common, manifesting as tachycardia, oscillations in blood pressure, and tachypnea.

Although several laboratory abnormalities have been reported in NMS, none are specific or pathognomonic for the diagnosis *(3)*. Instead, a comprehensive laboratory evaluation is essential in order to exclude other causes of hyperthermia and detect medical complications. Serum CPK is usually moderately elevated and occasionally reaches extraordinary levels reflecting massive rhabdomyolysis. Although elevations in CPK are not specific to NMS, monitoring of the enzyme level remains important as a measure of the severity of rhabdomyolysis and the attendant risk of myoglobinuric renal failure. Other frequently described laboratory abnormalities include metabolic acidosis, hypoxia, decreased serum iron, elevated serum catecholamines, electrolyte abnormalities, and coagulopathies *(3)*.

Nonfocal generalized slowing on electroencephalogram consistent with encephalopathy has been reported in over half of NMS cases. Brain imaging studies, cerebrospinal fluid examination, and sepsis evaluation are negative in NMS, allowing for infectious etiologies to be ruled out *(3)*.

NMS usually results from the neurochemical changes induced by neuroleptics during the initial stages of treatment or after dosages are increased. In a review by Caroff and Mann *(20)*, 16% of patients developed NMS within 24 hours of initiating neuroleptic treatment, 66% by 1 week, and 96% occurred within the first 30 days. Only 4% developed NMS beyond 30 days. Conversely, once neuroleptics

were discontinued, NMS was self-limited barring complications. Following discontinuation of oral neuroleptics, the mean recovery time has been estimated at 7 to 10 days *(3,20)*. About 63% recover within 1 week, and nearly all within 30 days.

In some cases, the course of NMS may be prolonged. For example, patients receiving long-acting depot neuroleptics may remain ill nearly twice as long *(3,20)*. Occasional patients may develop a residual catatonic-parkinsonian state that can persist for weeks to months if left untreated after the acute hyperthermic symptoms of NMS subside *(21)*. Although dopamine agonists and benzodiazepines have been advocated for treatment of this residual state, electroconvulsive therapy (ECT) appears to be more rapidly effective with reduced mortality in reported series *(21)*.

Early diagnosis and intervention have contributed to a decline in the mortality rate, but not all patients recover from NMS *(3)*. Fatalities may occur as a result of sudden cardiorespiratory arrest, aspiration pneumonia, pulmonary emboli, acute renal failure, or disseminated intravascular coagulation. Findings at autopsy are usually nonspecific and variable, depending on complications *(3)*. Persistent clinical sequelae of NMS are rare in patients who recover. However, cases of amnestic syndromes, extrapyramidal and cerebellar disorders, peripheral neuropathy, myopathy, and contractures have been reported *(3)*.

The differential diagnosis of NMS encompasses a broad range of disorders presenting with fever, requiring a thorough medical and neurological evaluation. Despite careful investigation, the cause of the syndrome in some patients may remain unclear or multifactorial *(3)*. Other disorders that can resemble NMS include primary disorders of the brain and systemic disorders that secondarily affect brain function. Among the former are infectious encephalitis, structural lesions, and rare cases of nonconvulsive status epilepticus *(3,9,22,23)*.

We have been consulted on several cases resembling the patient described in our first clinical vignette in which a patient with underlying encephalitis is initially misdiagnosed with a psychiatric condition and then develops NMS following administration of neuroleptics *(10,22)*. Some of the features in these cases are reminiscent of encephalitis lethargica. These observations led us to underscore the importance of considering encephalitis in the differential diagnosis of patients who present with new-onset psychosis, especially if they develop NMS after treatment with neuroleptics *(10,22)*. Such cases imply that encephalitic patients may be at increased risk for NMS and other neuroleptic-induced movement disorders *(10,22)*.

Advanced stages of psychotic disorders associated with excited or stuporous catatonia (delirious mania or malignant catatonia) can progress to exhaustion, hyperthermia, and death *(24,25)*. Although the occurrence of malignant or lethal catatonia has decreased, it still occurs and can be indistinguishable from NMS. Indeed, NMS has been conceptualized as a drug-induced iatrogenic form of malignant catatonia *(24,25)*. In either NMS or malignant catatonia, neuroleptics should be discontinued because most NMS episodes are self-limited and should subside within 2 weeks after drug discontinuation. In malignant catatonia, neuroleptics appear to be

ineffective and even detrimental *(3,24,25)*. In contrast, ECT appears to be the treatment of choice for malignant catatonia, and is often effective in NMS *(24–26)*.

In relation to systemic disorders, patients with common and benign forms of neuroleptic-induced parkinsonism or catatonia may develop fever from coincident infections or dehydration and be mistakenly diagnosed as having NMS. Neuroleptics have also been associated with rhabdomyolysis alone without other features of NMS; the relationship between these two drug-induced phenomena is unclear. Hyperthermia may be observed in patients with thyrotoxicosis and pheochromocytoma, which can be distinguished from NMS by the absence of rigidity. Systemic lupus erythematosus or other autoimmune diseases affecting the brain may present with fever and neurological signs. Heatstroke may develop in patients during hot weather and may be confused with NMS *(3,27)*. Furthermore, neuroleptic treatment may predispose to heat stroke by blocking central thermoregulatory heat loss pathways. Unlike NMS, however, muscle rigidity is unusual in heat stroke.

Many toxins and drugs have been associated with hyperthermia and must be considered in the differential diagnosis. Volatile anesthetics and succinylcholine are associated with MH during surgery, which can be confused with NMS if neuroleptics are administered perioperatively *(11)*. Although NMS has been reported before and after surgery, it appears unlikely to develop intraoperatively, in contrast with MH *(11)*. Furthermore, centrally derived muscle rigidity associated with NMS can be reversed by neuromuscular blockade, whereas rigidity associated with MH reflects a defect within skeletal muscle, which does not respond to paralyzing agents.

Abrupt withdrawal of levodopa or dopamine agonists in patients with PD has resulted in hyperthermic syndromes indistinguishable from NMS, reflecting the shared mechanism of acute dopamine deficiency. Abrupt discontinuation of oral or intrathecal administration of the GABAergic agent baclofen can produce a similar syndrome. Illegal stimulants and hallucinogens have been associated with hyperthermia, seizures, rigidity, rhabdomyolysis, and death. Anticholinergic drugs used to treat extrapyramidal disorders can result in atropinic toxicity manifested by fever without rigidity. Withdrawal states, such as delirium tremens, can also be difficult to distinguish from NMS, especially if neuroleptics have been administered to control agitation or psychotic symptoms.

Finally, serotonin syndrome is often considered in the differential of NMS, and has been increasingly reported in association with selective serotonergic agents introduced for the treatment of depression or migraine headaches *(28)*. Although serotonin syndrome can present as an NMS-like hypermetabolic state in its most severe form associated with monoamine oxidase inhibitors, it usually presents with milder and more transient symptoms indicative of an agitated delirium.

Our second vignette illustrates the need to exclude several of these conditions before settling on the diagnosis of NMS. This is a particularly challenging task in critical care units where fever commonly occurs as a result of infections or drug reactions. It is unusual for MH to occur postoperatively, and therefore MH was an

unlikely diagnosis in this case. In contrast, NMS has been reported in the context of neuroleptic treatment of postoperative agitation. Furthermore, this patient was alcohol-dependent, raising the possibility of a withdrawal reaction. Although CPK elevations can be observed in alcohol abusers as well as in NMS patients, the characteristic rigidity of NMS is not a typical feature of alcohol withdrawal. However, we have previously suggested that patients with severe withdrawal from alcohol or sedatives may be at increased risk of developing NMS *(3,23)*.

Both clinical vignettes illustrate the fact that the occurrence of NMS represents an interaction between patient susceptibility, stemming from primary or acquired subcortical brain dysfunction, and neuroleptic-induced effects.

TREATMENT

The mainstay of treatment of NMS includes risk reduction, early diagnosis, cessation of neuroleptic medications, and provision of intensive medical and nursing care *(26,29)*. There is less evidence and consensus concerning the comparative efficacy of specific pharmacologic agents and ECT in the treatment of NMS. This derives from the fact that with early recognition and prompt cessation of neuroleptics, NMS is a self-limited disorder in most cases, regardless of specific therapy. Furthermore, there is a scarcity of controlled clinical treatment trials. Nevertheless, there are rational theories and empirical clinical data to support consideration of specific pharmacological agents and ECT in the treatment of NMS.

Based on available evidence, we recommend that specific treatment of NMS should be individualized and based empirically on the character, duration, and severity of clinical signs and symptoms *(26,29)*; (Fig. 1). In many cases, supportive care alone with close monitoring for progression of symptoms or complications may be sufficient. Benzodiazepines are effective in reversing catatonia, easy to administer, and may be tried initially in most cases. Trials of bromocriptine, amantadine, or other dopamine agonists are a reasonable next step in patients with moderate symptoms of NMS. When severe symptoms render treatment by the oral route impractical, intravenous or subcutaneous administration of dopamine agonists (e.g., lisuride or apomorphine) becomes an excellent option *(30)*. In addition, newer dopamine agonists are being developed for transdermal delivery, which will facilitate parenteral administration of dopaminergic drugs under extreme circumstances.

Dantrolene appears to be beneficial only when significant rigidity and hyperthermia develop as manifestations of a full-blown hypermetabolic state. As an inhibitor of skeletal muscle hypermetabolism, dantrolene has been associated with rapid reduction of extreme temperature elevations in many cases. The above medications have not been reliably effective in all case reports of NMS. Furthermore, positive drug effects are usually observed during the first few days of treatment of NMS, whereas delayed administration is unlikely to produce a late response *(26,29)*.

If symptoms of NMS persist despite supportive care and pharmacotherapy, ECT may be effective even late in the course. ECT may be preferred if idiopathic lethal catatonia cannot be excluded, if NMS symptoms are refractory to other measures, in patients with prominent catatonic features, and in patients who develop a re-

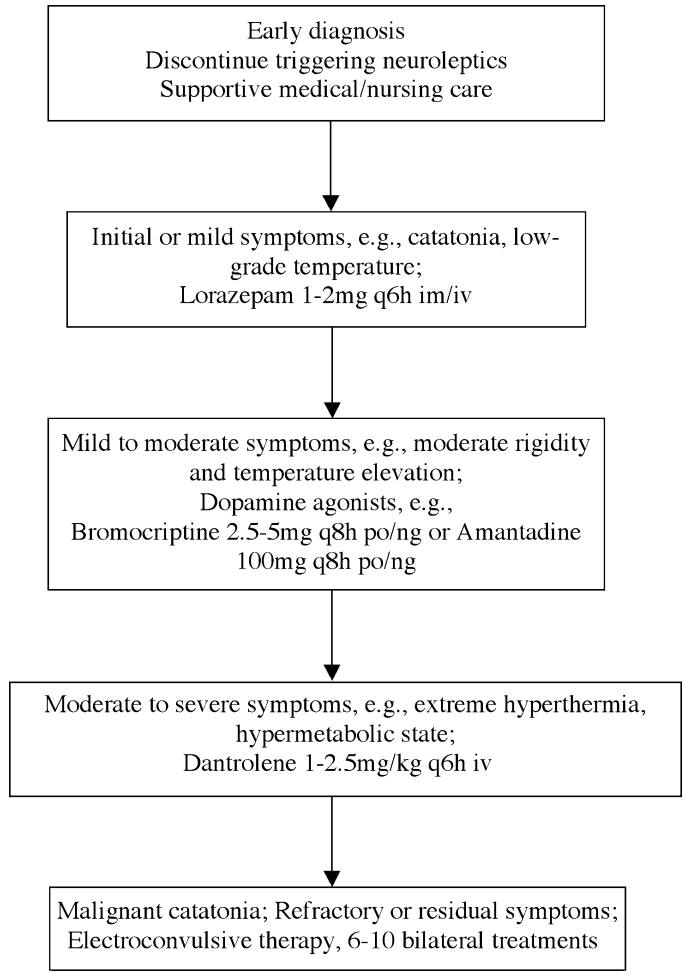


Fig. 1. Proposed empirical guidelines for the treatment of neuroleptic malignant syndrome. Treatment should be individualized based on character, severity and duration of symptoms. Agents may be co-administered. Potential side effects should also be reviewed and considered.

sidual catatonic-parkinsonian state or remain psychotic after NMS has resolved *(21,26,29)*.

Among patients who recover from NMS, there is a 30% risk of recurrent episodes following subsequent neuroleptic rechallenge *(3)*. However, the majority of patients who require neuroleptic therapy can be safely treated, provided precautions are taken. Reports of previous episodes should be checked for accuracy, indications for neuroleptics clearly documented, alternative medications considered,

informed consent obtained from patients and families, risk factors reduced, at least 2 weeks allowed to elapse following recovery before rechallenge, low doses of low-potency conventional neuroleptics or atypical neuroleptics titrated gradually after a test dose, and patients carefully monitored for incipient signs of NMS.

CONCLUSION

Neuroleptics are highly effective and safe medications that have achieved widespread use in medicine and psychiatry. However, they have been associated with NMS in about 0.2% of psychiatric patients. Significant progress has been achieved in recognizing, managing, and understanding this drug reaction since it was first described more than 40 years ago. Development of atypical antipsychotics, conservative prescribing guidelines, reduction of proposed risk factors, and education of staff has resulted in a reduced incidence of this disorder. Early diagnosis, cessation of neuroleptic medications, prompt medical intervention, and consideration of specific remedies can reduce morbidity and mortality when NMS occurs. It is therefore essential for all physicians and nurses to become familiar with the diagnosis and treatment of this uncommon but potentially lethal movement disorder emergency.

REFERENCES

1. Delay J, Pichot P, Lemperiere T, Elissade B, Peigne F. Un neuroleptique majeur non-phenothiazine et non reserpinique, l'haloperidol, dans le traitement des psychoses. Annales Medico-Psychologique 1960;118:145–152.
2. Caroff SN. The neuroleptic malignant syndrome. J Clin Psychiatry 1980;41:79–83.
3. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Med Clin N Am 1993;77:185–202.
4. Caroff SN, Mann SC, Campbell EC. Neuroleptic malignant syndrome. Adverse Drug Reaction Bulletin 2001;209:799–802.
5. Caroff SN, Mann SC, Campbell EC, Sullivan KA. Movement disorders associated with atypical antipsychotic drugs. J Clin Psychiatry 2002;63(suppl 4):12–19.
6. Caroff SN, Mann SC, Campbell EC. Atypical antipsychotics and neuroleptic malignant syndrome. Psychiatr Ann 2000;30:314–321.
7. Keck PE, Pope HG, Cohen BM, McElroy SL, Nierenberg AA. Risk factors for neuroleptic malignant syndrome. Arch Gen Psychiatry 1989;46:914–918.
8. Berardi D, Amore M, Keck PE Jr, Troia M, Dell'Atti M. Clinical and pharmacologic risk factors for neuroleptic malignant syndrome: a case control study. Biol Psychiatry 1998;44:748–754.
9. White DAC, Robins AH. Catatonia: harbinger of the neuroleptic malignant syndrome. Br J Psychiatry 1991;158:419–421.
10. Caroff SN, Mann SC, McCarthy M, Naser J, Rynn M, Morrison M. Acute infectious encephalitis complicated by neuroleptic malignant syndrome. J Clin Psychopharmacol 1998;18:349–351.
11. Caroff SN, Rosenberg H, Mann SC, Campbell EC, Gliatto MF, Sullivan KA. Neuroleptic malignant syndrome in the perioperative setting. Am J Anesthesiol 2001;28:387–393.
12. Mann SC, Caroff SN, Fricchione G, Campbell EC. Central dopamine hypoactivity and the pathogenesis of the neuroleptic malignant syndrome. Psychiatr Ann 2000;30:363–374.
13. Ueda M, Hamamoto M, Nagayama H, Okubo S, Amemiya S, Katayama Y. Biochemical alterations during medication withdrawal in Parkinson's disease with and without neuroleptic malignant-like syndrome. J Neurol Neurosurg Psychiatry 2001;71:111–113.
14. Nisijima K, Ishiguro T. Cerebrospinal fluid levels of monoamine metabolites and gamma-aminobutyric acid in neuroleptic malignant syndrome. J Psychiatr Res 1995;27:233–244.

15. Suzuki A, Kondo T, Otani K, et al. Association of the TaqIA polymorphism of the dopamine D2 receptor gene with predisposition to neuroleptic malignant syndrome. Am J Psychiatry 2001;158:1714–1716.
16. Ram A, Cao Q, Keck PE, et al. Structural change in the dopamine D2 receptor gene in a patient with neuroleptic malignant syndrome. Am J Med Genet 1995;60:228–230.
17. Gurrera RJ. Is neuroleptic malignant syndrome a neurogenic form of malignant hyperthermia? Clin Neuropharmacol 2002;25:183–193.
18. Caroff SN, Mann SC, Sullivan K, Macfadden W. Drug-induced hypermetabolic syndromes. In: Ohnishi ST, Ohnishi T, eds. Malignant Hyperthermia: A Genetic Membrane Disease. CRC, Boca Raton, Florida: 1994;118–132.
19. Velamoor VR, Norman RM, Caroff SN, Mann SC, Sullivan KA, Antelo RE. Progression of symptoms in neuroleptic malignant syndrome. J Nerv Ment Dis 1994;182:168-173.
20. Caroff SN, Mann SC. Neuroleptic malignant syndrome. Psychopharmacol Bull 1988;24:25–29.
21. Caroff SN, Mann SC, Keck PE Jr., Francis A. Residual catatonic state following neuroleptic malignant syndrome. J Clin Psychopharmacol 2000;20:257–259.
22. Caroff SN, Mann SC, Gliatto MF, Sullivan KA, Campbell EC. Psychiatric manifestations of acute viral encephalitis. Psychiatr Ann 2001;31:193–204.
23. Caroff SN, Mann SC, Lazarus A, Sullivan KA, Macfadden W. Neuroleptic malignant syndrome: diagnostic issues. Psychiatr Ann 1991;21:130–147.
24. Mann SC, Caroff SN, Bleier HR, Welz WK, Kling MA, Hayashida M. Lethal catatonia. Am J Psychiatry 1986;143:1374–1381.
25. Fricchione G, Mann SC, Caroff SN. Catatonia, lethal catatonia and neuroleptic malignant syndrome. Psychiatr Ann 2000;30:347–355.
26. Davis JM, Caroff SN, Mann SC. Treatment of neuroleptic malignant syndrome. Psychiatr Ann 2000;30:325–331.
27. Caroff SN, Mann SC, Campbell EC. Risk of fatal heatstroke after hospitalization. Psychiatr Serv 2000;51:938.
28. Keck PE Jr, Arnold LM. The serotonin syndrome. Psychiatr Ann 2000;30:333–343.
29. Caroff SN, Mann SC, Keck PE Jr. Specific treatment of the neuroleptic malignant syndrome. Biol Psychiatry 1998;44:378–381.
30. Rodriguez M, Luquin MR, Lera G, Delgado G, Salazar JM, Obeso JA. Neuroleptic malignant syndrome treated with subcutaneous lisuride infusion. Mov Disord 1990;5:170–172.

5

Malignant Catatonia

Stephan C. Mann, Stanley N. Caroff, E. Cabrina Campbell, Henry R. Bleier, and Robert A. Greenstein

PATIENT VIGNETTES

Patient 1: A 27-year-old woman with a personal and family history of bipolar disorder has taken no psychiatric medications for the past 6 months. One week prior to admission, she develops elevated mood, pressured speech, and flight of ideas. Over the ensuing days, she grows markedly agitated and unable to sleep, talks constantly, paces relentlessly, and refuses to eat or drink. On admission to the psychiatric unit, she requires four-point restraints. She is confused and intensely hyperactive, with periods of incoherent chatter alternating with hostile verbal outbursts. She frequently thrashes from side to side, is delusional, and appears to be responding to both auditory and visual hallucinations. She exhibits muscular rigidity, posturing, echolalia, and echopraxia. Temperature is 39°C with tachycardia, tachypnea, profuse diaphoresis, and a blood pressure of 170/120 mmHg. Laboratory abnormalities include leukocytosis, elevation in creatine phosphokinase (CPK) (2800 IU) and serum transaminases, and a serum iron of 38 μg/dL (75–175 μg/dL). Lumbar puncture, electroencephalogram and computed tomography scan of the head are normal.

During the next 24 hours, she lapses into stupor with increased rigidity and a temperature of 40.2°C. The diagnosis of malignant catatonia associated with a manic episode is made and electroconvulsive therapy (ECT) initiated. Body temperature and other vital signs return to normal after the first bilateral ECT treatment. She receives one bilateral ECT treatment daily for the next 5 days and three more over the next week. She responds with a marked decrease in agitation and progressive improvement in confusion, hallucinations, delusions, and catatonic features. She starts divalproex sodium and olanzapine with good response and is discharged 2 weeks later.

Patient 2: A 46-year-old schizophrenic man has taken no psychiatric medications for the past 2 years. He is admitted to the intensive care unit with a 1-week history of progressive mutism, immobility, negativism, and staring. On exam, he exhibits marked muscular rigidity. Temperature is 40.1°C with tachycardia, tachypnea, diaphoresis, and a blood pressure of 190/110 mmHg. Laboratory evaluation reveals el-

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

evated CPK and leukocytosis. All other studies are noncontributory. Malignant catatonia is diagnosed. Intravenous lorazepam (2 mg), administered four times daily for 2 days provides no benefit. He is referred for ECT and responds promptly.

INTRODUCTION

Catatonia is a syndrome of striking motor and behavioral abnormalities that may occur in association with diverse neurologic, drug-induced, and psychiatric illnesses. Catatonia may be conceptualized as a continuum, with milder forms at one end (termed *simple* or *benign*) and more severe forms, with hyperthermia and autonomic dysfunction (termed *malignant*), at the other *(1)*. The earliest description of malignant catatonia (MC) derives from an 1832 publication by Calmeil *(2)*, who reported on a rare but life-threatening psychotic disorder characterized by extreme motoric excitement that progressed to stuporous exhaustion. The entire course, passing through excitement into stupor, involved mounting hyperthermia, progressive autonomic dysfunction, clouding of consciousness, and catatonic features. In those cases ending in death, the paucity of findings on autopsy was puzzling.

MC was subsequently reported by Bell in 1849 *(3)* and was the subject of numerous American and foreign publications during the pre-antipsychotic drug era. Other names used to describe this same disorder included Bell's mania, acute delirious mania, delirium acutum, delire aigu, psychotic exhaustion syndrome, and Scheid's cyanotic syndrome, among others *(4–9)*. In 1934, Stauder *(10)* coined the term *lethal catatonia,* which became the most widely used designation for this condition for the next 60 years. More recently, stressing that not all cases are fatal, Philbrick and Rummans *(1)* have promulgated the term *malignant catatonia.*

Although the incidence of MC may have declined worldwide following the introduction of modern psychopharmacological agents, it has remained widely reported, particularly in Europe and Asia. In contrast, contemporary North American publications on MC have now become more limited. In this chapter, we review the historical and modern world literature on MC. On the basis of this review, we conclude that MC continues to occur and represents an uncommon but potentially fatal neuropsychiatric disorder. Lack of recognition appears to account for the scarcity of recent North American reports on MC.

Furthermore, our data indicate that MC, like simple catatonia, represents a syndrome rather than a specific disease. Although most often presenting as an outgrowth of the major psychoses, MC may also occur in association with diverse neurological, infectious, and toxic-metabolic conditions. From this perspective, neuroleptic malignant syndrome (NMS), a life-threatening complication of antipsychotic drug treatment *(9,11)*, may be viewed as a drug-induced form of MC. In addition, findings from our review indicate that MC and NMS share a common pathophysiology involving reduced dopaminergic neurotransmission within the basal ganglia–thalamocortical circuits. Recognition of the clinical features of MC and an appreciation of its diverse etiologies are essential for the effective management of patients who develop this catastrophic reaction.

CLINICAL PRESENTATION: PRE-ANTIPSYCHOTIC DRUG ERA

There is considerable uniformity to early clinical accounts of MC *(4–9)*. A prodromal phase was observed in most, but not all, cases. It lasted an average of 2 weeks and involved insomnia, anorexia, and labile mood. In about 90% of cases, the disease proper began with a phase of intense motor excitement that then continued almost without interruption (as exemplified by patient 1). Shulack's 1946 account *(12)* is representative. He describes excitement, which progresses to "a continual maniacal furor, in which the individual will tear off his clothes, tear the clothes to strips, take the bed apart, rip the mattress to pieces, bang and pound almost rhythmically on the walls and windows, dash wildly from the room, assault anyone in reach, and run aimlessly and without objective…If placed in restraints, he will strain ceaselessly." Features of this excited phase included refusal of all foods and fluids, clouding of consciousness, and somatic disturbances such as tachycardia, tachypnea, cyanosis, labile or elevated blood pressure, and profuse perspiration. Acrocyanosis and hematomas of the skin were often present. Excitement might be punctuated by intervals of catatonic stupor. Other catatonic signs including mutism, catalepsy, posturing, echolalia, and echopraxia were frequently noted. Speech became increasingly incoherent and bizarre delusions and hallucinations were often prominent. In this "classic" excited phase of MC, excitement was always associated with hyperthermia that could attain levels as high as 43.3°C prior to the final stuporous phase of MC. Excitement lasted an average of 8 days *(13)*.

In the final phase of MC, excitement gave way to stuporous exhaustion and extreme hyperthermia, often followed by coma, cardiovascular collapse, and death *(4)*. In all of Stauder's *(10)* 27 cases, skeletal muscle was found to be rigid during this terminal stupor, resembling NMS. Although additional early accounts of MC echoed the findings of Stauder, other reports noted musculature to be flaccid *(13)*. This differs from NMS where muscular rigidity represents a cardinal feature. In addition, it is important to emphasize that roughly 10% of cases reported during the pre-antipsychotic drug era involved catatonic stupor and hyperthermia occurring independent of a preceding excited phase—that is, they had a primarily stuporous course (patient 2).

During the pre-antipsychotic drug era, MC was reported fatal in 75% to 100% of cases *(4)*. It was observed to occur predominantly in young adults between the ages of 18 and 35, and affected women roughly seven times more often then men. During this period, MC was estimated to account for 0.25% to 3.5% of admissions to psychiatric hospitals and was noted to develop with equal frequency throughout the seasons. Stauder *(10)*, and others, reported findings consistent with a familial pattern of occurrence.

Kraepelin *(14)* was among a number of German authors of this period who considered MC a clinical syndrome, composed of characteristic symptoms and course but lacking a specific etiology. He believed that MC could occur as an outgrowth of diverse neurologic or medical conditions as well as in association with the major psychoses. In contrast, most early French authors viewed MC as an unusual but

deadly form of encephalitis preferentially involving the hypothalamus *(15)*. Following Stauder's *(10)* publication, however, MC was increasing, seen as confined to the major psychoses, although Stauder himself never fully dismissed the possibility that some or all of his patients may have had encephalitis. Most German and American authors emphasized lack of autopsy findings that could account for death, with the central nervous system abnormalities reported by the French either unconfirmed or deemed trivial. Bronchopneumonia and other infections were considered "opportunistic," occurring in an already exhausted and compromised host.

MODERN CLINICAL PRESENTATIONS

In 1986, we identified a series of 292 MC cases reported between 1960 and 1985 *(4)*. Two hundred and sixty-five cases came from 20 reports representative of more than 50 publications from Europe and Asia. The remaining 27 cases came from just 12 articles found in an exhaustive search of the North American literature. Most patients had received antipsychotic drug treatment. Since then, we have identified 77 additional cases reported in the world literature between 1986 and 2003, thus extending our series to 369 total cases *(4–9)*. Although MC remains more frequently mentioned in the foreign literature, the disparity in these most recent 77 cases appears somewhat reduced, suggesting improved recognition of this disorder in North America.

Among 322 cases in which gender was specified, 212 (66%) were female. The mean age of occurrence was 33, compared with age 25 during the pre-antipsychotic drug era. Of considerable interest, mortality, which exceeded 75% during the pre-antipsychotic drug era, and remained at 60% between 1960 and 1985 *(4)*, has fallen to 9% in the 77 cases reported since 1986 *(8,9)*. This recent decline is striking and presumably reflects enhanced awareness of MC, early diagnosis, and the rapid institution of appropriate treatment. Nevertheless, MC continues to represent a potentially lethal disorder. Among cases reported since 1960, MC was estimated to occur in 0.07% of psychiatric admissions *(16)* or annually in 0.0004% of community adults *(17)*.

Table 1 summarizes the clinical features of MC. Along with catatonic stupor and hyperactivity, they include hyperthermia, altered consciousness, and autonomic instability manifested by diaphoresis, tachycardia, labile or elevated blood pressure, and varying degrees of cyanosis. Catatonic signs aside from stupor and excitement are not uncommon. One large series *(18)* identified 62 patients with psychogenic MC and reported that each exhibited at least three catatonic features. In our 77 most recent cases, muscle rigidity was present in 27 of 34 (79%) cases in which muscle tone was characterized (Table 1).

Among the 77 recent MC cases, creatine phosphokinase (CPK) was elevated in 24 of 25 patients (96%) in whom it was tested. In this most recent series, leukocytosis was reported in 17 of 24 patients (71%) and serum transaminases were elevated in 10 of 20 patients (50%). Serum iron levels were obtained in only seven patients, but were decreased in all seven. Less consistent findings among the 77 recent cases included nonfocal generalized slowing on electroencephalography,

Table 1
Clinical Features of Malignant Catatonia

- Signs and symptoms
  - Hyperthermia
  - Catatonic excitement and/or stupor
  - Other catatonic features (e.g., mutism, negativism, catalepsy, posturing, echolalia, echopraxia, staring)
  - Muscular rigidity (variable)
  - Altered consciousness
  - Autonomic instability
    - Profuse diaphoresis
    - Tachycardia
    - Labile or elevated blood pressure
    - Tachypnea, cyanosis (variable)
- Positive laboratory findings
  - Most consistent—creatine phosphokinase elevation, leukcocytosis, low serum iron levels
  - Less consistent—elevated serum transaminases, generalized slowing on electroen cephalogram, hyperglycemia, elevated serum creatinine, hyponatremia, hypernatremia, dehydration, frontal atrophy on computed tomography or magnetic resonance imaging, decreased frontal perfusion on single photon-emission computed tomography

mild hyperglycemia, elevated serum creatinine, hyponatremia, hypernatremia, and dehydration. Philbrick and Rummans *(1)* found that three of five MC cases treated at their facility had evidence of frontal atrophy on computed tomography (CT) scans of the head. Furthermore, one patient with a normal head CT had decreased frontal perfusion on posttreatment single photon-emission computed tomography imaging. In 49 (13%) of the 369 contemporary cases, a preexisting illness was believed to have initiated the full syndromal picture of MC *(8)*. Reports of infectious causes predominated, including 19 cases of acute or postinfectious viral encephalitis; single cases of Borrelia encephalitis, general paresis, bacterial meningoencephalitis, viral hepatitis; bacterial septicemia that evolved from five cases of endometritis, and from single cases each of pyelonephritis, tuberculosis of the large intestine, aortitits, cholangitis, endocarditis, and gingival abscess *(4,8)*. In two cases of septic origin, the original focus of infection was not indicated *(4,8)*. Cerebrovascular thrombosis accounted for two cases, and MC developed in the context of normal-pressure hydrocephalus in another *(4,8)*. Reports of metabolic disorders causing MC included hyperthyroidism (two cases), and single cases of uremia, systemic lupus erythematosus, and cerebral anoxia *(4,8)*. Reports of toxic causes included single cases resulting from tetraethyl lead poisoning, sedative-hypnotic withdrawal, renal transplantation, toxic epidermal necrolysis, and therapeutic ingestion or overdose of cyclobenzaprine *(4,8)*.

Of the 369 cases, 320 (87%) were considered the outgrowth of a major psychotic disorder, diagnosed as schizophrenia in 126 cases, mania in 13 cases, major depression in 22 cases, psychotic disorder not otherwise specified in 22 cases, and "periodic catatonia" in 10 cases. Among these 320 MC cases arising from the major psychoses, 163 (51%) ended in death and 99 went to autopsy *(7,8)*. Seventy-nine of the 99 proved autopsy negative. In the remaining 20 cases, however, death could be attributed to specific consequences of catatonic immobility, such as deep venous thrombosis with pulmonary embolism. These cases of simple (benign) catatonia rendered fatal by severe intercurrent medical complications were differentiated from "genuine" psychogenic MC.

THE MALIGNANT CATATONIA SYNDROME

Our review of the modern world literature supports Kraepelin's belief that MC represents a syndrome rather than a specific disease, and that it may occur in association with diverse neurologic, medical, drug-induced, and psychiatric illnesses. Other causes of MC not found in the 369 cases but mentioned by recent reviewers include Addison's disease, Cushing's disease, brain tumors, seizure disorders, and traumatic brain injuries *(4,8)*. Furthermore, clinical pictures like that of MC, although not identified as such, are described elsewhere in the medical literature *(4,8)*. Although lesions of diencephalic and limbic structures are frequently reported, a wide array of additional toxic, metabolic, and generalized infectious causes are also mentioned. Table 2 summarizes known causes of the MC syndrome.

Consistent with a conceptualization of MC as a nonspecific syndrome, it is appropriate to consider its relationship to NMS. Among the 369 contemporary MC cases, the "classic" excited form (patient 1) involving extreme hyperactivity and progressive hyperthermia prior to the onset of stupor has continued to predominate, accounting for 67% of reported cases. Still, this represents a decrease from the pre-antipsychotic drug era when 90% of cases presented with excitement. Thirty-three percent of cases exhibited a primarily stuporous course (patient 2), up from 10% during the pre-antipsychotic drug era. Furthermore, a selective analysis of the 77 MC cases reported since 1986 indicates that this trend has continued, with 57% exhibiting excitement and 43% now presenting as stupor *(8,9)*. In many of these cases involving a primarily stuporous course, stupor and hyperthermia developed only after the initiation of antipsychotic drug treatment, giving rise to questions concerning the demarcation of MC from NMS.

On casual inspection, those psychogenic MC cases occurring during antipsychotic drug treatment in which stupor is preceded by a classic stage of extreme motoric excitement seem to resemble NMS, because NMS is often preceded by hyperactivity *(8,9,12)*. However, the hyperactivity observed in NMS prior to the onset of stupor is unassociated with the dramatically progressive temperature elevations characteristic of the excited stage of "classic" MC. Rather, in NMS, hyperthermia usually emerges with the onset of stupor and rigidity. Thus, "classic" MC that presents with initial excitement may be distinguishable from NMS on the

Table 2
Disorders Associated With Malignant Catatonia Syndrome

- Psychiatric disorders
  Schizophrenia
  Mood disorders
  Periodic catatonia
  Psychotic disorder not otherwise specified
- Cerebrovascular disorders
  Basilar artery thrombosis
  Bilateral hemorrhagic infarction of the anterior cingulate gyri
  Bilateral hemorrhagic lesions of temporal lobes
- Other central nervous system causes
  Normal-pressure hydrocephalus
  Seizure disorders
    Autonomic (diencephalic) epilepsy
    Petit mal status
  Cerebral anoxia
- Tumors
  Periventricular diffuse pinealoma
  Glioma of the third ventricle
  Glioma involving the splenium of the corpus callosum
  Angioma of the midbrain
- Head trauma
  Closed head trauma
  Surgical removal of lesions near the hypothalamus
- Infections
  Viral encephalitis—acute or postinfectious
  Borrelia encephalitis
  Bacterial meningoencephalitis
  General paresis
  Viral hepatitis
  Bacterial septicemia
- Metabolic disorders
  Hyperthyroidism
  Addison's disease
  Cushing's disease
  Uremia
  Wernicke's encephalopathy
  Systemic lupus erythematosus
- Toxic disorders
  Postoperative states
  Sedative-hypnotic withdrawal
  Tetraethyl lead poisoning
  Cyclobenzaprine toxicity
  Toxic epidermal necrolysis
  Neuroleptic malignant syndrome

basis of a well-documented history of extreme hyperthermia present in the excited phase.

However, we were able to identify 76 patients (21%) from the series of 369 MC cases whose clinical phenomenology appeared equally consistent with a diagnosis of NMS. These were patients who developed a hyperthermic catatonic stupor during antipsychotic drug treatment, and who, if initially excited, had been free of significant hyperthermia during that excited phase. Thus, 21% of the contemporary MC cases did, in fact, appear clinically indistinguishable from NMS. Viewing MC as a syndrome that may occur as an outgrowth of both the major psychoses and diverse conditions, we have suggested that NMS represents an antipsychotic drug-induced toxic or iatrogenic form of MC. Accordingly, the emergence of NMS as an antipsychotic drug-induced subtype of MC could help explain the increased frequency of primarily stuporous MC cases reported in the contemporary literature.

The recognition that MC is a well-defined neuropsychiatric syndrome that occurs in association with both medical and psychiatric disorders has significant clinical implications. The worldwide prevalence of MC has probably declined in recent years; the effects of modern psychopharmacological agents and other advances in medical care have likely altered the course of underlying disorders associated with the syndrome, thereby reducing the frequency with which these disorders progress to MC. However, it appears likely that lack of familiarity with MC resulting from barriers of time, language, culture, and diagnostic systems has contributed to the relatively rare mention in the contemporary North American literature. MC involves a dramatic admixture of medical and behavioral manifestations, and unless clinicians are armed with an appreciation of MC as a syndrome with diverse etiologies, patients are likely to be labeled "psychiatric" or "medical" largely on the basis of the treating physician's orientation.

Clearly, it is difficult for clinicians to accept that high fever and confusion may occur as a direct outgrowth of a psychiatric condition. Hafner and Kafner *(17)* concluded that even in Germany, where MC appears better recognized, neurologists and internists rather than psychiatrists now more commonly care for patients who previously would have been diagnosed with MC. These patients are likely to receive diagnoses such as "nonspecific organic encephalopathy with fever." Conversely, reports resembling those on viral encephalitis "imitating" catatonic schizophrenia indicate that failure to recognize MC may result in a narrow focusing on behavioral manifestations, with neglect of ominous physical signs *(20)*. Once developed, MC, independent of etiology, assumes an autonomous and frequently fatal course. Only with prompt recognition of this distinctive syndrome can the proper diagnostic evaluation and treatment be initiated.

PATHOPHYSIOLOGY

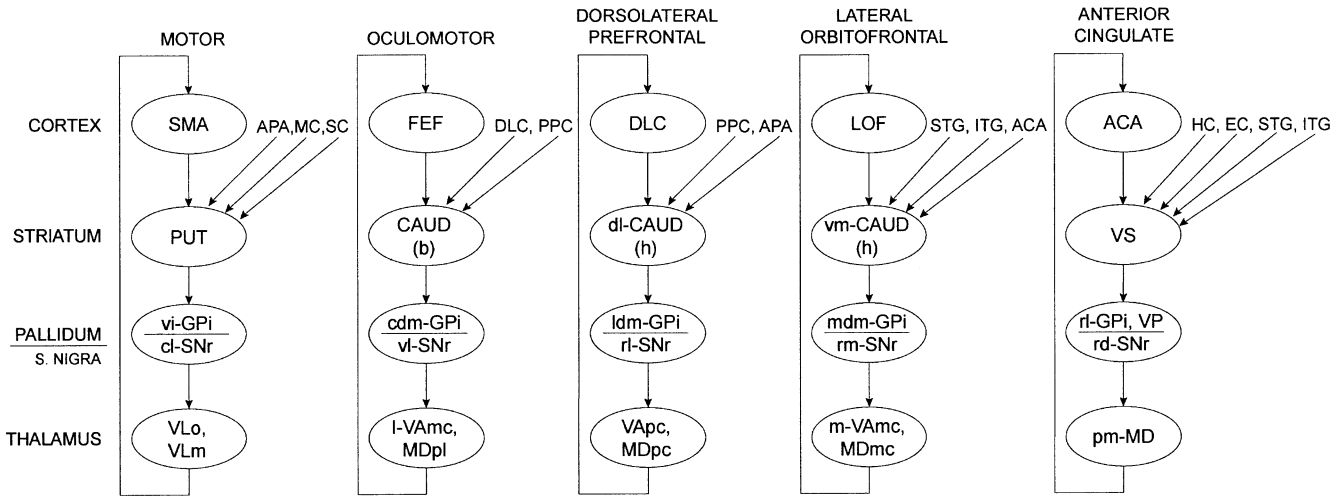
A consideration of the pathogenesis of MC with a particular focus on the dopamine system further supports a view of NMS as a subtype of this disorder. A number of authors have posited a key role for dopaminergic hypoactivity in triggering MC

(1,4,8,9,20,21). Furthermore, there is compelling clinical evidence implicating antipsychotic drug-induced dopamine receptor blockade in the pathogenesis of NMS *(8,22,23)*. Recently, Fricchione *(20,21)* along with our group *(8,9)* has proposed that the onset of MC coincides with a reduction in dopaminergic activity within the frontal subcortical circuits. As elucidated by Alexander *(24,25)*, these circuits represent one of the brain's principal organizational networks underlying brain–behavior relationships. Five circuits connecting the basal ganglia with their associated areas in the cortex and thalamus have been identified and are named according to their cortical site of origin (Fig. 1). They include the "motor circuit," the "oculomotor circuit," the " dorsolateral prefrontal circuit," the "lateral orbitofrontal circuit," and the "anterior cingulate circuit." Each circuit involves the same member structures, including an origin in a specific area of the frontal cortex; projections to the striatum (putamen, caudate, and ventral striatum); connections to the globus pallidus interna and the substantia nigra pars reticulata; which, in turn, project to specific thalamic nuclei; and a final link back to the frontal area from which they originated, thus creating a feedback loop.

Dopamine is in a key position to influence activity in each of these circuits. Mesocortical dopaminergic pathways project directly to circuit areas of origin in the motor area, frontal eye fields, and the prefrontal cortex. Additionally, dopamine modulates each circuit through its projections to the striatum *(26)*. The motor, the anterior cingulate, and the lateral orbitofrontal circuits represent the most likely candidates for involvement in the pathogenesis of MC and NMS.

Specifically, the onset of hypodopaminergia in the motor circuit may account for muscular rigidity *(8,9,23)*. In addition, hypodopaminergia developing in the anterior cingulate circuit could participate in causing diminished responsiveness, akinesia, mutism, and contribute to hyperthermia and autonomic dysfunction. Bilateral lesions of the anterior cingulate have been associated with akinetic mutism, a profound amotivational state in which patients remain akinetic, mute, and minimally responsive to environmental stimuli *(26)*. Akinetic mutism has been mistaken for simple psychogenic catatonia. Furthermore, certain cases of akinetic mutism have presented with hyperthermia and autonomic dysfunction, making them difficult to distinguish from MC *(8,9,22,23)*. In this regard, it is of considerable interest that the anterior cingulate subcortical circuit contains a spur, which projects from the ventral pallidum to the lateral hypothalamus *(27)*. This suggests that reduced dopaminergic activity could cause hyperthermia and autonomic dysfunction in MC through disruption of anterior cingulate circuit transmission to the lateral hypothalamus.

Finally, hypodopaminergia involving the lateral orbitofrontal subcortical circuit may mediate selected catatonic features observed in MC. Dysfunction in the lateral orbitofrontal region has been associated with utilization and imitation behaviors *(26)*. These behaviors involve automatic imitation of the gestures and actions of others or inappropriate use of objects such as tools or utensils. Utilization and imitation behaviors reflect enslavement to environmental cues *(26)* and share striking



ACA= anterior cingulate area
APA= arcuate premotor area
CAUD= caudate
(b)= body
(h)= head
DLC= dorsolateral prefrontal cortex
EC= entorhinal cortex
FEF= frontal eye fields
GPI= internal segment of globus pallidus
HC= hippocampal cortex
ITG= inferior temporal gyrus
LOF= lateral orbitofrontal cortex
MC= motor cortex

MD= medialis dorsalis
MDpl= medialis dorsalas pars paralamellaris
MDmc= medialis dorsalis pars magnocellularis
MDpc= medialis dorsalis pars parvocellularis
PPC= posterior parietal cortex
PUT= putamen
SC= somatosensory cortex
SMA= supplementary motor area
SNr= substancia nigra pars reticulata
STG= superior temporal gyrus
VAmc= ventralis anterior pars magnocellularis
VApc= ventralis anterior pars parvocellularis
VLm= ventralis lateralis pars medialis
VLo= ventralis lateralis pars oralis
VP= ventral pallidum
VS= ventral striatum

cl= caudolateral
cdm= caudal dorsalmedial
dl= dorsolateral
l= lateral
ldm= lateral dorsomedial
m= medial
mdm= medial dorsomedial
pm= posteromedial
rd= rostrodorsal
rl= rostrolateral
rm= rostromedial
vm= ventromedial
vl= ventrolateral

Fig. 1. Proposed basal ganglia-thalamocortical circuits. Parallel organization of the five basal ganglia-thalamocortical circuits. Each circuit engages specific regions of the cerebral cortex, striatum, pallidum, substantia nigra an thalamus. (Adapted from ref. *24* with permission.)

clinical similarities with catatonic features such as echopraxia, echolalia, and gegenhalten, all of which are viewed as stimulus-bound or motor perseverative phenomena consistent with frontal lobe dysfunction *(28)*. Utilization and imitation behaviors may also occur in association with dorsolateral prefrontal circuit dysfunction.

Recently, we have proposed that in addition to dopamine-2 receptor blockade, NMS is the product of preexisting central dopaminergic hypoactivity that represents a trait vulnerability marker for this disorder, coupled with state-related downward adjustments in the dopamine system occurring in response to acute or repeated exposure to stress *(8,23)*. Here, we suggest that such state and trait-related factors might also be critical in causing hypodopaminergia in the frontal subcortical circuits in MC. A number of lines of evidence indicate that certain individuals may exhibit baseline hypodopaminergia, including reduced homovanillic acid (HVA) levels in post-NMS patients; reduced striatal HVA levels or lack of elevated HVA to dopamine ratios in patients who died from MC or NMS; lower cerebrospinal fluid HVA levels and more severe baseline parkinsonian symptoms in patients with Parkinson's disease following recovery from NMS; and reports of abnormalities in the dopamine-2 receptor gene in NMS *(8,23)*.

Furthermore, the enhanced responsiveness of the dopamine system to stress may be implicated as a state-related co-factor predisposing to MC. In particular, the dopaminergic innervation of the medial prefrontal cortex in the rat is unique in that very mild stressors, such as limited foot shock or conditioned fear, activate it *(29)*. In addition, there is considerable data indicating a functional interdependence of dopamine systems innervating the medial prefrontal cortex and subcortical dopamine systems; changes in the medial prefrontal cortex dopamine system appear to have an inverse relationship with dopamine turnover in the dorsal and ventral striatum *(30)*. Accordingly, if stress activates the stress-sensitive mesocortical dopaminergic pathway to the medial prefrontal cortex, it could have direct feedback effects in the dorsal and ventral striatum, rendering these areas hypodopaminergic and predisposing to MC in individuals with preexisting central dopaminergic hypoactivity.

EVALUATION AND TREATMENT

Familiarity with the distinctive clinical features and varied etiologies of MC is essential for effective management of this potentially fatal condition. In both clinical vignettes, it was critical to exclude medical or drug-induced causes of MC before assigning a psychiatric etiology. The diagnostic evaluation should include a complete personal and family psychiatric history; a medical history; a drug use history with specific reference to antipsychotics and drugs of abuse; a complete physical examination with particular attention to neurological findings; and a comprehensive laboratory evaluation including a complete blood count, assessment of electrolyte levels, blood, urine, and sputum cultures for bacteria and fungi, viral studies, a urinalysis, a Venereal Disease Research Laboratory slide test, assessment of serum calcium, phosphorous, serum iron, and serum CPK levels, thyroid and

adrenocortical studies, an electroencephalogram, and a CT or magnetic resonance image of the head. Although "Amytal interviews" may be helpful in differentiating benign psychogenic catatonias from those with a medical basis, there is no available data concerning the value of this procedure in evaluating MC. The potential for severe autonomic symptoms and high rate of medical complications dictate early institution of intensive medical care focusing on fluid replacement, temperature reduction, and support of cardiac, respiratory, and renal functions. Careful monitoring for complications, particularly aspiration pneumonia, thromboembolism, and renal failure, is essential.

Many clinicians, not recognizing the syndrome they are witnessing, are apt to treat the patient's unusual symptoms with antipsychotic drugs. However, the bulk of evidence indicates that the dopamine receptor blocking effects of antipsychotics are likely to aggravate MC episodes, as in NMS where continuation of antipsychotic drug treatment clearly increases the likelihood of death. Antipsychotics should be withheld whenever MC is suspected.

Benzodiazepines have been highly effective in the treatment of simple (benign) catatonia, including antipsychotic drug-induced catatonia *(21,22)*. Philbrick and Rummans *(1)* observed that the benefits of benzodiazepines in MC appeared less uniform than in simple catatonia, but were nonetheless impressive at times. They asserted that even a partial response might be beneficial and retard the progression of MC until more definitive treatment can be initiated. Fricchione *(21,22)* suggested that if simple catatonia proves unresponsive to benzodiazepines after five days of treatment, electroconvulsive therapy (ECT) should be considered as a definitive measure. In MC, however, these researchers argued against a 5-day wait and urged that ECT be started if benzodiazepines do not briskly reverse the MC process. Such was the case in patient 2 where 2 days of intravenous lorazepam therapy was without benefit. Lack of response led to early initiation of ECT followed by dramatic resolution of MC.

Indeed, ECT has been viewed as a safe and effective treatment for MC when it occurs as an outgrowth of a major psychotic disorder *(4,5,8,9)*. Although controlled studies are lacking, case reports as well as series of consecutive cases indicate excellent results with its use. Among 50 patients reported in four large series *(4)*, 40 of 41 patients treated with ECT survived. In contrast, only 5 of 9 who received only antipsychotics and supportive care recovered. Similarly, in Philbrick and Rummans' *(1)* review of 18 MC cases, 11 of 13 treated with ECT survived, compared with only 1 of 5 who did not receive ECT.

ECT appears effective, however, only if initiated before severe progression of MC symptoms. Sedvic *(31)* reported that the onset of coma or a temperature in excess of 41°C predicts a poor response even to ECT. Arnold and Stepan *(12)* found that in 19 patients starting ECT within 5 days of the onset of hyperthermia, 16 survived, whereas in 14 patients who began treatment beyond this 5-day point, ECT had no effect in preventing a fatal outcome. Although earlier protocols called for particularly intensive treatment *(12)*, recent trials have indicated that ECT can be efficacious when given (usually bilaterally) once or twice daily or every other

day for a total of 5 to 15 treatments *(4,5)*. Substantial improvement often becomes evident after one to four treatments. There can be little doubt that prompt initiation of ECT represented a life-saving intervention in both of our clinical vignettes.

Other data, also anecdotal, suggests that MC resulting from the major psychoses can be effectively treated with adrenocorticotropic hormone (ACTH) and corticosteroids *(4,8,9)*. However, because severely ill patients have tolerated ECT without incident, and because the utility of hormonal therapy is less well documented, ECT appears to be the preferred treatment. ACTH and corticosteroids may be used if ECT proves ineffective. A few patients have been treated successfully with artificial hibernation *(4,8)*. Although this procedure is fraught with hazards, it may have a place in cases of MC that do not respond to ECT or hormonal treatment.

Several investigators have suggested that ECT in combination with dantrolene, a drug that inhibits contraction and heat production in muscle, represents the optimal treatment for MC *(8,9)*. Additional cases have involved successful treatment with dantrolene alone; bromocriptine, dantrolene, and ECT; bromocriptine and benzodiazepines; and dantrolene and bromocriptine *(8,9)*.

In MC occurring as an outgrowth of a medical illness, treatment must first be corrected at the underlying disorder. Nevertheless, anecdotal reports have described ECT as dramatically effective and at times life saving in suppressing the symptoms of MC-like states complicating a diversity of medical conditions *(4,5,8,9)*. In such cases, the efficacy of ECT appears largely independent of the underlying illness, and improvement is likely to be transient if the medical condition persists. If, however, the underlying disorder either remits or is corrected, permanent recovery may be possible. Consistent with the above discussion, ECT has used effectively in the treatment of NMS.

CONCLUSION

MC represents a life-threatening neuropsychiatric disorder described long before the introduction of antipsychotic drugs. A review of the world literature on MC indicates that although the incidence of the condition may have declined since the pre-antipsychotic drug era, it continues to occur and is now reported more frequently in foreign publications. Lack of recognition probably accounts for the relative paucity of contemporary North American reports of the disorder. Failure to recognize MC has significant clinical implications because once developed this condition assumes an autonomous and potentially fatal course.

Furthermore, MC is a syndrome rather than a specific disease entity. Although most often presenting as an outgrowth of the major psychoses, MC may occur in association with diverse medical conditions. From this perspective, NMS may be conceptualized as a drug-induced form of MC. The hypothesis that MC and NMS share a common pathophysiology involving reduced dopaminergic functioning in the frontal–subcortical circuits provides additional support for a view of NMS as a subtype of MC. ECT appears to be the preferred treatment for MC stemming from a major psychotic disorder and also may be effective in cases occurring as an out-

growth of a medical illness. However, it is imperative in the latter cases to identify and correct the underlying disorder. Antipsychotic drugs should be withheld whenever MC is suspected.

REFERENCES

1. Philbrick KL, Rummans TA. Malignant catatonia. J Neuropsychiatry Clin Neurosci 1994;6:1–13.
2. Calmeil LF. Dictionnaire de Medecine ou Repertoire General des Sciences. Medicales sous le Rapport Theorique et Practique (2nd ed). Bechet, Paris: 1832.
3. Bell LV. On a form of disease resembling some advanced stages of mania and fever. Am J Insanity 1849;6:97–127.
4. Mann SC, Caroff SN, Bleier HR, et al. Lethal catatonia. Am J Psychiatry 1986;143:1374–1381.
5. Mann SC, Caroff SN, Bleier HR, et al. Electroconvulsive therapy of the lethal catatonia syndrome: case report and review. Convuls Ther 1990;6:239–247.
6. Mann SC, Caroff SN. Lethal catatonia and the neuroleptic malignant syndrome. In: Stefanis CN, Rabavilas AD, Soldatos CR, eds. Psychiatry: A World Perspective, Vol 3. Elsevier Science, Amsterdam: 1990;287–292.
7. Mann SC, Auriacombe M, Macfadden W, et al. [Lethal catatonia: clinical aspects and therapeutic intervention. A review of the literature]. Encephale 2001;27:213–216.
8. Mann SC, Caroff SN, Keck PE Jr, et al. The Neuroleptic Malignant Syndrome and Related Conditions, Second Edition. American Psychiatric Publishing, Washington, DC: 2003.
9. Mann SC, Caroff SN, Fricchione G, et al. Malignant catatonia. In: Caroff SN, Mann SC, Francis A, et al., eds. Catatonia: From Psychopathology to Neurobiology, American Psychiatric Publishing, Washington, DC, 2004, pp. 105–119.
10. Stauder KH: Die todliche Katatonie. Archiv fur Psychiatr Nervenkrantz 1934;102:614–634.
11. Caroff SN. The neuroleptic malignant syndrome. J Clin Psychiatry 1980;41:79–83.
12. Shulack NR. Exhaustion syndrome in excited psychotic patients. Am J Psychiatry 1946;102:466–475.
13. Arnold OH, Stepan H. Untersuchungen zur Frage der akuten todlichen Katotonie. Wiener Zeitschrift fur Nervenheilkunde und Deren Grenzgebiete 1952;4:235–258.
14. Kraepelin E. Johnstone T, ed. Lectures on Clinical Psychiatry (2nd ed). William Wood, New York: 1905.
15. Ladame C. Psychose aigue idiopathique ou foudroyante. Schweizer Archiv fur Neurologic und Psychiatrie 1919;5:3–28.
16. Koziel-Schminda E. "Ostra Smierteina Katatonia" Typu Staudera O Przebiegu Letalnym (Analiza Materialow Kliniczynch I Sekcyjnch Szpitala W Kochborowie Z Lat 1950-1970). Psychiatr Pol 1973;7:563–567.
17. Hafner H, Kasper S. Akute lebensbedrohliche Katatonie: Epidemiologische und Klinische Befunde. Nervenzart 1982;53:385–394.
18. Singerman S, Raheja R. Malignant catatonia—a continuing reality. Ann Clin Psychiatry 1994;6:259–266.
19. Wilson LG. Viral encephalopathy mimicking functional psychosis. Am J Psychiatry 1976;133:165–170.
20. Fricchione G, Bush G, Fozdar M, et al. Recognition and treatment of the catatonic syndrome. J Intensive Care Med 1997;12:135–147.
21. Fricchione G, Mann SC, Caroff SN. Catatonia, lethal catatonia, and neuroleptic malignant syndrome. Psychiatr Ann 2000;3:347–355.
22. Mann SC, Caroff SN, Lazarus A. The pathogenesis of neuroleptic malignant syndrome. Psychiatr Ann 1991;21:175–180.
23. Mann SC, Caroff SN, Fricchione G, et al. Central dopamine hypoactivity and the pathogenesis of neuroleptic malignant syndrome. Psychiatr Ann 2000;30:363–374.
24. Alexander GE, DeLong MR, Strick PL. Parallel organization of functionally segregated circuits linking basal ganglia and cortex. Ann Rev Neurosci 1986;9:357–381.

25. Alexander GE, Crutcher MD, DeLong MD. Basal ganglia-thalamocortical circuits: parallel substrates for motor, oculomotor, "prefrontal" and "limbic" functions. Prog Brain Res 1990;85:119–146.
26. Cummings JL. Frontal-subcortical circuits and human behavior. Arch Neurol 1993;50:873–880.
27. Deutch AY, Bourdelais AJ, Zahm DS. The nucleus accumbens core and shell: accumbal compartments and their functional attributes. In Kalivas PW, Barnes CD, eds. Limbic Motor Circuits and Neuropsychiatry. CRC, Boca Raton FL: 1993;163–175.
28. Taylor MA. Catatonia: a review of a behavioral neurologic syndrome. Neuropsychiatry Neuropsychol Behav Neurol 1990;3:48–72.
29. Thierry AM, Tassin JP, Blanc G, et al. Selective activation of the mesocortical dopamine system by stress. Nature 1976;263:242–244.
30. Pycock CL, Kerwin RW, Carter CJ. Effects of lesion of cortical dopamine terminals on subcortical dopamine receptors in rats. Nature 1980;286:74–76.
31. Sedivic V. (Psychoses endangering life). Cesk Psychiatr 1981;77:38–41 (in Czech).

6

Abductor Paresis in Shy-Drager Disease

Eiji Isozaki

PATIENT VIGNETTES

Patient 1: A 55-year-old woman was admitted to our hospital because of progressive parkinsonism. She was diagnosed with striatonigral degeneration. Because of nocturnal snoring, a fiberoptic laryngoscopy was performed during wakefulness, showing a mild abduction restriction of the vocal cords. Arterial blood gas analysis was normal. Over the next year, she developed inspiratory stridor during wakefulness, especially while talking. A second fiberoptic laryngoscopy during wakefulness showed a narrower glottic aperture as compared with the previous examination. Arterial blood gas analysis showed only mild hypoxemia: pH = 7.44, pCO2 = 43 Torr, PO2 = 72 Torr. At this point, she had no dyspnea and could still speak and eat. Only 3 weeks after admission, she was found in a cardiopulmonary arrest in her bed at 8 PM, only 15 minutes after she was heard snoring as usual.

A diagnosis of multiple system atrophy (MSA) was confirmed on postmortem neuropathological examination. The posterior cricoarytenoid muscle—the laryngeal abductor—showed severe neurogenic atrophy. Neither pneumonia nor intratracheal secretions were present to explain her sudden death.

Patient 2: A 74-year-old man, who was diagnosed with MSA 9 years before, was readmitted to our hospital in 1999 because of pneumonia. A fiberoptic laryngoscopy showed no laryngeal abnormalities during wakefulness and diazepam-induced sleep (stage 0). In February 2000, he developed nocturnal snoring. On fiberoptic laryngoscopy, moderately severe vocal cord abductor paresis (VCAP) with abduction restriction during wakefulness and paradoxical movement during sleep was seen (stage 2). The posterior glottis could not be observed well. On an overnight recording of percutaneous arterial blood oxygen saturation (SpO2), no desaturation less than 90% was demonstrated. Arterial blood gas analysis on room air was normal. He was discharged on August 14, 2000, when he was still able to eat, and his nocturnal snoring was not so loud as to disturb other patients in the same room. Only 1 week later, he was readmitted to our hospital because of increasing snoring. Arterial blood gas analysis on oxygen inhalation with 2 l/m when awake showed pH = 7.39, pCO2 = 51 Torr, and pO2 = 88 Torr. On physical findings, his suprasternal recess became hollow during

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

every inspiration. On August 23, 2000, a fiberoptic laryngoscopy during wakefulness demonstrated severe VCAP with slit-like aperture of the glottis (stage 3), requiring emergency intratracheal intubation. After tracheostomy was performed 10 days later, he could speak with a speech valve. Arterial blood gas analysis on room air became normal: pH = 7.46. pCO2 = 45 Torr, pO2 = 82 Torr. No oxygen desaturation less than 90% of SpO2 was demonstrated on an overnight recording.

INTRODUCTION

In 1976, Holinger analyzed 389 patients with vocal cord abductor paresis (VCAP) in various diseases including poliomyelitis, Parkinson's disease (PD), cerebrovascular accidents, Guillain-Barré syndrome, and multiple sclerosis *(1)*. Spinocerebellar degeneration was not included in his list, and the concept of multiple system atrophy (MSA) was not established at that time. Investigators reported that patients with MSA, including olivopontocerebellar atrophy, striatonigral degeneration, and Shy-Drager syndrome, developed laryngeal complications such as velopharyngolaryngeal paralysis *(2)*, upper airway obstruction *(3)*, and vocal cord palsy *(4)*. In 1981, Bannister reported three necropsied MSA cases in which the posterior cricoarytenoid muscles showed neurogenic atrophy, whereas the nucleus ambiguus, innervating the abductor muscle, demonstrated no neuronal loss *(5)*. Selective neurogenic atrophy of the abductor muscle, among all the intrinsic laryngeal muscles, has been confirmed histologically *(2,5,6)* and electromyographically *(7)* in MSA. The myelinated nerve fibers of the recurrent laryngeal nerve (which innervates all the intrinsic laryngeal muscles) are decreased in number *(8)*. However, it is controversial whether the nucleus ambiguus is involved *(2,6)* or not *(5,9)*. Electromyographical studies support laryngeal dystonia *(10,11)* or dyskinesia *(12)* as possible mechanisms of VCAP.

MECHANISM

Although the pathophysiology of VCAP in MSA has not been fully clarified, we propose the following hypothesis (Fig. 1): neurogenic atrophy of the posterior cricoarytenoid muscle, the sole abductor of the vocal cords, is caused by neuronal loss in the nucleus ambiguus. In addition to weakening of the abductor, initiation of abduction becomes delayed. During normal inspiration, the laryngeal abductor muscles contract first, and then the diaphragm contracts to avoid upper airway collapse. However, in patients with MSA and VCAP, inspiratory negative pressure caused by diaphragm contraction occurs concurrent with or even before full opening of the vocal glottis, because of the delay in abductors. This results in laryngeal collapse *(13)*. Paradoxical movement of the vocal cords occurs, with inspiratory adduction and expiratory abduction *(14)*. Sleep enhances VCAP because it increases upper airway resistance *(15)*. In the early stage of VCAP, the stenotic breathing from obstruction in the upper airway is recognized as a snoring only during sleep. Then, in the advanced stage, audible daytime inspiratory stridor occurs, often on talking. This daytime inspiratory stridor can be misdiagnosed as pseudo-steroid resistant asthma *(16)*.

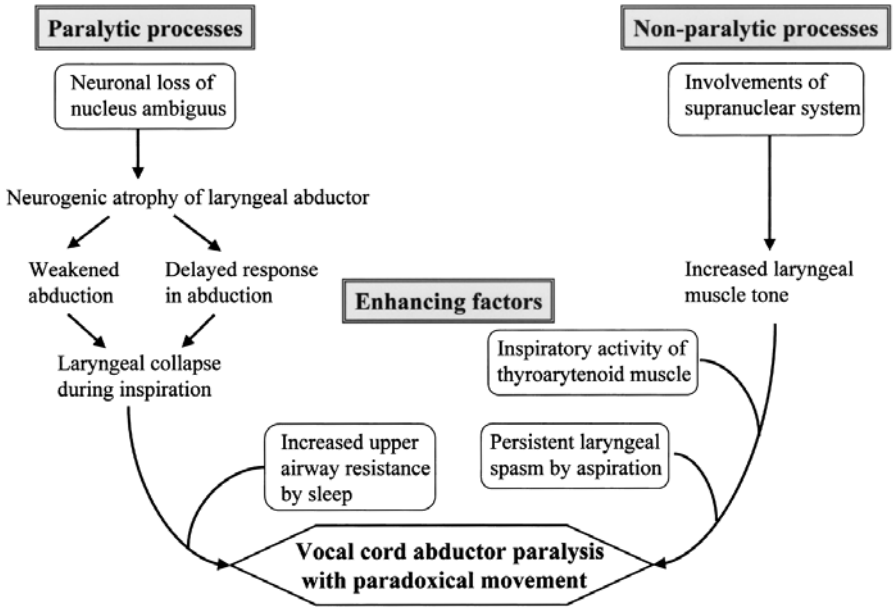


Fig. 1. Mechanism of vocal cord abductor paralysis (VCAP) in multiple system atrophy. VCAP is caused by multifactorial mechanisms including paralytic processes, nonparalytic processes, and enhancing factors.

In addition to abductor denervation, degenerative changes of the pyramidal and the extrapyramidal tracts in MSA contribute to increased laryngeal muscle tone. Inspiratory phasic activity of the thyroarytenoid muscle, one of the vocal cord adductors, may also participate in the development of VCAP *(17,18)*. Aspiration, if present, may stimulate the laryngeal mucosa intermittently, resulting in laryngeal reflective narrowing as a defensive response. This reflex may be exaggerated by pseudobulbar palsy as a result of pyramidal tract involvements, resulting in prolonged laryngospasm. A nonparalytic mechanism with the increased adductor tone resembles VCAP in PD, in which no morphological abnormalities are found in the abductor *(19)*. Thus, VCAP in MSA is multifactorial, including paralytic and nonparalytic mechanisms.

EVALUATION AND TREATMENT

VCAP can appear at any time in the course of MSA, even as an initial *(20)* or an isolated *(21)* symptom. From our study of 23 cases of MSA with VCAP, VCAP tended to appear around the time when urinary incontinence was noticed *(22)*.

Symptoms suggestive of VCAP include loud nocturnal snoring, daytime inspiratory stridor, and inspiratory hollow at the suprasternal recess. On auscultation, snoring and daytime inspiratory stridor are louder in the neck than the chest. Snor-

ing is loud and high-pitched with some limpidity *(13,21)*, often described as metallic, croup-like, or "donkey-braying" in quality *(5)*. Although respiration during sleep is often tachypneic in MSA patients presenting with VCAP *(17)*, apnea or hypopnea may also occur. Loud snoring may be the sole symptom both in patients with VCAP and sleep apnea; however, these conditions are quite different in etiology, and should be distinguished as shown in Table 1.

A definite diagnosis of VCAP is made by fiberoptic laryngoscopy performed during both wakefulness and sleep. We classified the severity of VCAP into four stages from stage 0 (normal) to stage 3 (severe VCAP), according to the mobility of the vocal cords (Table 2) *(14)*. VCAP in MSA is characterized by paradoxical movement of the vocal cords and sleep-induced exacerbation (Fig. 2). The vocal glottis consists of two parts: the anterior glottis, mainly involved with voicing, and the posterior glottis, which is involved with respiration. The patency of the posterior glottis determines the severity of VCAP. Therefore, we further divided stages 1 and 2 into two types according to the patency, or shape of the posterior glottis *(24)*. Triangular shape with some airway space (a), and slit-like shape with marked respiratory difficulties (b), are shown in Fig. 3. Needless to say, type b (stages 1b and 2b) is more serious than type a (stages 1a and 2a). In some cases, stage 1b is more serious than stage 2a.

Figure 4 shows a flow-chart for the diagnosis and evaluation of VCAP. In practice, when patients with MSA develop nocturnal snoring, a fiberoptic laryngoscopy is performed during both wakefulness, and sleep induced by intravenous administration of diazepam, in order to identify the source of the snoring. If the larynx is the culprit, stage classification of VCAP is determined according to the vocal cord movements shown in Table 2. In cases of stage 3 (and often severe stage 2b) VCAP, an emergency tracheostomy is indicated. In less severe stages, including stages 1a, 2a, 1b, and mild 2b, an overnight recording of blood oxygen saturation (SpO2) is performed. This examination gives the value of "%90," the percentage of time spent at less than 90% of SpO2. If the value of %90 is less than 20%, follow-up studies with fiberoptic laryngoscopy or overnight recording of SpO2 are repeated. However, if it is more than 20%, a tracheostomy is often needed. Thus, a tracheostomy is proposed when severity of VCAP approaches stage 2b (or sometimes stage 1b) and when the value of %90 reaches 20%. After sleep laryngoscopic examination, we routinely administer flumazenil to awaken the patient fully. Otherwise, the patient may fall sleep again, resulting in an unexpected exacerbation of VCAP.

There have been only a few reports on the acoustic analysis of nocturnal snoring *(13,23,25)*. Our previous study with a sound analyzer (Computerized Speech Lab, Model 4300, Kay Elemetrics Corp.) showed that the narrower the glottic aperture became, the higher the fundamental frequency of the vocal cord oscillation and the lower the voice turbulence index. Voice turbulence index is an acoustic parameter that shows the relative energy level of high-frequency noise. This index is thought to correlate with the turbulence caused by incomplete or loose adduction of the vocal cords.

Table 1
Difference Between Vocal Cord Abductor Paralysis and Sleep Apnea Syndrome

	Vocal cord abductor	Sleep apnea syndrome
1. Snoring		
Sound source	Larynx (vocal cord)	Pharynx (tongue base, etc.)
Fundamental frequency	Higher (200–500 Hz)	Lower (100–300 Hz)
Body position change	Almost noneffective	Usually effective
Nasal airway tube	Noneffective	Usually effective
Daytime inspiratory stridor	Existent	Nonexistent
2. Sleep apnea	Existent, but often tachypneic	Always present
3. Relationship with REM sleep	Poorer	Closer

REM, rapid eye movement.

Table 2
Stage Classification of Vocal Cord Abductor Paralysis on a Fiberoptic Laryngoscopy

Stage	Awake	Asleep	Posterior glottal shape during sleep[a]
0 (normal)	normal	unchanged	
1 (mild)	normal	paradoxical	1a: triangular, 1b: slit-like
2 (moderately)	abduction restriction	paradoxical	2a: triangular, 2b: slit-like
3 (severe)	midline fixation	midline fixation	

[a]Posterior vocal glottis is still patent with a triangular shape (a) and almost closed with a slit-like shape (b).

VCAP usually takes two different courses: slowly progressive and rapidly progressive. In the former, VCAP worsens gradually over 1 to 3 years as a result of paralytic denervation of the abductor. Repeated measurements of the value of %90 may be useful in evaluating a gradual progression of oxygen desaturation. In the rapidly progressive type, an emergency tracheostomy or a tracheal intubation is often needed, even if the patient is already known to have VCAP. This type seems to be caused by nonparalytic mechanisms, based on increased laryngeal muscle tone. In rapid exacerbations, however, one should also consider mechanical obstruction by secretions in the upper airway, and severity of SpO2 related to sleep depth in an overnight recording may be underestimated. If sleep depth is insufficient, VCAP may not be induced fully, resulting in seemingly "higher" SpO2 values than actual values. Often a rapid exacerbation appears after a slowly progressive course.

Tracheostomy is believed to be the most reliable, yet most invasive, procedure for VCAP. Other therapeutic options include arytenoidectomy, cord lateralization, cordectomy *(26)*, and botulinum toxin injection to the adductors *(27)*. Among these,

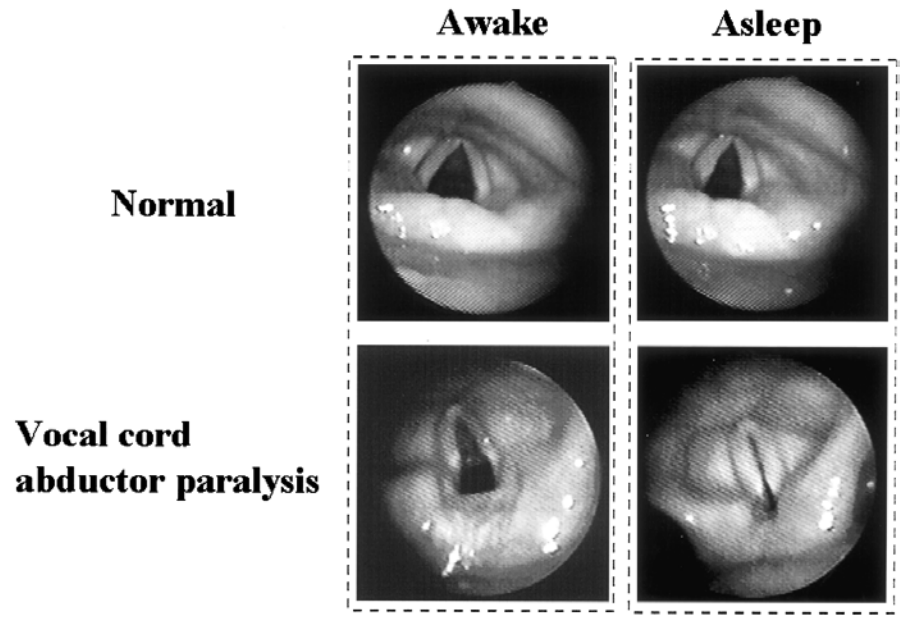


Fig. 2. Sleep-induced paradoxical movement of the vocal cords in multiple system atrophy (MSA). Vocal cord movement is almost not changed between wakefulness and sleep in normal subject. In patients with MSA, vocal cords show some abduction restriction during wakefulness, and adduct strongly with a slit-like glottis during sleep. Each fiberscopic photograph shows the inspiratory position of the vocal cords.

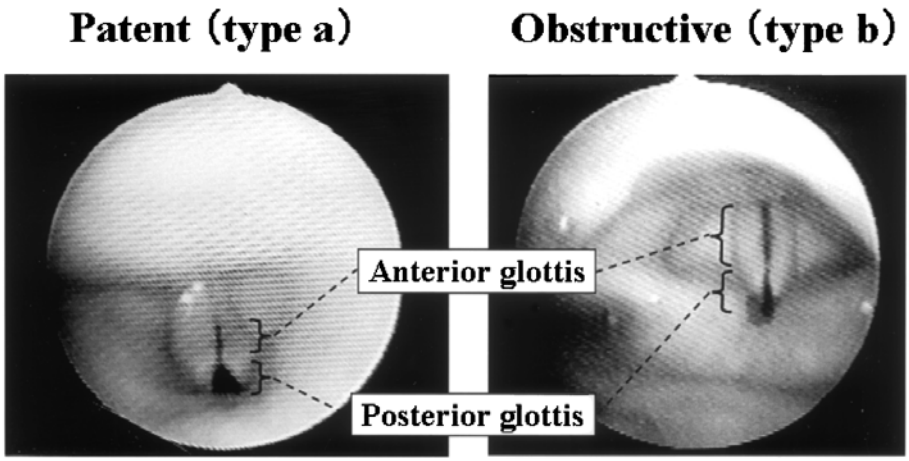


Fig. 3. Posterior glottis in the different two multiple system atrophy patients with vocal cord abductor paralysis. The posterior glottis is still patent, indicating type a (left), while almost closed with a slit-like aperture, indicating type b (right).

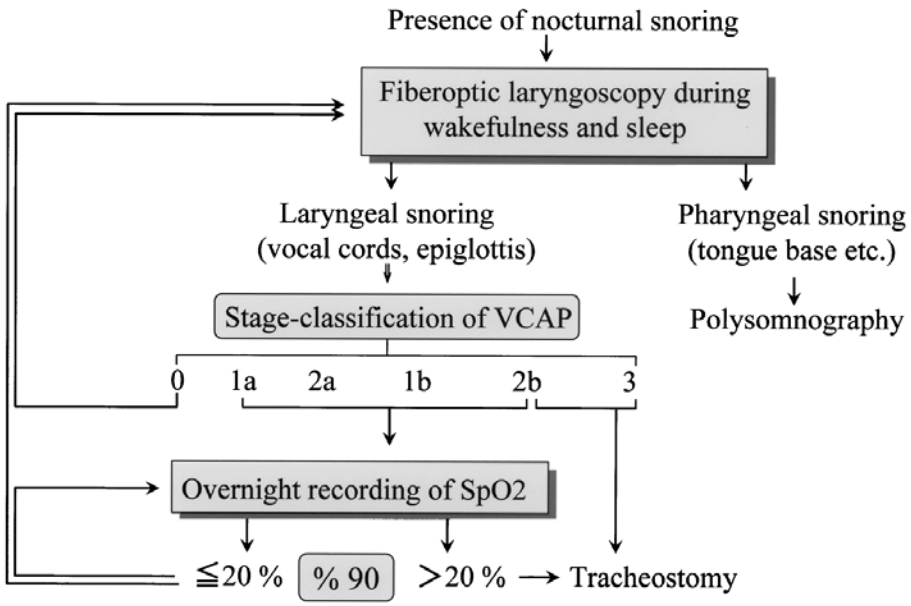


Fig. 4. A flow-chart for diagnosis and evaluation of vocal cord abductor paralysis (VCAP). A fiberoptic laryngoscopy is performed during wakefulness and sleep to identify the obstructive site causing snoring, and to classify the severity of VCAP. Application of a tracheostomy is determined by both findings of laryngoscopy and overnight recordings of SpO2.

only the first two have been attempted in patients with MSA *(28,29)*. Recently, an airway splint with nasal continuous positive airway pressure (CPAP) was used with some efficacy *(30,31)*. Although noninvasive and simple, the following problems have been reported: hypopharyngeal airway obstruction by a large and lax epiglottis in a patient with obstructive sleep apnea *(32)*, CPAP-induced laryngospasm in the experimental study using dogs *(33)*, and sudden death after bilevel positive airway pressure in a patient with primary pulmonary hypertension with central sleep apnea *(34)*. We have also seen an MSA patient with VCAP in whom CPAP eliminated paradoxical vocal cord movements.

The most difficult decision after making a diagnosis of VCAP is when therapeutic procedures, such as a tracheostomy, should be performed. There are no generally acceptable guidelines on the appropriate time to intervene with tracheostomy—too early, and patient's quality of life suffers; too late, and the patient may suffer sudden death. Patients 1 and 2 illustrate the difficult nature of this decision. Patient 1 could still eat and speak when the second fiberoptic laryngoscopy revealed an exacerbation of VCAP. Her arterial blood gas analysis on room air showed only mild hypoxemia. In this situation, can tracheostomy be recommended with confidence? Her sudden death only 3 weeks after admission without

Table 3
Vocal Cord Abductor Paralysis (VCAP) in Multiple System Atrophy

1. Clinical signs and symptoms
   - 1-1. Loud and high-pitched snoring, often associated with tachypnea
   - 1-2. Daytime inspiratory stridor during wakefulness in advanced stage
   - 1-3. Inspiratory hollow of the suprasternal recess
2. Diagnosis and stage classification
   - 2-1. Restricted abduction and full adduction of the vocal cords
   - 2-2. Paradoxical movement of the vocal cords showing inspiratory adduction and expiratory abduction
   - 2-3. Sleep-induced exacerbation or manifestation of VCAP
   - 2-4. Six stages in the severity of VCAP on a fiberoptic laryngoscopy (stage 0, 1a, 1b, 2a, 2b, 3)
3. Pathophysiology
   VCAP is caused by multifactorial mechanisms as described below:
   - 3-1. Paralytic mechanism derived from denervation of the laryngeal abductor muscle
   - 3-2. Nonparalytic mechanism derived from increased laryngeal muscles tone
   - 3-3. Other mechanisms enhancing VCAP such as sleep and aspiration
4. Therapy
   - 4-1. Tracheostomy
     Time to perform tracheostomy is stage 2b on the laryngoscopic classification and nearly 20% of %90 on an overnight recording of SpO2
   - 4-2. Local laryngosurgery including arytenoidectomy, cordectomy, cord lateralization, and so on
   - 4-3. Airway splints: continuous/bilevel positive airway pressure with a nasal mask
   - 4-4. Botulinum toxin injection to the laryngeal adductor muscle

definite cause indicates that she probably succumbed to the advanced VCAP. Retrospectively, a tracheostomy should have been performed after the second fiberoptic laryngoscopy, as the rapid exacerbation of VCAP may have been related to the abnormally increased laryngeal muscle tone in addition to paresis of the abductor. Daytime inspiratory stridor is an ominous sign in advanced VCAP. A similar case has been reported *(35)*. Considering that her laryngeal complications were limited to respiration, an airway splint with nasal CPAP equipment may have been a reasonable option.

In patient 2, the rapid progression of VCAP resembled that in patient 1. In February 2000, an overnight recording of SpO2 was normal, although a fiberoptic laryngoscopy showed moderately severe VCAP (stage 2). What should have been done for such discrepant results? In retrospect, a repeat sleep laryngoscopy and overnight recording of SpO2 would have been useful. Because the posterior glottis, which is important for airway integrity, is often difficult to observe fiberscopically, its patency should have been checked carefully. Another noteworthy point is to keep the influence of sleep depth on SpO2 in mind. If sleep depth is insufficient (shallow sleep), VCAP can be "masked." Therefore, when analyzing an overnight recording of SpO2, it should be considered whether or not the patient slept well.

FUTURE QUESTIONS

Which sedative is preferable in a sleep laryngoscopy to evaluate upper airway dynamics, including vocal cords movements? Diazepam, which we routinely use, is a muscle relaxant and a respiratory center suppressant. A recent study showed that the mechanism of respiratory insufficiency in nonintubated patients with drug-induced coma from benzodiazepines is an increase in upper airway resistance *(36)*. It is also unknown how sleep depth (both in drug-induced or natural sleep) influences the severity of VCAP. Because SpO2 may depend in part on sleep depth, semi-quantitative methods for evaluating sleep depth are needed to assess the overnight recording of SpO2.

The most pressing question is, which therapy is most suitable for a given patient with MSA and VCAP: tracheostomy, laryngosurgery for glottal opening, nasal CPAP, or botulinum toxin injection? In the future, we hope to choose appropriate treatments according to features of VCAP in each patient.

REFERENCES

1. Holinger LD, Holinger PC, and Holinger PH. Etiology of bilateral abductor vocal cord paralysis: a review of 389 cases. Ann Otol Rhinol Laryngol 1976;4:428–436.
2. Lapresle J, Annabi A. Olivopontocerebellar atrophy with velopharyngolaryngeal paralysis: a contribution to the somatotopy of the nucleus ambiguus. J Neuropathol Exp Neurol 1979;38:401–406.
3. Israel RH, Marino JM. Upper airway obstruction in the Shy-Drager syndrome. Ann Neurol 1977;2:83.
4. Williams A, Hanson D, Calne DB. Vocal cord paralysis in the Shy-Drager syndrome. J Neurol Neurosurg Psychiatry 1979;42:151–153.
5. Bannister R, Gibson W, Michaels L et al. Laryngeal abductor paralysis in multiple system atrophy. A report on three necropsied cases with observations on the laryngeal muscles and the nuclei ambigui. Brain 1981;104:351–368.
6. Isozaki E, Hayashida T, Oda M, et al. Morphometric study of nucleus ambiguus in multiple system atrophy presenting with vocal cord abductor paralysis. Clin Neuropathol 2000;19:213–220.
7. Guindi GM, Bannister R, Gibson WPR, et al. Laryngeal electromyography in multiple system atrophy with autonomic failure. J Neurol Neurosurg Psychiatry 1981;44:49–53.
8. Hayashi M, Isozaki E, Oda M, et al. Loss of large myelinated nerve fivers of the recurrent laryngeal nerve in patients with multiple system atrophy and vocal cord palsy. J Neurol Neurosurg Psychiatry 1997;62:234–238.
9. Benarroch EE, Schmeichel AM, Parisi JE. Preservation of branchimotor neurons of the nucleus ambiguus in multiple system atrophy. Neurology 2003;60:115–117.
10. Simpson DM, Kaufmann H, Sanders I, et al. Laryngeal dystonia in multiple system atrophy. Muscle Nerve 1992;15:1213–1215.
11. Merlo LM, Occhini A, Pacchetti C, et al. Not paralysis, but dystonia causes stridor in multiple system atrophy. Neurology 2002;58:649–652.
12. Aragane N, Katoh O, Yamada H, et al. Respiratory failure due to vocal cord dyskinesia in olivo-ponto-cerebellar atrophy. Chest 1989;96:1212–1214.
13. Isozaki E. Clinicopathological, electromyographical, and phoniatric studies on bilateral vocal cord paralysis in multiple system atrophy. Kitakanto Med J 1991;41:389–409.
14. Isozaki E, Naito A, Horiguchi S, et al. Early diagnosis and stage classification of vocal cord abductor paralysis in patients with multiple system atrophy. J Neurol Neurosurg Psychiatry 1996;60:399–402.
15. Bassetti CL, Gugger M. Sleep disordered breathing in neurologic diseases. Swiss Med Wkly 2002;132:109–115.

16. Thomas PS, Geddes DM, Barnes PJ. Pseudo-steroid resistant asthma. Thorax 1999;54:352–356.
17. Isozaki E, Osanai R, Horiguchi S, et al. Laryngeal electromyography with separated surface electrodes in patients with multiple system atrophy presenting with vocal cord paralysis. J Neurol 1994;241:551–556.
18. Isono S, Shiba K, Yamaguchi M, et al. Pathogenesis of laryngeal narrowing in patients with multiple system atrophy. J Physiol 2001;536:237–249.
19. Isozaki E, Shimizu T, Takamoto K, et al. Vocal cord abductor paralysis (VCAP) in Parkinson's disease: difference from VCAP in multiple system atrophy. J Neurol Sci 1995;130:197–202.
20. Wu YR, Chen CM, Ro LS, et al. Vocal cord paralysis as an initial sign of multiple system atrophy in the central nervous system. J Formos Med Assoc 1996;95:804–806.
21. Hughes RG, Gibbin KP, Lowe J. Vocal fold abductor paralysis as a solitary and fatal manifestation of multiple system atrophy. J Laryngol Otol 1998;112:177–178.
22. Isozaki E, Miyamoto K, Osanai R, et al. Clinical studies of 23 patients with multiple system atrophy presenting with vocal cord paralysis. Rinsho Shinkeigaku 1991;31:249–254
23. Kakitsuba N, Sadaoka T, Kanai R, et al. Peculiar snoring in patients with multiple system atrophy: its sound source, acoustic characteristics, and diagnostic significance. Ann Otol Rhinol Laryngol 1997;106:380–384.
24. Isozaki E, Hayashi M, Hayashida T, et al. Vocal cord abductor paralysis in multiple system atrophy—paradoxical movement of vocal cords during sleep. Rinsho Shinkeigaku 1996;36:529–533
25. Miyazaki S, Itasaka Y, Ishikawa K, et al. Acoustic analysis of snoring and the site of airway obstruction in sleep related respiratory disorders. Acta Otolaryngol Supp 1998;537:47–51.
26. Merite DA, Laccourreye O, Brasnu D, et al. Partial posterior cordectomy with laser CO2 in bilateral recurrent paralysis. Ann Otolaryngol Chir Cervicofac 1992;109:235–239.
27. Ptok M, Schonweiler R. Botulinum toxin type A-induced "rebalancing" in bilateral vocal cord paralysis? HNO 2001;49:548–552.
28. Umeno H, Ueda Y, Mori K, et al. Management of impaired vocal fold movement during sleep in a patient with Shy-Drager syndrome. Am J Otolaryngol 2000;21:344–348.
29. Kenyon GS, Apps MCP, Traub M. Stridor and obstructive sleep apnea in Shy-Drager syndrome treated by laryngofissure and cord lateralization. Laryngoscope 1984;94:1106–1108.
30. Iranzo A, Santamaria J, Toloza E, et al. Continuous positive air pressure eliminates nocturnal stridor in multiple system atrophy. Lancet 2000;356:1329–1330.
31. Miyamoto M, Miyamoto T, Katayama S, et al. Effective nasal CPAP therapy for heavy snoring and paradoxical respiration during sleep in a case of multiple system atrophy. Rinsho Shinkeigaku 1998;38:1059–1063.
32. Andersen APD, Alving J, Lildholdt T, et al. Obstructive sleep apnea initiated by a lax epiglottis; a contraindication for continuous positive airway pressure. Chest 1987;621–623.
33. Silva DA, Sanders I. Continuous positive airway pressure as a promoter of laryngospasm during halothane anesthesia. Ann Otol Rhinol Laryngol 1992;101:893–896.
34. Shiomi T, Guilleminault C, Sasanabe R, et al. Primary pulmonary hypertension with central sleep apnea—sudden death after bilevel positive airway pressure. Jpn Cir J 2000;64:723–726.
35. Silber MH, Levine S. Stridor and death in multiple system atrophy. Mov Disord 2000;15:699–704.
36. Gueye PN, Lofaso F, Borron SW, et al. Mechanism of respiratory insufficiency in pure or mixed drug-induced coma involving benzodiazepines. J Toxicol Clin Toxicol 2002;40:35–47.

7

Movement Disorder Emergencies of the Upper Aerodigestive Tract

Boris Bentsianov, Ajay Chitkara, Anthony Cultrara, and Andrew Blitzer

PATIENT VIGNETTE

A 52-year-old man was transferred to the emergency room of a major hospital from a referral facility because of recent slurred speech. He had been admitted to the facility the week before for treatment of alcohol abuse. Upon his arrival in the emergency room, the neurology resident was called to evaluate the patient after a normal computed tomography scan was obtained. Examination revealed normal comprehension and expression, slurring of speech, and an inability to fully open his jaw and protrude his tongue. There were no defects in visual field perception, power, or sensation. Review of the medical record from the referring institution revealed that the patient had been started on 5 mg of haloperidol four times daily on his admission to the referral facility as part of his treatment for alcohol abuse—he was unaware he was receiving the medication. An acute dystonic reaction was diagnosed, and 25 mg of intravenous diphenhydramine was administered, with resolution of dysarthria and jaw restriction within 90 seconds of infusion. He was maintained on oral diphenyhydramine 25 mg twice daily for one week after discharge.

INTRODUCTION

Respiratory emergencies secondary to movement disorders are a rare but a potentially life-threatening phenomenon. Clinicians treating this patient population should be aware of the differential diagnosis and proper treatment to prevent adverse outcomes. The primary goal of intervention is to ensure a secure airway and to prevent respiratory embarrassment. Breathing disturbances of the larynx may be caused by primary movement disorders or may be iatrogenically induced, for example secondary to neuroleptic agents, as in the patient described above. In general, movement disorders of the upper aerodigestive tract lead to gradual respiratory compromise by diminishing the ability of the larynx to protect the lungs from aspiration. In this chapter, we focus on movement disorders that produce acute airway

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

obstruction as a result of mechanical blockage by glottic dysfunction. Laryngeal anatomy and physiology, history and physical exam, differential diagnosis, and treatment of airway emergencies are discussed.

LARYNGEAL ANATOMY AND PHYSIOLOGY

The larynx serves as an organ for respiration, airway protection, and phonation. The larynx is lined with mucosa and is composed of cartilages, ligaments, membranes, and muscles. A detailed anatomic review is beyond the scope of this text; therefore, we concentrate instead on the function and innervations of the intrinsic laryngeal muscles, whose role it is to control breathing, protect the airway, and phonate.

The afferent sensory and intrinsic musculature of the larynx is under the control of the vagus nerve (cranial X). The vagus originates from the nucleus ambiguus located within the brainstem and exits the cranial vault via the jugular foramen along with cranial nerves IX (glossopharyngeal) and XI (spinal accessory). It courses through the neck, thorax, and abdomen to supply its target organs with either somatic sensory, somatic motor, autonomic, or taste functions. The vagal branches responsible for laryngeal sensory and intrinsic motor functions are the superior laryngeal nerve (SLN) and the recurrent laryngeal nerve (RLN).

The SLN is further divided into the internal and external branches. The internal branch pierces the thyrohyoid membrane and supplies sensory innervation to the glottis and supraglottic structures. The external branch supplies the cricothyroid muscle, which tenses the vocal folds by rotating the thyroid cartilage anteriorly and inferiorly relative to the cricoid cartilage. The RLN supplies sensory innervation to the subglottic larynx and provides motor function to the remaining intrinsic laryngeal musculature. We may divide the intrinsic laryngeal muscles supplied by the RLN into the adductor group (thyroarytenoid, lateral cricothyroid, interarytenoid), which medially deviate the vocal folds, and the abductors (posterior cricoarytenoid), which cause lateral excursion of the vocal folds. During inspiration the vocal folds abduct (ABD) to allow airflow, and partially adduct (ADD) during expiration. Neurological abnormalities that interfere with abduction or adduction may impair normal breathing, phonation, or airway protection.

The management of any patient with potential airway compromise starts with a rapid and accurate assessment of the severity and urgency of the clinical problem. Airway management can usually be classified as emergent, urgent, or chronic. An accurate history, patient assessment, and physical examination will help categorize various patients, allowing potentially life-saving measures to be executed appropriately.

Basic history with respect to the airway includes several key items. Whereas dyspnea, or shortness of breath, is often the focus, this symptom may occur late in the course of events and herald a true airway emergency. More subtle findings occur earlier, and are critical to recognize. Stridor or “noisy breathing” suggests a disturbance of the normal laminar airflow pattern. It may be noted during inspira-

tion, suggesting a glottic or supraglottic origin; during expiration, suggesting a subglottic or tracheal origin; or it may be biphasic. This symptom may not necessarily be audible to the unaided ear and may require auscultation with a stethoscope over the trachea for early detection. Vocal quality, often described as dysphonia or hoarseness, is an important early finding. Questions about onset (acute vs chronic), duration (continuous vs episodic), and type of change (harsh, raspy, breaking, breathy, fatiguable) give important information about airway stability.

The physical examination of the upper airway depends on accurate interpretation of findings on flexible fiberoptic laryngoscopy. Neurological conditions present a particular challenge because there is often no anatomic distortion of laryngeal anatomy. Instead, they often manifest as complex functional disturbances requiring an experienced, trained observer. Failure of bilateral vocal fold ABD may warrant emergency intervention, cricothyroidotomy, or tracheotomy. As discussed previously, early discoordination or generalized hypomobility may herald an impending emergency, requiring preventative action. The specific history and physical findings of each of the neurological emergencies of the airway, including ADD breathing dystonia, Shy-Drager syndrome (SDS), and iatrogenic-related emergencies are discussed later.

Many neurological airway emergencies will respond to medical intervention including high concentration humidified oxygen via a face tent, intravenous infusion of steroids, and continuous pulse oximetry monitoring (preferably in a critical care unit). These measures help stabilize the situation, either completely obviating the need for definitive airway management or at least allowing trained surgical staff to arrive for assistance. Great caution should be taken prior to attempted intubation in this patient group, as bilateral true vocal fold ADD may leave the vocal folds in a median or paramedian position making tube cannulation difficult or impossible even for experienced staff. Repeated attempts can further aggravate the situation by traumatizing the larynx and true vocal folds, causing bleeding and edema in an already compromised airway. Fiberoptic-guided intubation performed by highly trained staff with backup surgical staff on hand and equipment ready in the room is far superior if time allows. If this option is not available or the situation is too acute, cricothyroidotomy by incision into the cricothyroid membrane and insertion of a small endotracheal tube (e.g., no. 5.0 or no. 5.5) can be performed. This should be followed by conversion to tracheotomy as early as possible to prevent injury to the subglottis and potential further injury to the larynx and vocal folds.

BREATHING DISTURBANCES FROM PRIMARY DISORDERS

Spasmodic Dysphonia

Dystonia is defined as involuntary sustained muscle contractions frequently causing twisting and repetitive movements or abnormal postures that may be sustained or intermittent. Spasmodic dysphonia (SD) is a clinical term used to describe focal laryngeal dystonia. The vocal apparatus usually functions normally during respiration, and laryngeal dystonia is triggered by speech. Most SD is idiopathic;

however, it may occur secondary to neurological disorders (Wilson's disease, parkinsonism, Huntington's disease, ceroid lipofuscinosis), environmental factors (posttraumatic, postinfectious, vascular, neoplastic, toxic), and may even be psychogenic *(1)*. SD is generally categorized into an ADD form, ABD form, or mixed type.

In the ABD variant of SD, inappropriate contraction of the posterior cricoarytenoid muscles (the sole laryngeal abductors) results in hyperabduction of the vocal folds. The voice quality is breathy, and aphonic breaks occur during connected speech. In ADD SD, inappropriate hyperadduction of the laryngeal adductors (primarily the thyroarytenoids) results in a choked, strained voice quality with breaks in phonation. Laryngeal dystonias are task-specific (i.e., they occur only during speaking) and generally do not interfere with normal breathing; therefore, respiratory compromise is not seen. Some studies have suggested that the sensation of dyspnea experienced by patients with laryngeal dystonia may be exacerbated by desynchronized contractions of the diaphragm *(2)*. The primary treatment of SD is with botulinum toxin injections to partially chemically denervate the specific laryngeal muscles responsible for the abnormal movements.

Adductor Laryngeal Breathing Dystonia

As mentioned earlier, focal laryngeal dystonias usually do not interfere with respiration; however, patients with ADD laryngeal breathing dystonia present with ADD spasms, which occur during inspiration. This usually presents as stridor of unknown etiology. Gerhardt first described this disorder, attributing it to paralysis of the ABD muscles. In 1992, Marion *(3)* studied three patients with Gerhardt's syndrome with laryngeal electromyography to show that ADD muscles were hyperactive. No weakness or denervation of the ABDs was present, suggesting that the syndrome occurred as the result of ADD dystonia. In 1994, our group reported seven patients with stridor and paradoxical movement of the vocal folds *(4)*. They had normal abduction on coughing and laughing, but during inspiration they had closure of the vocal folds, increasing airway resistance and producing stridor. Hyperactive ADD muscles were demonstrated on electromyogram (EMG), although normal activity was seen in the ABD muscles. None of these patients desaturated on pulse oximetry, and none required tracheostomy or ventilatory assistance. Stridor disappeared during sleep, typical of dystonia, and reappeared on awakening. All of the patients improved with injections of botulinum toxin to weaken the ADD muscles. ADD breathing dystonia has also been reported in association with Lubag syndrome *(5)* (X-linked dystonia-parkinsonism) and with multiple system atrophy (MSA) *(6)*.

Shy-Drager Abductor Weakness

SDS, the autonomic variety of MSA, is a parkinson-plus disorder characterized by orthostatic hypotension, loss of sweating, and urinary and/or rectal incontinence. Upper aerodigestive manifestations may include airway obstruction and/or swallowing difficulties that may lead to recurrent aspiration and pneumonia *(7)*. Airway obstruction occurs secondary to progressive vocal fold dysfunction, typically pre-

senting as stridor that occurs first in sleep. A full discussion of this topic is presented in Chapter 6. Vocal fold paresis and paralysis have been documented; however, the etiology of the vocal fold dysfunction is still elusive. Some authors have postulated that there is progressive weakness of the laryngeal ABDs, whereas others suggest a dyskinesia or dystonia of the ADDs leading to paradoxical vocal fold movement. Some authors have demonstrated adductor hyperfunctioning by laryngeal EMG in patients with MSA, which responded to botulinum toxin injection to the thyroarytenoid muscles *(6)*. Flexible endoscopic evaluation usually reveals vocal fold adduction during inspiration. As the laryngeal dysfunction progresses, patients may require tracheotomy to protect the airway.

There is no cure for SDS, and life expectancy is generally 7 to 10 years after diagnosis; medical treatment is symptomatic. Surgical intervention may be necessary to provide alternatives for nutritional support secondary to dysphagia and/or tracheotomy to secure the dysfunctional airway.

IATROGENIC CAUSES OF BREATHING DISTURBANCES

Spasmodic Dysphonia: Airway Obstruction Secondary to Botulinum Toxin Treatment

The treatment of SD entails manipulation of the larynx in order to deliver botulinum toxin to the appropriate laryngeal muscles. Airway compromise may occur iatrogenically as the result of laryngospasm, excessive volume injection, or paralysis of the laryngeal ABDs bilaterally. Laryngospasm is a sudden, sustained adduction of the vocal folds resulting in occlusion of the airway. This reflex is mediated via the vagus nerve and usually occurs in response to irritation of the vocal folds. It is thought to be a protective response that prevents irritants from reaching the lower airway. The treatment of ADD SD requires botulinum toxin injection under EMG guidance into the thyroarytenoid muscles. The needle is advanced through the cricothyroid membrane into the body of the thyroarytenoid muscle. In some individuals, the needle may stimulate laryngospasm, resulting in acute airway obstruction. Initial treatment requires the patient to remain calm and to inhale nasally ("sniffing" maneuver) until the spasm breaks. This technique is often successful in breaking the spasm. Failure of the spasm to break with conservative measures may require securing the airway via intubation, cricothyroidotomy, or tracheotomy. In the operating room, laryngospasm may be arrested with positive pressure ventilation, or with paralytic agents followed by endotracheal intubation.

Injection of excessive volume into the vocal folds may lead to dyspnea and subsequent mechanical obstruction of the glottic inlet. In our practice, the senior author tries to limit the injection to 0.1 mL per vocal fold to avoid stridor and/or glottic obstruction.

The treatment of ABD spasmodic dysphonia requires botulinum toxin injection under EMG guidance into the posterior cricoarytenoid muscles. Because these are the only intrinsic laryngeal muscles responsible for abducting the vocal folds, bilateral paralysis can result in acute laryngeal obstruction. To prevent this from occur-

ring, we inject only one side at a time. Approximately 2 weeks later, after the peak effect of the botulinum toxin has passed, flexible nasolaryngoscopy is performed to evaluate the ABD capability of the injected vocal fold. If there is satisfactory motion of the treated vocal fold, the contralateral posterior cricoarytenoid muscle is treated. Precise unilateral injection is mandatory to prevent inadvertent bilateral posterior cricoarytenoid muscle paralysis by direct injection or local diffusion.

There are no antidotes for mechanical obstruction of the larynx caused by overzealous injection of the vocal folds or inadvertent bilateral paralysis of the laryngeal ABDs. Treatment is guided by the severity of the obstruction, and may include intubation and/or procurement of a surgical airway.

Drug-Induced Tardive Dystonia

Typical neuroleptics and antipsychotics may trigger tardive dyskinesia or tardive dystonia, which can cause acute respiratory compromise if the larynx is involved. The extra-pyramidal side effects of neuroleptic and antipsychotic medication have been extensively reviewed in the literature *(8–10)*. We focus on tardive dystonia, as laryngeal involvement may precipitate acute respiratory embarrassment and sudden death if not properly diagnosed and treated. Tardive dyskinesia typically presents as involuntary choreic movements of oral, buccal, and lingual areas, whereas tardive dystonia produces involuntary spasmodic movements of the head, neck, tongue, and mouth (Fig. 1, patient vignette at the beginning of this chapter). When the dystonia involves the laryngeal musculature, respiratory compromise may ensue as a result of vocal fold spasms. The diagnosis of tardive dystonia of the larynx should always be suspected in patients with a history of neuroleptic use. Patients may present with acute stridor without obvious precipitating cause. The diagnosis is based on history and clinical examination including endoscopy to rule out other causes of airway obstruction *(11)*. Primary medical management of tardive dystonia is with anticholinergics such as diphenhydramine, which should be administered parenterally in the acute setting. Once the patient is stabilized, pharmaceutical treatment should be continued orally as an outpatient for 3 to 5 days. Patients with laryngeal dystonia may require resuscitative treatment (i.e., intubation, cricothyroidotomy, or tracheotomy) while antidotal therapy is rendered *(12)*. Fortunately, tardive dystonias respond promptly when properly diagnosed and treated.

SWALLOWING EMERGENCIES

Deglutition is a complex act of the laryngopharynx, requiring the successful passage of a food bolus into the upper esophagus and simultaneous protection of the laryngotracheal airway. This act relies on the complex interrelationship of neuromuscular coordination of the oral cavity, oropharynx, hypopharynx, and larynx. Breakdown in the neuromuscular coordination of deglutition causes dysphagia (difficulty swallowing) or aspiration (food bolus passing into the airway distal to the level of the true vocal folds). Emergencies of swallowing can be categorized into

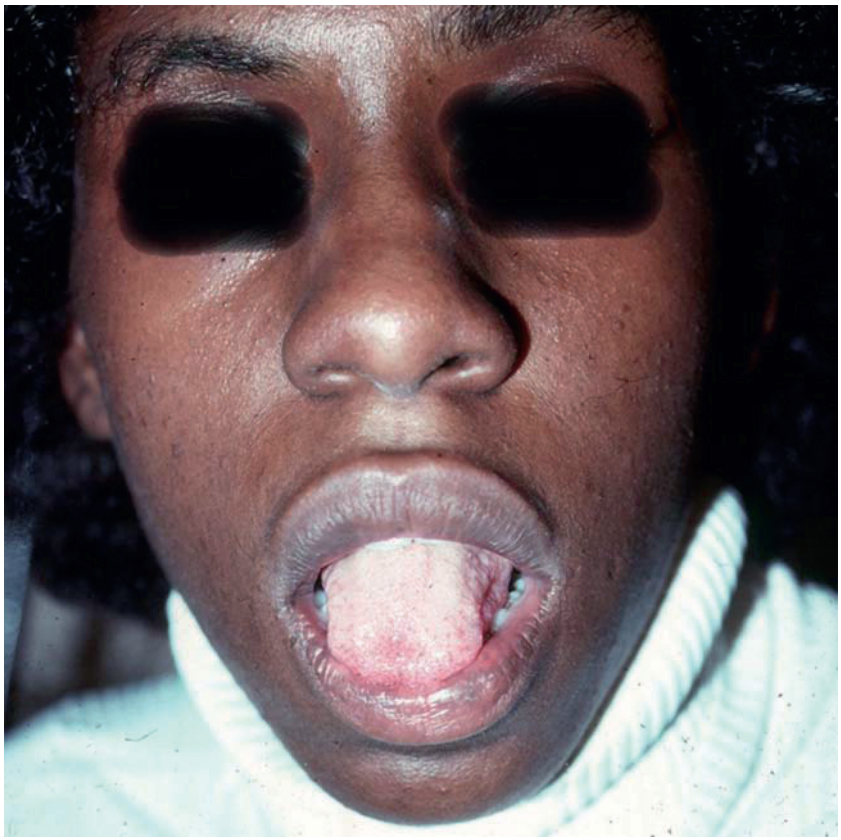


Fig. 1. This patient experienced an episode of acute lingual dystonia after taking a dose of compazine.

those related to dysmotility and those related to aspiration. In the first, the patient is unable to maintain nutritional sustenance via oral intake, and in the second, the patient is unsafe to maintain an oral diet as a result of impaired airway protection. These swallowing emergencies rarely require immediate attention but often benefit from urgent intervention to allow adequate nutritional intake.

Swallowing Physiology

Deglutition describes the mechanical passing of a food bolus from the oral cavity into the esophagus and stomach. This can be divided into three phases: oral, pharyngeal, and esophageal. Deglutition begins with the introduction of food into the oral cavity. The oral preparatory phase (mastication) mechanically breaks down the food particles into a manageable bolus while mixing the food with salivary

secretions to provide lubrication and early enzymatic digestion. The voluntary oral phase then propels the bolus into the pharynx by elevation of the tongue to the palate. Once the bolus stimulates afferents at the base of tongue and the faucial arches, the pharyngeal phase of deglutition is initiated *(13)*. This is associated with closure of the velopharyngeal port, glottic, supraglottic, and epiglottic closure, and elevation of the larynx. The pharyngeal phase is involuntary and involves the peristaltic contraction of the pharyngeal constrictors followed by the relaxation of the cricopharyngeus muscle, allowing the bolus to pass into the cervical esophagus. The third phase of swallowing is then initiated and proceeds with involuntary repetitive peristaltic contractions of the esophagus. The involuntary pharyngeal phase of swallowing lasts approx 1 second. The temporal coordination of this phase is crucial for successful passage of the bolus into the esophagus and concomitant protection of the laryngotracheal airway *(13)*.

The neurological control of swallowing is a complicated interaction of voluntary, involuntary, efferent, and afferent impulses. Centers in both the pons and the medulla have been implicated in the swallowing mechanism. There are two regions at the level of the pons that, when stimulated, evoke the swallowing process *(13)*. The reticular formation lies immediately dorsal to the trigeminal motor nucleus and transmits sensory input to the thalamus. The descending cortical–subcortical pathway is ventral to the motor trigeminal nucleus. Stimulation in this region induces mastication and swallowing. These two regions in the pons, however, do not comprise the core pathways of motor control in deglutition. The core pathway interneurons are situated in the medulla. Similar to the pons, there are two regions in the medulla that, when stimulated, can evoke swallowing *(13)*. A dorsal region of the reticular formation, which includes part of the nucleus tractus solitarius, and a ventral portion of the reticular formation in proximity to the nucleus ambiguus, comprise the medullary swallowing centers *(13)*. Peripheral afferents involved with initiating the involuntary swallow include the maxillary division of the trigeminal nerve, pharyngeal branches of the glossopharyngeal nerve, and sensory branches of the superior and recurrent laryngeal nerves *(13)*.

Swallowing Evaluation

The swallowing evaluation should include a history of types and quantities of foods tolerated, weight loss or gain, and history of coughing or choking. The clinical exam should include a comprehensive head and neck evaluation including nasopharyngoscopy and fiberoptic laryngoscopy to assess the anatomy and function of the pharyngeal musculature and the larynx. In addition, the specific act of deglutition should be witnessed.

Objective methods of evaluating swallowing function include modified barium swallow (MBS) and fiberoptic endoscopic evaluation of swallowing (FEES). The MBS *(14)* involves videofluoroscopic evaluation in both anteroposterior and lateral views of swallowing while the patient is given barium-coated foods of different consistencies (thin and thick liquid, puree, and solid). The examiner assesses for dysfunction in either structural or mechanical dysmotility during swallowing in the

oral, pharyngeal, and upper esophageal phases. In order to evaluate the entire esophagus, a barium esophagram, which involves the patient swallowing liquid barium, is performed. Views are taken before, during, and after the barium is administered. If a difficulty is identified, feeding position and strategy can be tested using the barium to evaluate the efficacy of the compensatory maneuvers. FEES allows direct visualization of swallowing with a flexible laryngoscope in place during deglutition *(15,16)*. The patient is offered food boluses of different consistencies with food coloring added. The swallow is observed through the flexible videolaryngoscope. Many aspects of the swallow can be assessed in this manner, except during velopharyngeal closure when the view is transiently obstructed. FEES can be performed at the bedside or in the office. MBS and FEES, when performed by experienced examiners, have similar specificity and sensitivity *(17)*.

Laryngeal sensory testing is a method of evaluating the afferents of the laryngopharynx *(16)*. This is done at the same time as the FEES and evaluates the laryngeal ADD reflex. When present, the reflex implies that sensory input to the larynx is intact. A calibrated air puff stimulus is applied to the aryepiglottic fold mucosa while the ADD reflex is watched for. Sensory deficits have been shown to contribute to aspiration *(18)*; however, the role of sensation in dysphagia associated with movement disorders requires further investigation.

Esophageal function can also be evaluated with manometry. This technique measures the sequential muscular function of the esophagus and can thus confirm dysmotility disorders of the esophagus *(19)*. This technique may be combined with videoflouroscopy, which adds information about bolus location *(20)*.

Treatment of Swallowing Disorders

The treatment of dysphagia begins with behavior modification and speech and swallowing therapy. This entails both positional and functional maneuvers to improve swallowing efficiency and prevent aspiration of the food bolus into the trachea. In severe cases, oral feeding may be inadequate for nutritional sustenance and tube feeding required for supplementation. Early intervention is crucial to maintaining adequate caloric needs. Nasogastric tube feeding is appropriate for initiating enteral feeds. Percutaneous endoscopic gastrostomy (PEG) or open gastrostomies are long-term, reversible means of maintaining enteral feeding in patients with debilitating dysphagia. In some cases, treating the underlying movement disorder may improve the symptoms of dysphagia.

Aspiration of food bolus can result in aspiration pneumonia, which carries a significant morbidity in patients with degenerative movement disorders. Behavioral modifications through speech and swallowing therapy are first implemented. If vocal fold immobility is contributing to aspiration, then medialization laryngoplasty may help the patient to swallow safely *(21)* (Fig. 2). Gastric tube feeding bypasses the upper aerodigestive tract and may decrease the frequency of aspiration. Tube feeding, however, does not prevent the aspiration of oral secretions, and patients may develop aspiration pneumonia even with a PEG. Patients who continue to aspirate oral secretions despite the presence of a gastric feeding tube may

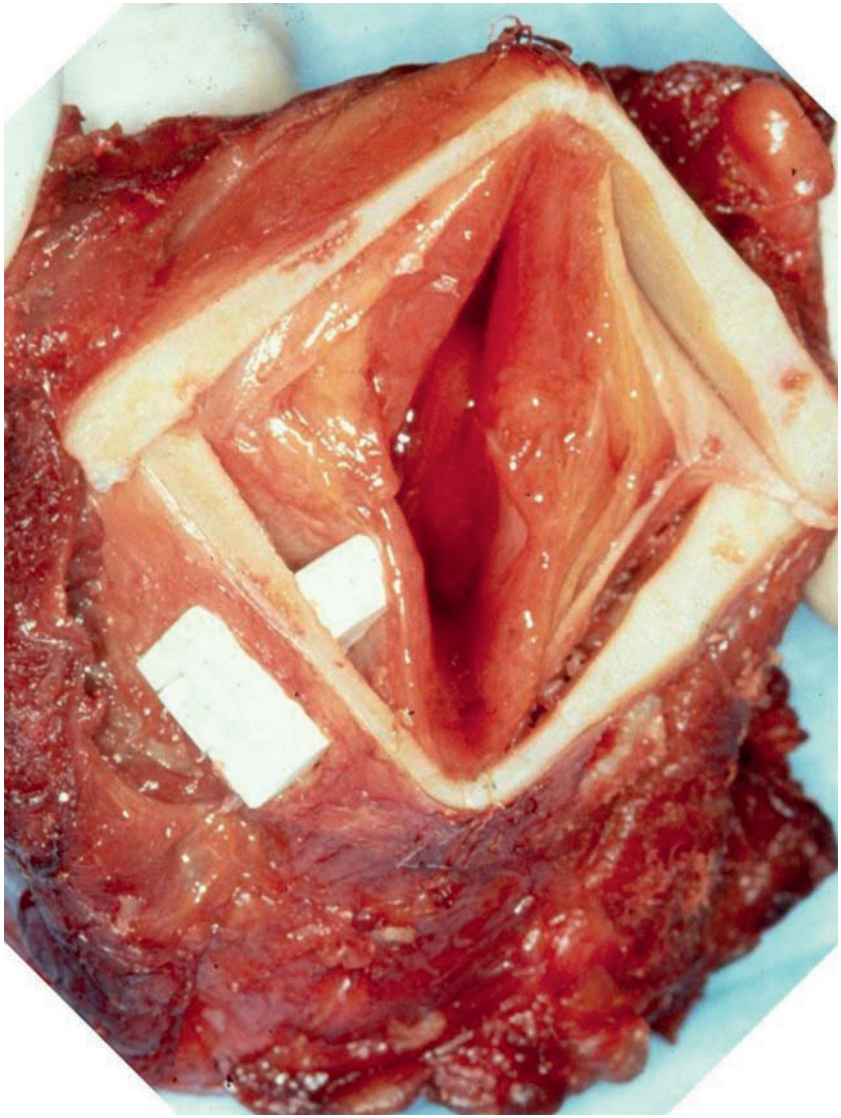


Fig. 2. This photograph is a cross-section of a dog larynx showing the white ceramic medialization implant in place. This procedure allows a paralyzed or weakened vocal fold to be supported and return glottal competence during speaking, coughing, and swallowing.

benefit from surgical airway protection. This includes glottic closure, epiglottic closure, laryngotracheal separation (Fig. 3), and total laryngectomy *(22,23)*. Tracheotomy does not prevent aspiration, and it may actually increase the risk of aspi-

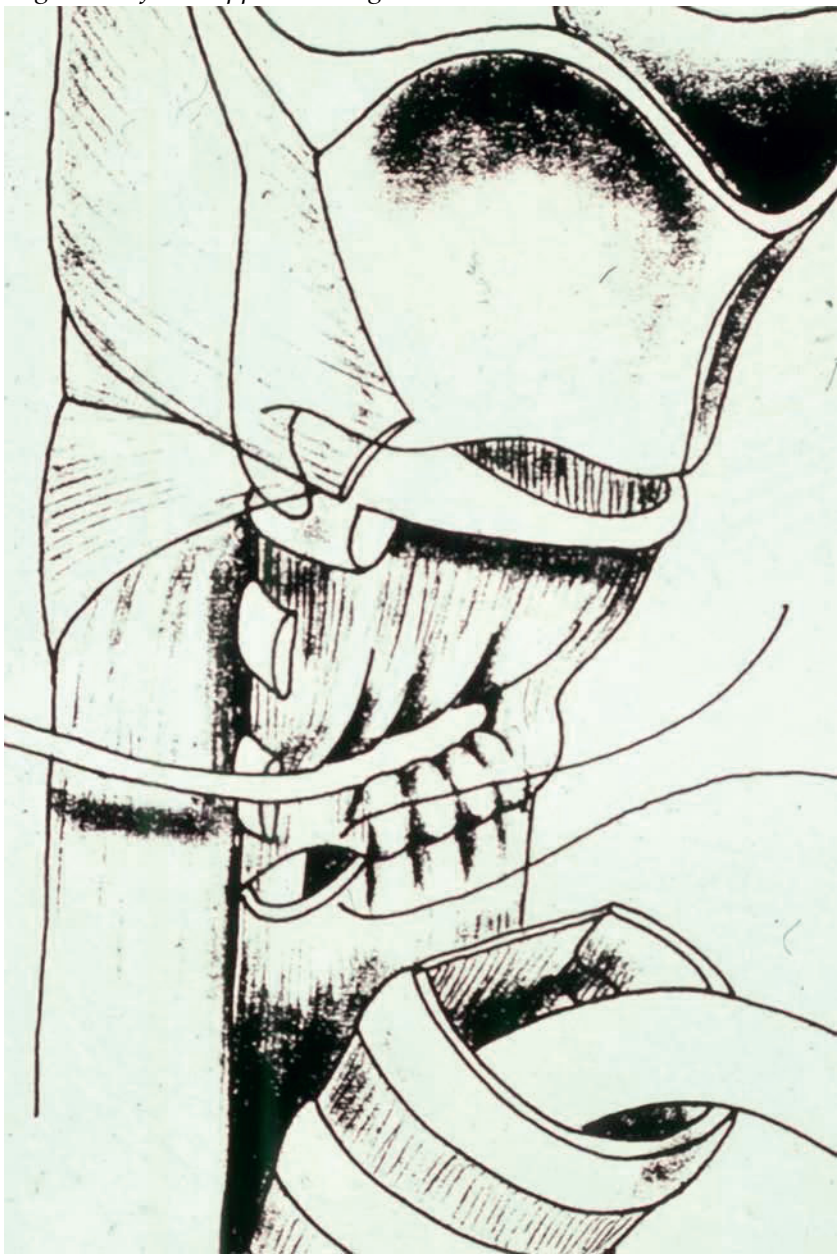


Fig. 3. This illustration demonstrates a surgical laryngotracheal bypass procedure. In this procedure, the trachea is transected at about the second or third tracheal ring. The upper end is sewn end-to-side to the esophagus. The lower end is brought out to the skin as if the patient had a laryngectomy. This allows the patient to eat, and the material that would have been aspirated into the airway now goes back into the esophagus. If the patient ever recovers normal function, the procedure may be reversed.

ration. This is a result of the tethering effect of the trachea, which may inhibit laryngeal elevation and the ability to create adequate subglottic pressure during the swallow. Tracheotomy does improve pulmonary toilet.

SPECIFIC DISORDERS RELATED TO SWALLOWING EMERGENCIES

Oromandibuloloingual Dystonia

Oromandibulolingual dystonia (OMD) *(24,25)* is a form of focal dystonia involving the masticatory, lower facial, and tongue musculature, producing spasms and often jaw deviation. In the early 16th century, Brueghel often painted faces with open mouths and contracted facial muscles, perhaps as a result of OMD *(26)*. In 1899, Gowers *(27)* described conditions producing tonic and clonic jaw contractions. The differential diagnosis of tonic jaw spasms includes dystonia, tetanus, trauma, hysteria, brainstem lesions, and hypothermia. Just after the turn of the century, Meige *(28)* reported a syndrome of spasms of the eyelids in addition to contractions of the pharyngeal, jaw, and tongue muscles. These spasms were often provoked by voluntary action (talking and/or eating), and lessened by humming, singing, yawning, or voluntarily opening the mouth. Some patients with Meige's syndrome developed other signs of dystonia, including torticollis, spasmodic dysphonia, or writer's cramp. In 1976, Marsden *(29)* realized that blepharospasm and oromandibular dystonia were both forms of adult-onset focal dystonia, a view supported by others *(30–40)*. In the most severe cases of OMD, dysphagia and/or airway obstruction can occur (Fig. 4). One such case was published in which a patient who sustained hypoxic brain injury presented several years later with intermittent respiratory distress requiring tracheostomy *(41)*.

The etiology and differential diagnosis of OMD is similar to that of other forms of focal dystonia *(42)*. Misdiagnosis is common. Sustained or repetitive muscle contractions associated with bruxism typically occur in sleep, and OMD disappears in sleep. Many patients are initially diagnosed as having temporomandibular disorders and are treated with a variety of appliances *(43)*. Dental appliances may be useful, as sensory tricks help orofacial dyskinesiasa and OMD. On the basis of clinical exam, patients can be classified as having predominantly jaw-closing, jaw-opening, or jaw-deviation dystonia. Drug therapy is the mainstay of treatment, with anticholinergics, benzodiazepines, and baclofen being most effective *(44,45)*. We and others have reported success in managing OMD with local injections of botulinum toxin *(46)* (Fig. 5). There have been reports of successful management of the jaw spasms using anesthetic and alcohol, suggesting an important role for modulating afferents in OMD *(47)*. Side effects and complications of botulinum toxin injection of OMD are uncommon. In our initial report, there were 14 instances of dysphagia, most in jaw-opening dystonia where the anterior digastric muscles were injected. This injection can cause weakness of the suprahyoid muscle, in turn causing a poor elevation of the larynx on swallowing and also changing the effectiveness of the tongue base on swallowing. One patient had severe dysphagia requiring

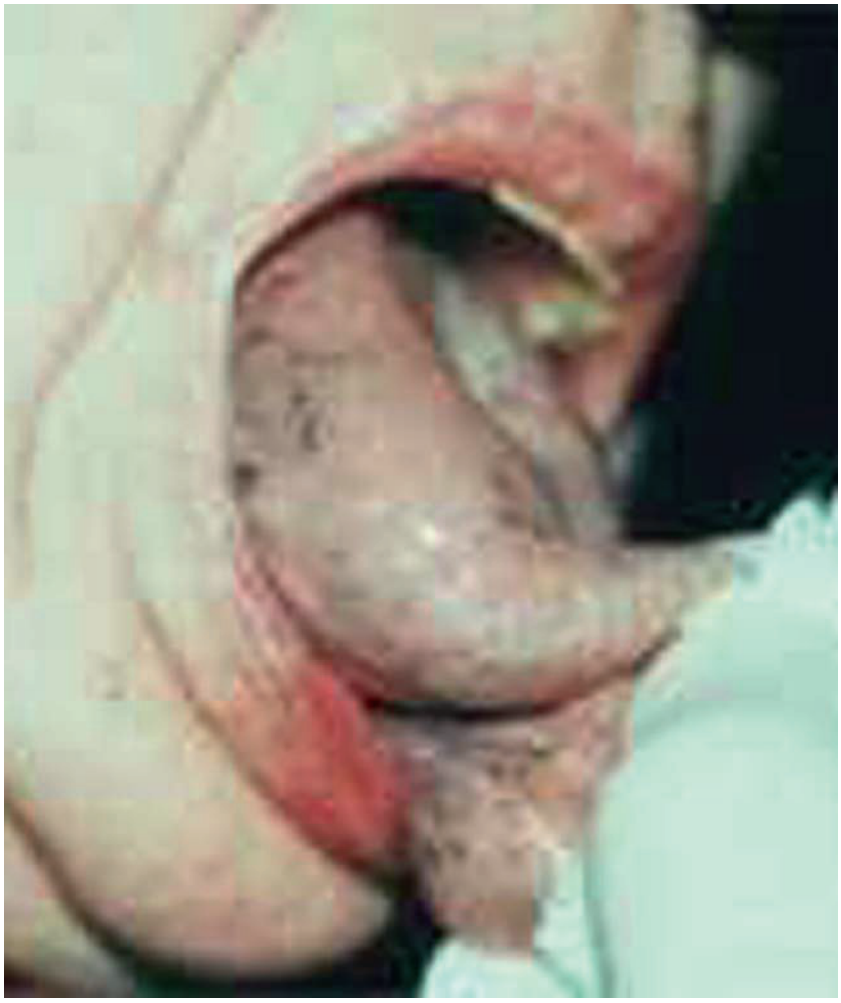


Fig. 4. This patient has a 1-year history of oromandibulolingual dystonia. Her tongue posturing is so bad that she bites her tongue chronically and cannot eat. Her tongue postures, mostly during eating, pushing most of her food out of her mouth.

a change of diet. One patient with jaw-closing dystonia had marked weakness of jaw closing and required an elastic bandage wrapped around his jaw to assist chewing. Injection of the external pterygoid muscles occasionally caused rhinolalia or nasal regurgitation when drinking liquids. One patient with severe jaw-opening dystonia was treated too aggressively and developed antibodies to botulinum toxin type A *(48)*. We initially treated a number of patients with severe lingual dystonia that caused posturing of the tongue or even prevented jaw-closing. However, this

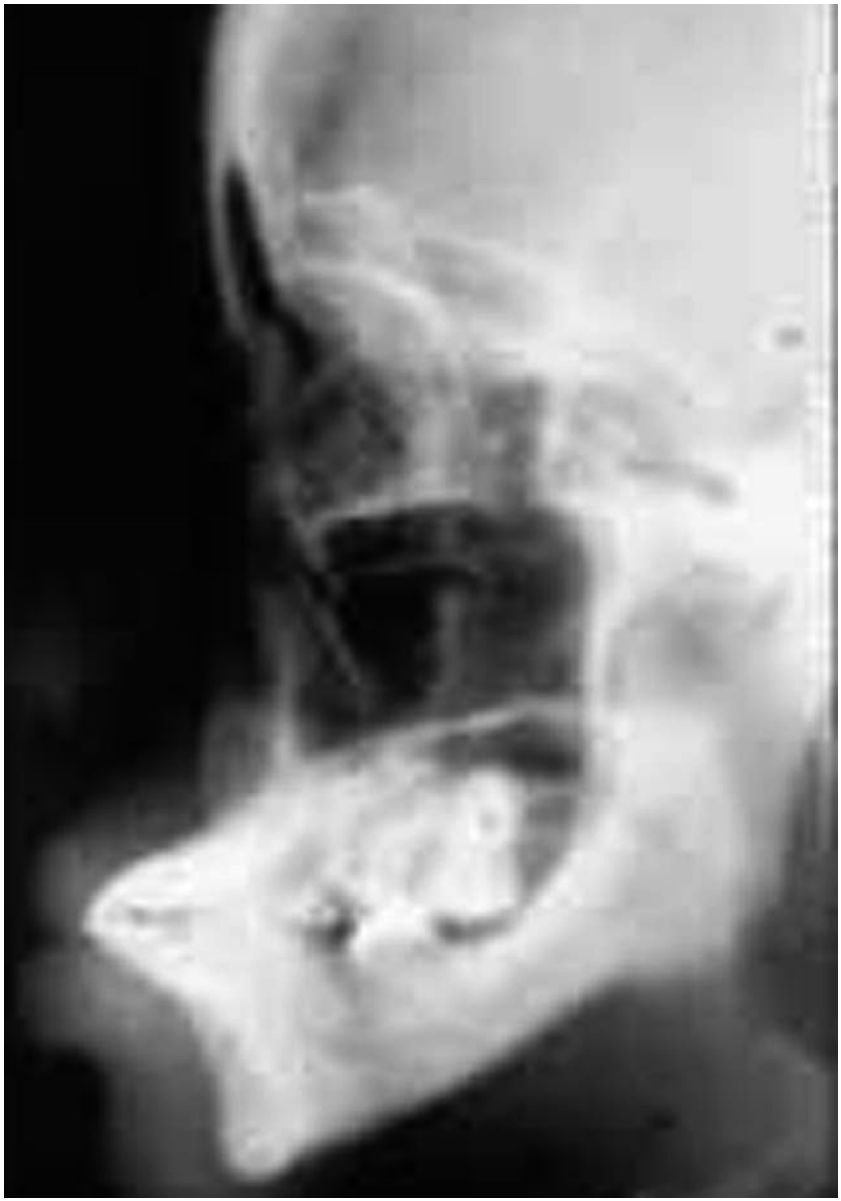


Fig. 5. This lateral skull X-ray is of a patient with severe jaw-closing oromandibualar dystonia. Severe jaw-closing spasms have created a LeForte 2 pyramidal fracture of the entire maxilla. It essentially free floats in its soft tissue attachments. Her spasms prevented her from eating. She was treated with Botulinum toxin injections of her masseter, temporalis, and internal pterygoid muscles. This allowed her to undergo reconstructive surgery and to be able to once again feed by mouth.

approach converts a hyperfunctional tongue to a hypofunctional tongue. In most cases, we found the disability from the treatment worse than the disease. We recommend not treating the tongue, particularly the tongue base, because this worsens speech and swallowing. In our initial series, six patients experienced such severe dysphagia that they required a temporary nasogastric tube for alimentation for 3 to 8 weeks. Two patients with severe lingual dystonia (their tongues remained postured out of their mouths most of the time) were treated successfully because they already had a tracheostomy and a gastrostomy tube. In these cases, a hypofunctional tongue was a clinical improvement *(49,50)*. Some authors report benefit with low dose injections of lingual musculature *(51)*.

Multiple System Atrophy

The main laryngopharyngeal deficit in patients with multiple system atrophy is vocal fold immobility (VFI), which may be related to ABD paresis *(6)*. Persistent activity of the cricopharyngeus muscle during swallowing has also been noted in EMG studies *(6)*. Clinically, patients with advanced stages of MSA are more likely to have VFI. This, along with dysfunction of the cricopharyngeus muscle, contributes to dysphagia. There is an increase in bolus stasis at the level of the piriform sinuses and the cricopharyngeus *(52)*. The presence of VFI has been associated with increased risk of aspiration in patients with MSA, and therefore increased risk of aspiration pneumonia *(52)*. Patients with laryngopharyngeal deficits related to MSA often require a tracheotomy to maintain the airway as the disease advances. At this point, there is often the need for gastric tube feeding to maintain adequate nutrition in these patients.

Multiple Sclerosis

Dysphagia is a secondary symptom of multiple sclerosis (MS), and a leading cause of morbidity and mortality in patients with MS *(53)*. Difficulty swallowing can lead to dehydration, malnutrition, and aspiration pneumonia. Dysphagia may be present in up to 43% of patients with MS *(53)*, and the severity of the disease does not correlate with the degree of dysphagia *(53)*. Dysphagia is caused by dysmotility at the level of the pharyngeal constrictors. This can result in penetration of the food bolus into the laryngeal vestibule. Slowing of the laryngopharyngeal phase of swallowing results in pharyngeal dysmotility *(53)*. Because there is no specific correlation between the disease state and the degree of dysphagia in MS, any complaint of swallowing dysfunction should be evaluated and treated as needed regardless of the patient's overall disability. Speech and swallowing therapy may be beneficial to help compensate for the laryngopharyngeal dysfunction. Patients at risk for aspiration or unable to maintain oral intake may require tube feeding for maintenance of nutrition.

Amyotrophic Lateral Sclerosis

Dysphagia in amyotrophic lateral sclerosis (ALS) usually manifests several months after the onset of the disease *(54)*. Dysphagia in these patients may progress

to aspiration pneumonia, malnutrition, and dehydration. Dysphagia in ALS is related to dysfunction at various phases of swallowing. There is generalized weakness of the perioral, submental, and suprahyoid muscles, and the tongue. This affects the oral preparatory and oral phases of swallowing and can result in difficulty controlling liquids and purees *(54)*. There is a delay in triggering of the pharyngeal phase of swallowing in patients with early, moderate dysphagia. In addition, there is a delay in laryngeal elevation in ALS patients with dysphagia. These patients also exhibit decreased tonic pause duration of the cricopharyngeus muscle with laryngeal elevation, resulting in shorter periods of upper esophageal sphincter opening *(55)*. ALS patients with dysphagia have weakness of laryngeal and respiratory muscles. They also exhibit brisk mandibular and gag reflexes. In advanced stages of dysphagia, patients can lose all voluntary control of the swallow, resulting in a spontaneous reflex swallow *(55)*.

Speech and swallowing therapy may provide compensatory techniques for early and moderate dysphagia. As the disease progresses and dysphagia becomes debilitating, gastric tube feedings are required. Some patients with severe aspiration of secretions may benefit from surgical airway protection via glottal closure, laryngotracheal separation, or total laryngectomy.

Parkinson's Disease

Swallowing dysfunction is present in 30–52% of patients with Parkinson's disease (PD) *(56)*. Dysphagia and aspiration in the setting of respiratory insufficiency are a major cause of death in patients with PD *(57)*. In patients with PD, there is a positive correlation between dysphagia and both disease duration and severity *(58)*. Potulska *(56)* compared swallowing function in patients with PD with normal subjects using EMG and pharyngoesophageal scintigraphy. Patients with PD exhibited either subclinical dysphagia or overt dysphagia. Overall pharyngeal transit times, laryngeal movement times, and esophageal transit times were prolonged in PD patients with overt dysphagia. As the dysphagia progressed, the pharyngeal phase of swallowing became more disrupted. Furthermore, the dysphagia limit (maximum bolus volume safely swallowed) was significantly less in patients with overt dysphagia compared with patients with subclinical dysphagia *(56)*. EMG studies showed prolonged triggering of the swallowing reflex and prolonged duration of the pharyngeal reflex time without disturbance in the function of the cricopharyngeus muscle *(55)*. Patients with PD with dysphagia may benefit from speech and swallowing therapy to compensate for the impaired swallowing mechanism. If the dysphagia progresses such that oral nutrition is either inadequate or unsafe, then tube feeding should be implemented (Fig. 6).

Huntington's Disease

Huntington's disease (HD) is a neurodegenerative disorder of the basal ganglia resulting in choreic movements, dementia, and neuropsychiatric features. These patients have impaired motor control of nearly all voluntary muscles. Death occurs

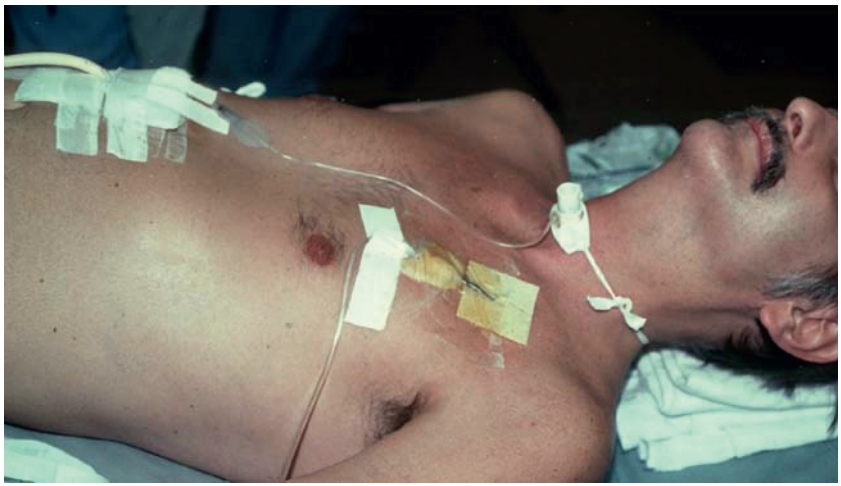


Fig. 6. This picture illustrates a patient with Parkinson's disease in crisis, the result of significant dysphagia and aspiration. As a result of aspiration pneumonia, the patient was given a tracheostomy, a subclavian line, and a percutaneous endoscopic gastrostomy, creating a dependent state. There are a number of other surgical options that can allow the patient to eat by mouth without soiling the airway.

within 20 years in most patients, and often as a result of aspiration pneumonia *(59)*. HD-related dysphagia is classified as hyperkinetic or bradykinetic *(59)*. The hyperkinetic variant is the more prevalent of the two. This type is associated with uncoordinated, hyperactive movements of the tongue, mandible, and soft palate. There is also reduced activity of the suprahyoid, cricopharyngeus, and extrinsic muscles of the larynx *(59)*. In addition, there are abrupt swallowing and involuntary respiratory maneuvers associated with the hyperkinetic variant. Tachyphagia is a unique characteristic of HD-related dysphagia. The bradykinetic variant of HD manifests with reduced motor function, range of motion, and coordination of the lips, mandible, tongue, and extrinsic laryngeal musculature *(59)*. Lingual sensory deficits may be present in both hyperkinetic and bradykinetic variants of HD *(59)*. Kagel and Leopold *(59)* reviewed patients with HD by videoflouroscopic swallowing study over a 16-year period and found that 28 of 29 patients had severe oral phase dysphagia and 17 of 29 patients had severe pharyngeal phase dysphagia, yet only 2 of 29 patients penetrated or aspirated. It should be noted that these swallow studies were performed with the patients in specially designed chairs to facilitate safe swallowing via postural fixation and spinal extension *(59)*. Over one-half of the patients studied exhibited uncoordinated and asynchronous vocal fold function. This laryngeal chorea resulted in almost one-third of the patients with a potentially unprotected tracheal airway *(59)*.

Treatment of swallowing dysfunction in patients with HD should begin with speech therapy and dietary modifications. This technique is limited by each patient's cognitive decline and ability to cooperate. Other techniques to optimize safe swallowing include specially designed chairs and prostheses, which limit some of the choreic activity and increase the efficiency of swallowing. When the disease progresses to unsafe swallowing, gastric tube feeding is recommended.

Palatal Myoclonus

Palatal myoclonus is a form of focal myoclonus that manifests as repetitive contractions of the soft palate and uvula. It may affect only one side, although bilateral, symmetric involvement is more common. Continuous, synchronous contractions of the uvula and soft palate occur at a frequency of 100–150 beats per minute *(60)*. The myoclonic activity persists during sleep. There may be associated focal myoclonic involvement of the larynx, extraocular muscles, neck, diaphragm, tongue, and face *(60)*. Palatal myoclonus is classified as symptomatic or essential. Symptomatic myoclonus occurs secondary to an underlying central nervous system disturbance, most commonly a brainstem stroke *(61)*. Other causes of symptomatic myoclonus include trauma, brainstem tumors or lesions, MS, encephalitis, progressive bulbar palsy, syringobulbia, obstructive hydrocephalus, and infectious causes (syphilis, malaria) *(60–62)*. There may be a latency between the brainstem insult and onset of myoclonus of 3 weeks to 3 years *(60)*. Essential myoclonus, which is much less common, has no identifiable etiology *(61)*. The essential variant is associated with earlier onset (30–40 years), equal incidence in men and women, lower frequency, and often presents with the sole complaint of ear clicking *(60)*. Symptomatic palatal myoclonus usually occurs in older males with less frequent subjective complaints *(60)*. There are occasional reports of palatal myoclonus contributing to dysphagia, dysarthria, and aspiration *(62)*.

Treatment regimens for palatal myoclonus may include medical therapy with or without speech and swallowing therapy. Unfortunately, palatal myoclonus is often refractory to drug therapy. Occasionally, successful medications include anticholinergics and clonazepam, and botulinum toxin has been used as well *(61)*. Swallowing therapy can also benefit patients with significant dysphagia and aspiration related to palatal myoclonus. Behavioral techniques such as the supraglottic swallow can allow safe oral feeding with previous aspiration *(62)*.

CONCLUSION

Movement disorder emergencies of the aerodigestive tract are dramatic and often life-threatening. With appropriate timely evaluation and intervention, most patients can be effectively managed, and major morbidity avoided.

REFERENCES

1. Brin, MF, Fahn, S, Blitzer, A, Ramig, LO, Stewart, C. Movement Disorders of the Larynx. In: Neurologic Disorders of the Larynx. Thieme Medical, New York: 1992;248–278.
2. Braun N, Abd A, Baer J, Blitzer A, Stewart C, Brin M. Dyspnea in dystonia. A functional evaluation. Chest 1995;107:1309–1316.

3. Marion, MH, Klap, P, Perrin, A, Cohen, M. Stridor and focal laryngeal dystonia. Lancet 1992;339:815.
4. Grillone GA, Blitzer A, Brin MF, Annino DJ Jr, Saint-Hilaire MH. Treatment of adductor laryngeal breathing dystonia with botulinum toxin type A. Laryngoscope 1994;104:30–32.
5. Lew MF, Shindo M, Moscowitz CB, Wilhemsen KC, Fahn S, Waters CH. Adductor laryngeal breathing dystonia in a patient with lubag (X-linked dystonia-Parkinsonism syndrome). Mov Disord 1994;9:318–320.
6. Merlo IM, Occhini A, Pacchetti C, Alfonsi E. Not paralysis, but dystonia causes stridor in multiple system atrophy. Neurology 2002;58:649–652.
7. Smith RL, Brown DH. Shy-Drager syndrome: an otolaryngology perspective. J Otolaryngol 2000;29:59–61.
8. Wirshing WC. Movement disorders associated with neuroleptic treatment. J Clin Psychiatry 2001;21:15–18.
9. Glazer WM. Extrapyramidal side effects, tardive dyskinesia, and the concept of atypicality. J Clin Psychiatry 2000;61:16–21.
10. Marsden CD, Jenner P. The pathophysiology of extrapyramidal side effects of neuroleptic drugs. Psychol Med 1980;10:55–72.
11. Rowley H, Lynch T, Keogh I, Russell J. Tardive dystonia of the larynx in a quadriplegic patient: an unusual cause of stridor. The J Laryngol Otol 2001;115:918–919.
12. Fines RE, Brady WJ Jr, Martin ML. Acute laryngeal dystonia related to neuroleptic agents. Am J Emerg Med 1999;17:319–320.
13. Miller AJ. Neurophysiological basis of swallowing. Dysphagia 1986;1:91–100.
14. Logemann J. Manual for the videoflouroscopic study of swallowing. Proed, Austin, TX: 1993.
15. Bastien RW. Videoendoscopic evaluation of patients with dysphagia: an adjunct to the modified barium swallow. Otolaryngol Head Neck Surg 1991;104:339–350.
16. Aviv JE, Kin T, Sacco RL, et al. FEESST: a new bedside endoscopic test of the motor and sensory components of swallowing. Ann Otol Rhinol Laryngol 1998;107:378–387.
17. Aviv JE. Prospective randomized outcome study of endoscopy versus modified barium swallow in patients with dysphagia. Laryngoscope 2000;110:563–574.
18. Setzen M, Cohen MA, Mattucci KF, Perlman PW, Ditkoff MK. Laryngopharyngeal sensory deficits as a predictor of aspiration. Otolaryngol Head Neck Surg 2001;124:622–624.
19. McConnel FMS. Analysis of pressure generation and bolus transit during pharyngeal swallowing. Laryngoscope 1988;98:71–78.
20. McConnel FMS, Cevenko D, Mendelsohn MS. Manofluorographic analysis of swallowing. Otolaryngol Clin NA 1988;21:625–635.
21. Flint PW, Purcell LL, Cummings CW. Pathophysiology and indications for medialization thyroplasty in patients with dysphagia and aspiration. Otolaryngol Head Neck Surg 1997;16:349–354.
22. Strome SE. Aspiration. In: Gates G, ed. Current Therapy in Otolaryngology Head and Neck Surgery, 6th ed. Mosby, St. Louis: 1998;453–456.
23. Wisdom G, Krespi YP, Blitzer A. Surgical therapy for chronic aspiration. Oper Tech Otolaryngol Head Neck Surg 1997;8:199–208.
24. Brin MF, Blitzer A, Herman S, Stewart C. Oromandibular Dystonia: Treatment of 96 Patients with Botulinum Toxin Type A. In: Jankovic J, Hallett M, eds. Therapy with Botulinum toxin. Marcel Dekker, NY: 1994;429–435.
25. Brin MF, Danisi F, Blitzer A. Blepharospasm, oromandibular dystonia, Meige's syndrome and hemifacial spasm. In: Moore P, ed. Handbook of Botulinum Toxin Treatment. 2nd ed. Blackwell Science, London: 2003;119–141.
26. Parkes D, Schachter M. Meige, Breughel, or Blake. Neurology 1981;31:498.
27. Gowers WR. Manual of diseases of the nervous system, 3rd edition. Churchill, London: 1899;200.
28. Meige H. Les convusions de la face: une forme clinique de la convulsions faciales, bilateral et mediane. Rev Neurol (Paris) 1910;21:437–443.
29. Marsden CD. Blepharospasm-oromandibular dystonia syndrome (Brueghel's syndrome). A variant of adult-onset torsion dystonia? J Neurol Neurosurg Psychiatry 1976;39:1204–1209.

30. Thompson PD, Obeso JA, Delgato G, Gallego J, Marsden CD. Focal dystonia of the jaw and the differential diagnosis of unilateral jaw and masticatory spasm. J Neurol Neurosurg Psychiatry 1986;49:651–656.
31. Jankovic J. Blepharospasm and oromandibular-laryngeal-cervical dystonia: a controlled trial of botulinum A toxin therapy. Adv Neurol 1988;50:583–591.
32. Tolosa E, Marti MJ. Blepharospasm-oromandibular dystonia (Meige's syndrome): clinical aspects. Adv Neurol 1988;49:73–84.
33. Tolosa E, Kulisevsky J, Fahn S. Meige syndrome: primary and secondary forms. Adv Neurol 1988;50:509–515.
34. Tolosa ES. Clinical features of Meige's disease (idiopathic orofacial dystonia). A report of 17 cases. Arch Neurol 1981;38:147–151.
35. Jankovic J, Ford J. Blepharospasm and orofacial-cervical dystonia: clinical and pharmacological findings in 100 patients. Ann Neurol 1983;13:402–411.
36. Berardelli A, Rothwell J, Day B, Marsden CD. Pathophysiology of blepharospasm and oromandibular dystonia. Brain 1985;108:593–608.
37. Nutt JG, Hammerstad JP. Blepharospasm and oromandibualr dystonia (Meige's syndrome) in sisters. Ann Neurol 1981;9:189–191.
38. Marsden CD. Problems of adult-onset idiopathic torsion dystonia and other isolated dyskinesias in adult life. Adv Neurol 1976;14:259–276.
39. Defazio G, Lamberti P, Lepore V, Livrea P, Ferrari E. Facial dystonia: clinical features, prognosis, and pharmacology in 31 patients. Ital J Neuro Sci 1989;10:553–560.
40. Jordan DR, Patrinely JR, Anderson RL, Thiese SM. Essential blepharospasm and related dystonias. Surv Ophthalmol 1989;34:123–132.
41. Kirton CA, Riopelle RJ. Meige syndrome secondary to basal ganglia injury: a potential cause of acute respiratory distress. Can J Neurol Sci 2001;28:167–173.
42. Brin MF. Advances in dystonia: genetics and treatment with botulinum toxin. In: Smith B, Adelman G, eds. Neuroscience year, supplement to the encyclopedia of neuroscience. Birkhauser, Boston: 1992;56–58.
43. Blitzer A, Brin MF, Greene PE, Fahn S. Botulinum toxin injection for the treatment of oromandibular dystonia. Ann Otol Rhinol Laryngol 1989;98:93–97.
44. Greene P, Shale H, Fahn S. Analysis of open-label trial in torsion dystonia using high dosages of anticholinergics and other drugs. Mov Disord 1988;3:46–60.
45. Gollomp SM, Fahn S, Burke RE, Reches A, Ilson J. Therapeutic trials in Meige syndrome. Adv Neurol 1983;37:207–213.
46. Tan EK, Jankovic J. Botulinum toxin A in patients with oromandibular dystonia: long-term follow-up. Neurology 1999;53:2102–2107.
47. Yoshida K, Kaji R, Shibasaki H, Iizuka T. Factors influencing the therapeutic effect of muscle afferent block for oromandibular dystonia and dyskinesia: implications for their distinct pathophysiology. Int J Oral Maxillofac Surg 2002;31:499–505.
48. Adler CH, Factor SA, Brin MF, Sethi KD. Secondary nonresponsiveness to botulinum toxin A in patients with oromandibular dystonia. Mov Disord 2002;17:158–161.
49. Brin MF, Blitzer A, Greene PE, Fahn S. Botulinum toxin therapy for the treatment of oromandibulolingual dystonia (OMD). Neurology (suppl 1) 294:1988.
50. Blitzer A, Brin MF, Fahn, S. Botulinum toxin injections for lingual dystonia. Laryngoscope 1991;101:799.
51. Charles, PD, Davis, TL, Shannon, KM, Hook, MA, Warner, JS. Tongue protrusion dystonia: treatment with botulinum toxin. South Med J 1997;90:522–525.
52. Higo R, Tayama N, Watanabe T, et al. Vocal fold motion impairment in patients with multiple system atrophy: evaluation of its relationship with swallowing function, J Neurol Neurosurg Psychiatry 2003;74:982–984.
53. Abraham SS, Yun PT. Laryngopharyngeal dysmotility in multiple sclerosis. Dysphagia 2002;16:69–74.

54. Eretkin C, Aydogdu I, Yuceyar N, et al. Pathophysiological mechanisms of oropharyngeal dysphagia in amyotrophic lateral sclerosis. Brain 2000;123:125–140.
55. Eretkin C, Tarlaci S, Aydogdu I, et al. Electrophysiological evaluation of pharyngeal phase of swallowing in patients with Parkinson's disease. Mov Disord 2002; 17,5:942–949.
56. Potulska A, Friedman A, Krolicki L, et al. Swallowing disorders in Parkinson's disease. Parkinsonism Relat Dis 2003;9:349–353.
57. Fuh JL, Lee RC, Wang SJ, et al. Swallowing difficulty in Parkinson's disease. Clin Neurol Neurosurg 1997;99:106–112.
58. Edwards LL, Quigley EM, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease: frequency and pathophysiology. Neurology 1992;42:726–732.
59. Kagel MC, Leopold NA. Dysphagia in Huntington's disease: a 16-year retrospective. Dysphagia 1992;7:106–114.
60. Pappert E, Goetz C. Myoclonus. In: Kurlan, ed. Treatment of Movement Disorders. JB Lippincott, Philadelphia: 1995;247–336.
61. Rivest J. Myoclonus. Can J Neurol Sci 2003;30:S53–S58.
62. Drysdale AJ, Ansell J, Adeley J. Palato-pharyngo-laryngeal myoclonus: an unusual cause of dysphagia and dysarthria. J Laryngol Otol 1993;107:746–747.

8

Dystonic Storm

Melissa J. Nirenberg and Blair Ford

PATIENT VIGNETTES

Patient 1: A 16-year-old non-Jewish boy had an 8-year history of idiopathic torsion dystonia resulting from the DYT1 mutation. At baseline, he was able to sit upright in a chair, but required help with activities of daily living, including feeding, dressing, and bathing. Treatment with a combination of baclofen, trihexyphenidyl, and clonazepam alleviated some of his symptoms. Trials of levodopa, diazepam, carbamazepine, and phenytoin provided no additional benefit.

At 16 years old, he developed severe, relentless dystonic spasms over a period of 5 days, with no clear precipitant. He was febrile to 40°C, with a creatinine phosphokinase (CPK) level of 1032 U/L. He had severe dystonia of the face and all four extremities, and opisthotonic posturing. Supportive care was initiated, including admission to the pediatric intensive care unit, intravenous hydration, and administration of antipyretics (acetaminophen). An intravenous lorazepam drip (and later a midazolam drip) was used as a temporizing measure to sedate the patient, suppress the dystonic spasms, and reduce the risk of medical complications (such as rhabdomyolysis) while other treatments were initiated. Dystonia-specific therapy consisted of increased doses of his outpatient medications (baclofen, trihexyphenidyl, and clonazepam) and the gradual addition of gabapentin, clonazepam, and dantrolene. Repeated attempts to wean him from intravenous benzodiazepines were unsuccessful because of recurrent dystonic spasms.

When noninvasive dystonia-specific therapy failed, a test bolus of intrathecal baclofen (50 μg) was administered and shown to temporarily alleviate his symptoms. An intrathecal baclofen pump was therefore placed. The procedure was complicated by initial worsening of his dystonia and pain at the pump site. A week later, however, his dystonic spasms began to remit. He was discharged on a combination of intrathecal baclofen (900 μg/day), oral baclofen (10 mg/day), trihexyphenidyl (60 mg/day), dantrolene (100 mg/day), and clonazepam (6 mg/day).

Eight months later, when tolerance to the intrathecal baclofen developed, a bilateral pallidotomy was performed. There was an immediate improvement in his dystonia, with no associated neurosurgical complications. After 15 months, he required a repeat right pallidotomy for persistent left arm dystonia. Because of ongoing severe dystonia, he subsequently underwent bilateral deep brain stimulation of the globus

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

pallidus interna at the age of 20. Although there were no surgical complications, there was minimal addition benefit; he continues to suffer from intractable generalized dystonia.

Patient 2: A 13-year-old boy of Ashkenazi Jewish ancestry had a 9-year history of idiopathic torsion dystonia related to the DYT1 mutation which ran in his family. At baseline, he had painful dystonic spasms of the lower extremities that at times rendered him unable to walk. Treatment with a combination of baclofen, trihexyphenidyl, benztropine, and reserpine was moderately helpful. Trials of levodopa (300 mg/day), carbamazepine, and clonazepam were ineffective or poorly tolerated.

At the age of 13, he developed severe, generalized dystonic contractions with no clear precipitant. He was admitted to a tertiary care hospital for urgent management of dystonic storm. Supportive care was initiated, including transfer to the pediatric intensive care unit, cardiopulmonary monitoring, and intravenous hydration. His pain was managed with codeine and acetaminophen. The serum CPK level was followed closely, and never exceeded the admission level of 4782 U/L. Renal function and urine output were also monitored, and remained within normal limits. Temporizing measures (such as intravenous sedation or general anesthesia) were not necessary. Dystonia-specific therapy consisted of increasing his usual doses of reserpine and lorazepam and gradually adding dantrolene. By hospitalization day 23, his symptoms had stabilized. He was discharged on a combination of dantrolene (150 mg/day), trihexyphenidyl (75 mg/day), benztropine (4 mg/day), baclofen (80 mg/day), reserpine (2.25 mg/day), and lorazepam (6 mg/day). Unfortunately, in the subsequent weeks he continued to have painful and debilitating dystonic spasms.

Two months after discharge, he underwent bilateral deep brain stimulation of the globus pallidus interna, with no operative complications. Seven months later, he developed a *Staphylococcus aureus* infection at the left cranial pulse generator site, necessitating surgical revision. Despite this setback, he showed ongoing improvement in his dystonia. Now, 2 years later, he continues to have an excellent functional outcome on lower doses of oral medications.

INTRODUCTION

Dystonia is defined as a syndrome of sustained muscular contractions, frequently causing twisting and repetitive movements, or abnormal postures. It may be restricted to specific parts of the body, or generalized in distribution *(1,2)*. When generalized dystonia "rapidly escalate[s] from its baseline to a presentation of extreme, forceful, continuous generalized contractions," it has the potential to precipitate a severe, life-threatening crisis that requires urgent evaluation and treatment. This was first reported by Jankovic and Penn in 1982 when they described a patient with "severe dystonia and myoglobinuria," in whom hyperpyrexia and rhabdomyolysis resulted from powerful dystonic spasms *(3)*. In 1984, Marsden and his colleagues reported two similar cases of severe, refractory generalized dystonia, which they referred to as "desperate dystonia" *(4)*. More recently, the terms "status dystonicus" *(5,6)* and "dystonic storm" *(7–9)* have been used to describe severe, relentless, and life-threatening generalized dystonia. These terms are valuable in that they convey the serious nature of this neurological emergency.

DIAGNOSIS AND MANAGEMENT

The risk of dystonic storm appears to correlate with the severity of dystonia *(3)*. It most commonly occurs in patients in whom there is poorly controlled generalized dystonia at baseline. The etiology of the underlying dystonia varies widely. Dystonic storm occurs in idiopathic torsion dystonia with or without the DYT1 mutation *(5,7,8,10)*. It has also been reported in secondary dystonia resulting from trauma *(5)*, encephalitis *(5)*, cerebral palsy *(5,11–13)*, or acute neuroleptic use *(14,15)*. Several neurodegenerative disorders in which dystonia is prominent have also presented with dystonic storm. These include Wilson's disease *(6)*, infantile striatal necrosis *(5)*, neuroacanthocytosis *(5)*, and pantothenate kinase-associated neurodegeneration *(9,16)*.

Dystonic storm often occurs after a triggering event such as fever *(9)*, intercurrent infection *(5)*, or medication exposure. Drugs that have been implicated include dopamine receptor-blocking agents (DRBAs) *(14,15)*, penicillamine (in a case of Wilson's disease) *(6)*, and possibly clonazepam *(5)*. Abrupt tapering or cessation of tetrabenazine, lithium, or anticholinergic medications may also precipitate dystonic storm *(3,5)*. In many cases, however, no inciting factors can be identified *(5,8–10)*.

The clinical presentation of dystonic storm is characterized by severe generalized muscle stiffness (as a result of dystonia), pain, hyperpyrexia, and even rhabdomyolysis *(3–10,13)*. Other features may include aphagia and anarthria *(4–7,9)*. Patients may require endotracheal intubation and mechanical ventilation because of bulbar dysfunction, decreased ventilatory capacity, muscular fatigue, or exhaustion *(5,7,9)*. Secondary complications may include tongue biting with lingual swelling *(10,15)*, dehydration, inanition *(9)*, cardiac dysfunction *(4,5)*, gastrointestinal hemorrhage *(4,9)*, hypotension *(6)*, aspiration pneumonia, and nosocomial infections *(5)*. When rhabdomyolysis occurs, there is a high risk of associated acute renal failure and metabolic acidosis *(5,6,14,15)*.

When a patient with dystonic storm is brought to medical attention, it is important to exclude other disorders that may have a similar clinical presentation (Fig. 1). The differential diagnosis includes neuroleptic malignant syndrome, malignant hyperthermia, serotonin syndrome, acute withdrawal from intrathecal baclofen, and bacterial meningitis *(5,8,12,17)*. Lumbar puncture to exclude the possibility of meningitis is critical, particularly when there is altered mental status, fever, or headache. It is also especially important in patients with intrathecal baclofen pumps, who are at an increased risk for bacterial meningitis *(18)*.

Once the diagnosis of dystonic storm has been established, prompt and aggressive treatment is indicated. Dystonic storm is a rare, life-threatening, fluctuating disorder. There are unfortunately no evidence-based management guidelines. The approach is therefore empiric, based on a compilation of effective treatments derived from case reports in the literature *(9)*. We subdivide management into three major components: supportive care, temporizing measures, and dystonia-specific therapy. An algorithm is shown in Fig. 2.

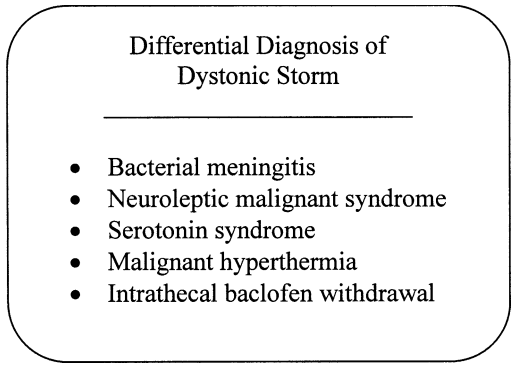


Fig. 1. Differential diagnosis of dystonic storm.

Supportive Care

Supportive care is directed at minimizing the systemic complications of severe dystonia. Most patients are admitted to an intensive care unit where cardiopulmonary monitoring is available *(5,8,9)*. Airway and respiratory status should be rapidly evaluated and closely observed; endotracheal intubation and mechanical ventilation should be performed when clinically indicated *(3–5,7,9,11)*. Hyperpyrexia should be treated with cooling blankets and antipyretics *(3,7,8)*. Pain is nearly universal *(3–5,9)*; analgesic medications such as fentanyl or morphine are therefore indicated until dystonia-specific therapy takes effect *(5,8)*.

Intravenous hydration is critical in all cases *(3,8–10,15)*. The serum creatinine phosphokinase, creatinine, and urine output should be followed closely, given the high risk of rhabdomyolysis *(5)*. Alkalinization of the urine is indicated if rhabdomyolysis occurs *(10,15)*; if rhabdomyolysis progresses to acute renal failure, then dialysis may be needed *(14)*. If the dystonia cannot be controlled quickly, then tube feedings or parenteral nutrition should be initiated to prevent inanition *(9,14)*.

Potential triggers for the development of dystonic storm should also be identified and treated. When there is suspicion of an underlying bacterial infection, broad-spectrum antibiotic therapy should be administered *(5)*. When dystonic storm has been precipitated by a specific medication, discontinuation of the offending agent is prudent, but unlikely to abort the crisis *(6)*.

Temporizing Measures

Temporizing measures are often critical for halting the relentless and life-threatening cascade of events and protecting the patient until dystonia-specific medications reach therapeutic levels. Sedative-hypnotics are frequently used as first-line therapy because they allow the patient to remain awake and carry a low risk of causing hypotension or other cardiovascular complications. A continuous midazolam drip is a good initial choice because it is a direct muscle relaxant, has a

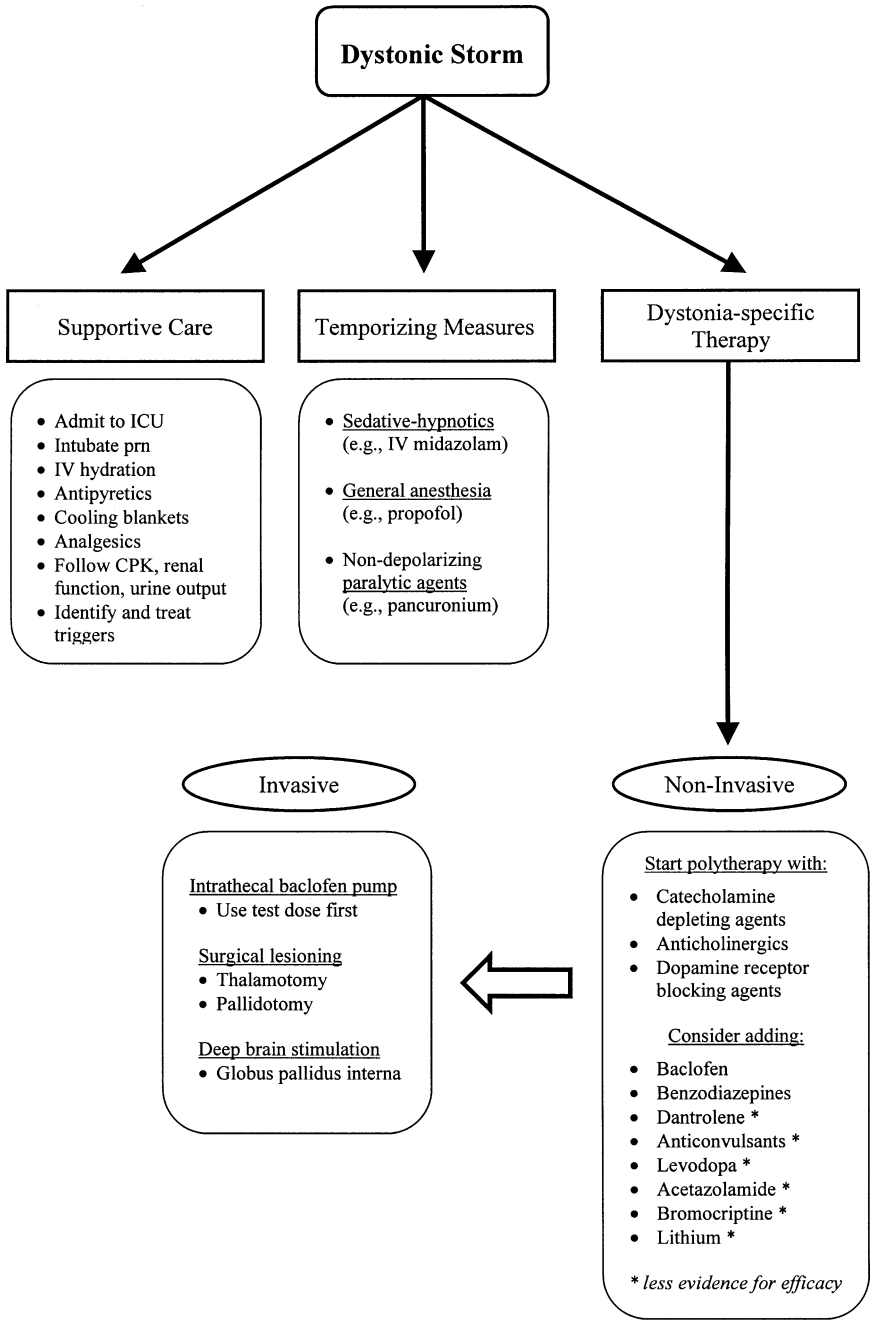


Fig. 2. An algorithm for the management of dystonic storm.

relatively short half-life, and has little effect on cardiovascular function *(5,8)*. In refractory cases, general anesthesia (often in combination with paralytic agents) may be necessary to control overwhelming dystonic spasms. A variety of general anesthetics have been used for this purpose *(4,5,9,10)*. Of these, propofol is probably the best choice because of its short half-life. Various paralytic agents have also been used for dystonic storm *(3,5,9,11)*, but nondepolarizing agents such as pancuronium are preferable, because depolarizing agents may precipitate or exacerbate rhabdomyolysis. Although there have been no direct comparisons between these strategies, they are highly effective in controlling the symptoms of dystonic storm. Unfortunately, these interventions do not affect the underlying dystonic symptoms, which typically recur as soon as the agents are withdrawn *(8,9)*.

Dystonia-Specific Therapy

Dystonia-specific therapy is used to abort the crisis. Marsden and his colleagues reported success with a combination of drugs (now referred to as the "Marsden cocktail") consisting of a fixed dose of tetrabenazine (75 mg/day), to which a DRBA and then an anticholinergic medication were gradually added as tolerated *(4)*. Manji advocated use of the same medications with a different titration schedule *(5)*. The regimen began with a trial of levodopa therapy in all patients (to exclude the possibility of dopa-responsive dystonia); when that was unsuccessful, anticholinergic medications, followed by tetrabenazine and then a dopamine receptor blocking agent such as pimozide were used. Each agent was started slowly, and titrated gradually to minimize side effects *(4,19)*. Even so, serious medication side effects required discontinuation of the offending agent in several cases. Pimozide in particular precipitated a superimposed acute dystonic reaction in one case *(4)* and cardiotoxicity in several others *(5)*. Reversible, dose-dependent side effects of these dystonia-specific medications also occurred frequently. These included drug-induced parkinsonism, akathisia, depression, drowsiness, cognitive impairment, and urinary retention *(4,5,9)*. Whereas these side effects are a major concern in an outpatient setting, they are more easily managed in the intensive care unit.

Regardless of the titration schedule, anticholinergics, catecholamine-depleting agents, and DRBAs appear to be the most effective agents for the treatment of dystonic storm. These medications have been tested in combination with dantrolene, benzodiazepines (e.g., clonazepam or diazepam), baclofen, anticonvulsants (e.g., carbamazepine, valproic acid, primidone, phenytoin), lithium, bromocriptine, levodopa, and acetazolamide with variable results *(3,5,7–10)*. Unfortunately, even with aggressive polytherapy, the dystonia often remains staunchly unresponsive to oral medications *(5,6,9)*. Moreover, because the patients are virtually always treated concurrently with several different medications, it is often unclear which one(s) may be responsible for clinical improvement.

When oral medications fail, more invasive approaches are warranted. Intrathecal baclofen therapy is well established as an effective treatment for spasticity *(20,21)*, and has been used with variable success in the chronic management of

generalized dystonia *(17,22–26)*. Intrathecal baclofen was first shown to provide benefit in a case of refractory dystonic storm in 1992 *(11)* and has been used in subsequent cases *(8)*. Major advantages include the potential to relieve pain from muscular spasms *(17,27,28)*, prevent the need for general anesthesia *(8)*, and provide long-term therapy for the underlying dystonia after the acute crisis has resolved. Potential disadvantages include the high rate of complications, particularly with long-term use. These range from mild, reversible symptoms to severe, life-threatening emergencies. Potentially serious complications include cerebrospinal fluid leak, meningitis, seizures, mechanical failure (which may precipitate a life-threatening withdrawal syndrome), and overdose (which may result in bradycardia, hypotension, respiratory depression, or coma) *(16–18,20,29)*. The role of intrathecal baclofen in the treatment of dystonic storm is uncertain *(17)*. Until there is better data regarding the safety and efficacy of this procedure, it should probably be reserved only for medically refractory cases.

In recent years, thalamotomy, pallidotomy, and high-frequency deep brain stimulation (DBS) of the globus pallidus interna have played an increasingly important role in the management of medically refractory dystonia *(30–37)*. Although these procedures offer the potential of providing long-term control of the underlying dystonia, their safety and efficacy in the management of dystonic storm remain unclear. Surgical intervention is relatively contraindicated in the acute setting, where renal failure and other organ system dysfunction may increase surgical morbidity and mortality *(8)*. Moreover, even in stable patients, up to 9% may have serious complications including stroke, cognitive symptoms, visual field deficits, dysarthria, dysphagia, hypophonia, and infection *(38–42)*. These procedures, particularly DBS, also have a delayed onset to maximal benefit that may limit their utility in the acute setting *(31,34,39)*. Nonetheless, several reports have illustrated the safe and effective use of thalamotomy, pallidotomy, or pallidal DBS in the management of dystonic storm *(3,5,8,43)*. Thus, neurosurgical intervention should be considered in patients who fail to respond to more conservative therapy.

The prognosis of patients with dystonic storm is highly variable, and depends both on the quality of supportive care and the underlying etiology for the dystonia *(5)*. In some cases, there may be complete recovery with no residual dystonia, or a return to the baseline level of disability *(5)*. In more severe cases, patients may accrue new, permanent neurological deficits, such as loss of the ability to ambulate independently or to swallow without aspirating *(4,5)*. Some cases have had a fatal outcome, even with early and appropriate treatment *(5,6,9)*.

CONCLUSION

Dystonic storm is a rare, life-threatening manifestation of generalized dystonia that must be promptly recognized and treated. Aggressive intervention by an experienced team of neurologists and intensivists is critical to reduce morbidity and mortality from this neurological emergency.

REFERENCES

1. Fahn S. Concept and classification of dystonia. Adv Neurol 1988;501–508.
2. Friedman J, Standaert DG. Dystonia and its disorders. Neurol Clin 2001;19:681–705.
3. Jankovic J, Penn AS. Severe dystonia and myoglobinuria. Neurology 1982;2:1195–1197.
4. Marsden CD, Marion MH, Quinn N. The treatment of severe dystonia in children and adults. J Neurol Neurosurg Psychiatry 1984;47:1166–1173.
5. Manji H, Howard RS, Miller DH, et al. Status dystonicus: the syndrome and its management. Brain 1998;121:243–252.
6. Svetel M, Sternic N, Pejovic S, et al. Penicillamine-induced lethal status dystonicus in a patient with Wilson's disease. Mov Disord 2001;16:568–569.
7. Opal P, Tintner R, Jankovic J, et al. Intrafamilial phenotypic variability of the DYT1 dystonia: from asymptomatic TOR1A gene carrier status to dystonic storm. Mov Disord 2002;17:339–345.
8. Dalvi A, Fahn S, Ford B. Intrathecal baclofen in the treatment of dystonic storm. Mov Disord 1998;13:611–612.
9. Vaamonde J, Narbona J, Weiser R, et al. Dystonic storms: a practical management problem. Clin Neuropharmacol 1994;17:344–347.
10. Paret G, Tirosh R, Ben-Zeev B, et al. Rhabdomyolysis due to hereditary torsion dystonia. Pediatr Neurol 1995;13:83–84.
11. Narayan RK, Loubser PG, Jankovic J, et al. Intrathecal baclofen for intractable axial dystonia. Neurology 1991;41:1141–1142.
12. Samson-Fang L, Gooch J, Norlin C. Intrathecal baclofen withdrawal simulating neuroepileptic malignant syndrome in a child with cerebral palsy. Dev Med Child Neurol 2000;42:561–565.
13. Watemberg N, Leshner RL, Armstrong BA, et al. Acute pediatric rhabdomyolysis. J Child Neurol 2000;15:222–227.
14. Ravi SD, Borge GF, Roach FL. Neuroleptics, laryngeal-pharyngeal dystonia and acute renal failure. J Clin Psychiatry 1982;43:300.
15. Cavanaugh JJ, Finlayson RE. Rhabdomyolysis due to acute dystonic reaction to antipsychotic drugs. J Clin Psychiatry 1984;45:356–357.
16. Delhaas EM, Brouwers JR. Intrathecal baclofen overdose: report of 7 events in 5 patients and review of the literature. Int J Clin Pharmacol Ther Toxicol 1991;29:274–280.
17. Ford B, Greene P, Louis ED, et al. Use of intrathecal baclofen in the treatment of patients with dystonia. Arch Neurol 1996;53:1241–1246.
18. Teddy P, Jamous A, Gardner B, et al. Complications of intrathecal baclofen delivery. Br J Neurosurg 1992;6:115–118.
19. Fahn S. High dosage anticholinergic therapy in dystonia. Neurology 1983;33:1255–1261.
20. Penn RD. Intrathecal baclofen for spasticity of spinal origin: seven years of experience. J Neurosurg 1992;77:236–240.
21. Kravitz HM, Corcos DM, Hansen G, et al. Intrathecal baclofen. Effects on nocturnal leg muscle spasticity. Am J Phys Med Rehabil 1992;71:48–52.
22. Ford B, Greene PE, Louis ED, et al. Intrathecal baclofen in the treatment of dystonia. Adv Neurol 1998;78:199–210.
23. Hou JG, Ondo W, Jankovic J. Intrathecal baclofen for dystonia. Mov Disord 2001;16:1201-1202.
24. Albright AL, Barry MJ, Shafton DH, et al. Intrathecal baclofen for generalized dystonia. Dev Med Child Neurol 2001;43:652–657.
25. Walker RH, Danisi FO, Swope DM, et al. Intrathecal baclofen for dystonia: benefits and complications during six years of experience. Mov Disord 2000;15:1242–1247.
26. Silbert PL, Stewart-Wynne EG. Increased dystonia after intrathecal baclofen. Neurology 1992;42:1639–1640.
27. Jaffe MS, Nienstedt LJ. Intrathecal baclofen for generalized dystonia: a case report. Arch Phys Med Rehabil 2001;82:853–855.
28. Penn RD, Gianino JM, York MM. Intrathecal baclofen for motor disorders. Mov Disord 1995;10:675–677.

29. Siegfried RN, Jacobson L, Chabal C. Development of an acute withdrawal syndrome following the cessation of intrathecal baclofen in a patient with spasticity. Anesthesiology 1992;77:1048–1050.
30. Kupsch A, Kuehn A, Klaffke S, et al. Deep brain stimulation in dystonia. J Neurol 2003;250:I47–I52.
31. Yianni J, Bain PG, Gregory RP, et al. Post-operative progress of dystonia patients following globus pallidus internus deep brain stimulation. Eur J Neurol 2003;10:239–247.
32. Krauss JK, Loher TJ, Weigel R, et al. Chronic stimulation of the globus pallidus internus for treatment of non-dYT1 generalized dystonia and choreoathetosis: 2-year follow up. J Neurosurg 2003;9:785–792.
33. Yianni J, Bain P, Giladi N, et al. Globus pallidus internus deep brain stimulation for dystonic conditions: a prospective audit. Mov Disord 2003;18:436–442.
34. Krauss JK. Deep brain stimulation for dystonia in adults. Overview and developments. Stereotact Funct Neurosurg 2002;78:168–182.
35. Vercueil L, Pollak P, Fraix V, et al. Deep brain stimulation in the treatment of severe dystonia. J Neurol 2001;248:695–700.
36. Krack P, Vercueil L. Review of the functional surgical treatment of dystonia. Eur J Neurol 2001;8:389–399.
37. Ondo WG, Desaloms JM, Jankovic J, et al. Pallidotomy for generalized dystonia. Mov Disord 1998;13:693–698.
38. Beric A, Kelly PJ, Rezai A, et al. Complications of deep brain stimulation surgery. Stereotact Funct Neurosurg 2001;77:73–78.
39. Lozano AM, Kumar R, Gross RE, et al. Globus pallidus internus pallidotomy for generalized dystonia. Mov Disord 1997;12:865–870.
40. Abosch A, Lozano A. Stereotactic neurosurgery for movement disorders. Can J Neurol Sci 2003;30:S72–S82.
41. Hariz MI, De Salles AA. The side effects and complications of posteroventral pallidotomy. Acta Neurochir Suppl (Wien) 1997;68:42–48.
42. Hariz MI. Complications of deep brain stimulation surgery. Mov Disord 2002;S3:S162–S166.
43. Angelini L, Nardocci N, Estienne M, et al. Life-threatening dystonia-dyskinesias in a child: successful treatment with bilateral pallidal stimulation. Mov Disord 2000;15:1010–1012.

9

Pseudodystonic Emergencies

Beom S. Jeon and Jong-Min Kim

PATIENT VIGNETTES

Patient 1: A 6-year-old boy presented to the outpatient department for head tilt. Since the age of 2, head tilt to the right side had been noted. When he was 4 years old, cervical spine imaging was performed. Congenital laminar fusion on the right at the C2–3 vertebrae was found. At age 6, posterior *in situ* fusion of the C2–3 vertebrae with iliac bone graft was performed. However, head tilt was not relieved. The patient was referred to a neurologist. Examination revealed head tilt to the right with painful contraction of the neck muscles. Manual rotation of the neck to either side and straightening of the neck caused severe pain. The images obtained before and after operation were reviewed. There was an enhancing lesion anterior to atlas, axis, and C3 vertebra. It appeared to be an inflammatory lesion, whose exact etiology was not clear. Anti-inflammatory drugs and muscle relaxant were started. Painful contractions of neck muscles were somewhat reduced, resulting in mild improvement in head tilt.

Patient 2: A 54-year-old woman came to the emergency room with severe muscle spasms of the neck and inability to speak or swallow. She had been healthy until progressive muscle spasms developed about 1 week prior to her visit. Examination revealed retrocollic posture with restriction of neck movements in any direction. She had difficulty in opening her mouth as a result of jaw trismus. She recalled that she had suffered a minor scratch on her left shoulder about 1 week before developing her symptoms. Continuous trains of muscle firing were seen on electromyogram. She was diagnosed with localized tetanus, and high doses of diazepam relieved much of the pain and spasm. She improved gradually over the next 3 months.

INTRODUCTION

Dystonia is a syndrome of sustained muscle contractions, causing abnormal postures, twisting, and repetitive movements *(1)*. The etiological classification divides the causes of dystonia into four major categories: primary (or idiopathic), dystonia-plus syndromes, secondary (or symptomatic), and heredodegenerative diseases in which dystonia is a prominent feature *(2)*. However, there are other neurological diseases in which sustained abnormal postures may be present without true dystonia. These disorders mimic dystonia, and hence are called pseudodystonia.

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

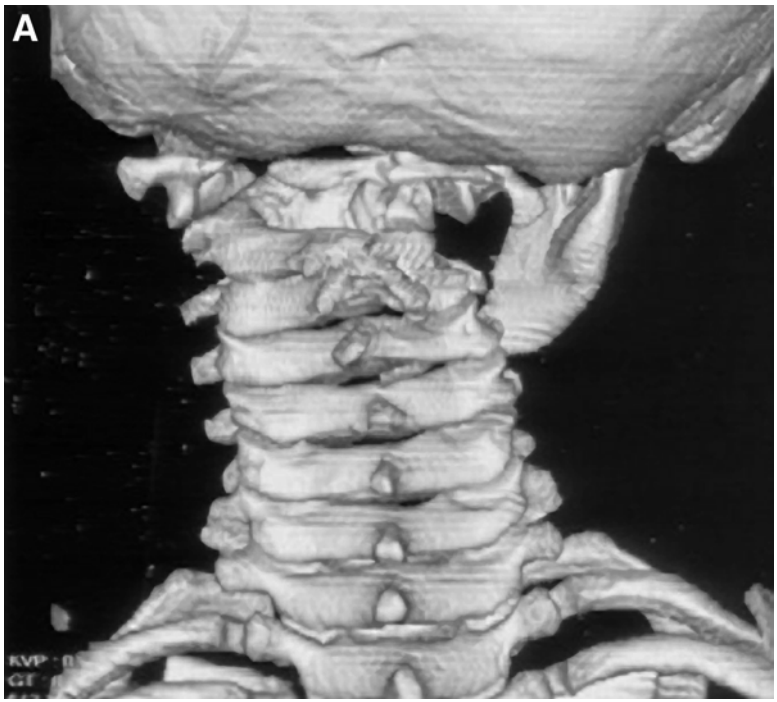
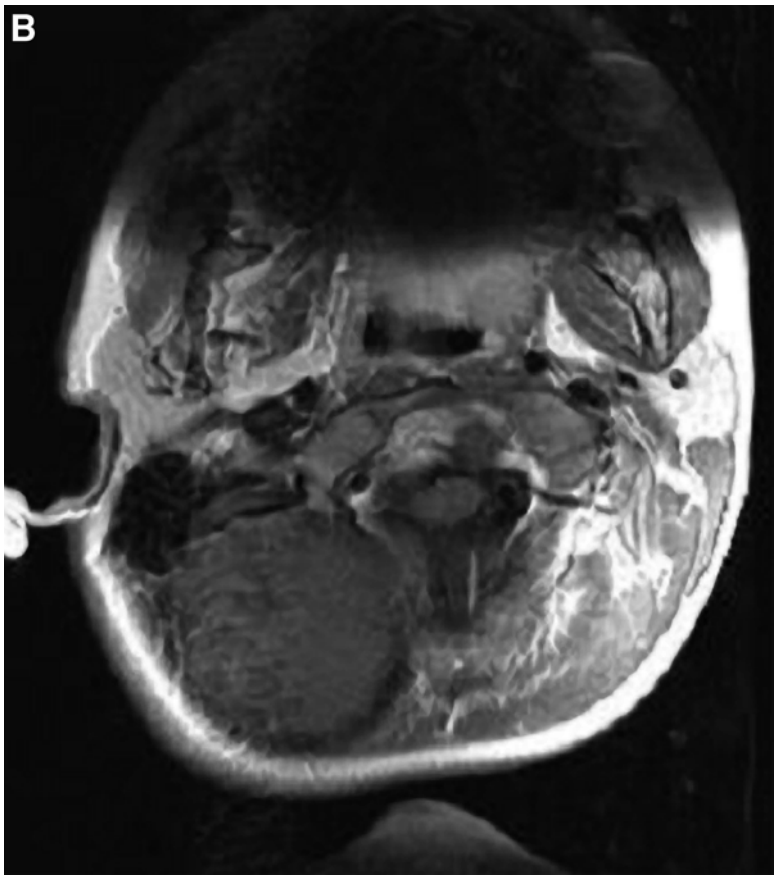


Fig. 1. Radiographic findings from Patient 1. **(A)** Three-dimensional reconstructed computed tomography image demonstrates laminar fusion at C2–3 vertebrae (posterolateral aspect of cervical spines). **(B)** Cervical spine magnetic resonance image shows a partially enhancing lesion anterior to the atlas and axis. The confirmative diagnosis of this lesion is not yet known.

The differential diagnosis of pseudodystonia includes stiff-person syndrome *(3)*, Isaacs' syndrome *(4)*, Sandifer's syndrome *(5)*, juvenile rheumatoid arthritis *(6)*, tetanus *(7)*, torticollis associated with pharyngitis *(8,9)*, torticollis as a result of spinal cord astrocytoma *(10,11)*, congenital muscular torticollis, ocular muscular torticollis (compensatory for strabismus and diplopia), and others (Table 1). Musculoskeletal abnormalities of the spine (Satoyoshi syndrome *[12]*, atlanto-axial subluxation in Down syndrome *[13]*, congenital laminar fusion, ligament absence, congenital Klippel–Feil syndrome *[14]*), syringomyelia *(15)*, and Arnold-Chiari malformation inducing torticollis are other examples of pseudodystonic conditions.

PSEUDODYSTONIC EMERGENCIES

Recognition and differentiation of pseudodystonia from dystonia is critically important, as the treatment of pseudodystonia is directed at the underlying cause.



Some pseudodystonic disorders may present as movement disorder emergencies. Atlanto-axial subluxation, tetanus, neoplastic torticollis, and infectious torticollis are pseudodystonic conditions requiring emergent evaluation and treatment (Table 2). Atlanto-axial subluxation is a serious cause of acute torticollis in childhood. Children are vulnerable to developing this condition because of the increased laxity of the spinal ligaments of the atlas and axis. The trauma needed to produce atlanto-axial subluxation can be trivial, and it may even occur spontaneously without a history of trauma *(16)*. The typical manifestations of atlanto-axial subluxation are acute head tilt, contralateral head rotation, and mild neck flexion. The neck muscles paradoxically appear loose. The spinous process of the axis may be palpable in the same direction as the head rotation. The patient is usually unable to rotate the neck past midline *(17)*. The consequences of overlooked atlanto-axial subluxation in children may be devastating *(18)*. Early diagnosis and intervention are critical to ensure complete recovery. Axial traction combined with rotation to the neutral po-

Table 1
Pseudodystonia: Differential Diagnosis

1. Stiff-person syndrome
2. Isaacs' syndrome
3. Sandifer syndrome
4. Musculoskeletal or developmental abnormality (Satoyoshi syndrome, atlanto-axial subluxation in Down syndrome, congenital laminar fusion, ligament absence, laxity, damage, congenital Klippel–Feil syndrome, congenital muscular torticollis, compensatory act for strabismus and diplopia, syringomyelia, Arnold–Chiari malformation)
5. Atlanto-axial subluxation, spontaneous, or associated with trauma, juvenile rheumatoid arthritis, or inflammatory head and neck process
6. Tetanus: localized, cephalic, generalized
7. Neoplastic torticollis (posterior fossa tumor, spinal cord astrocytoma)
8. Infectious torticollis (nonspecific pharyngitis, tonsillitis or adenoiditis, retropharyngeal or tonsillar abscess, mastoiditis or otitis media, cervical adenitis, acute rheumatic fever, parotitis, syphilitic pharyngeal ulcer, or influenza)
9. Seizures manifesting as sustained twisting postures
10. Torticollis from arteriovenous fistula at craniocervical junction

Table 2
Pseudodystonic Emergencies

1. Atlanto-axial subluxation resulting from trauma, or spontaneous
2. Tetanus: localized, cephalic, generalized
3. Neoplastic torticollis
4. Infectious torticollis

sition is the treatment of choice. If the diagnosis is delayed for more than one month, axial traction may not be helpful, and operative intervention is required, at the expense of limited range of motion of the cervical spine.

Tetanus may affect a limb or the neck (localized), the face (cephalic), or it may be generalized *(19)*. Generalized tetanus presents with pain or stiffness over the back or neck, usually followed within 24 hours by trismus and autonomic disturbance. Cephalic or localized tetanus may be misdiagnosed as acute focal dystonia with potentially catastrophic consequences. Cephalic tetanus usually follows a facial injury. Trismus mimics dystonia of the jaw. Fiorillo reported a 10-year-old boy who developed continuous painful spasm of the foot after a peripheral injury *(7)*. Initially, the diagnosis was delayed. He was treated with tetanus immunoglobulin and antibiotics and recovered, although foot spasms continued for 4 months.

Spinal cord tumor occasionally presents with pseudotorticollis *(10)*. Shafir reported a disaster in an infant with congenital torticollis as a result of an undiagnosed spinal cord astrocytoma *(11)*. Chiropractic manipulation prior to the correct

diagnosis triggered a respiratory arrest and quadriplegia as a result of tumor necrosis. The authors suggest, and we agree, that all children with torticollis, even those with congenital torticollis, should have a radiological evaluation before any physical therapy is instituted.

The most common cause of emergent pseudotorticollis is as a presentation of infectious or inflammatory processes of the head or neck. Known as Grisel's syndrome, torticollis may follow nonspecific pharyngitis, tonsillitis or adenoiditis, retropharyngeal or tonsillar abscess, parotitis, mastoiditis or otitis media, acute rheumatic fever, or influenza *(8)*. All children presenting with acute nontraumatic torticollis should be assumed to have an inflammatory or neoplastic head or neck process until proven otherwise. Initial management should include cervical immobilization. Computed tomography or magnetic resonance imaging imaging is necessary to delineate the atlanto-axial joint—plain radiographs are insufficient.

CONCLUSION

All patients presenting with acute torticollis should be assumed to harbor a traumatic or inflammatory head and neck process. Initial management should include cervical immobilization. All children with torticollis, even those with congenital torticollis, must have a neurological and radiological evaluation before any physical therapy. Computed tomography or magnetic resonance imaging is necessary to delineate the atlanto-axial joint, and to identify space-occupying lesions in the head and neck. All patients with persistent torticollis must be assumed to harbor an atlanto-axial subluxation until proven otherwise. Definitive treatment of pseudodystonia is directed at the underlying cause.

REFERENCES

1. Fahn S. Concept and classification of dystonia. Adv Neurol 1988;50:1–8.
2. Fahn S, Bressman SB, Marsden CD. Classification of dystonia. Adv Neurol 1998;78:1–10.
3. Meinck HM, Thompson PD. Stiff man syndrome and related conditions. Mov Disord 2002;17:853–866.
4. Arimura K, Sonoda Y, Watanabe O, et al. Isaacs' syndrome as a potassium channelopathy of the nerve. Muscle Nerve 2002;S11:55–58.
5. Mandel H, Tirosh E, Berant M. Sandifer syndrome reconsidered. Acta Paediatr Scand 1989;78:797–799.
6. Uziel Y, Rathaus V, Pomeranz A, Solan H, Wolach B. Torticollis as the sole initial presenting sign of systemic onset juvenile rheumatoid arthritis. J Rheumatol 1998;25:166–168.
7. Fiorillo L, Robinson JL. Localized tetanus in a child. Ann Emerg Med 1999;33:460–463.
8. Berry DS, Moriarty RA. Atlantoaxial subluxation related to pharyngitis: Grisel's syndrome. Clin Pediatr 199;38:673–675.
9. Bredenkamp JK, Maceri DR. Inflammatory torticollis in children. Arch Otolaryngol Head Neck Surg 1990;116:310–313.
10. Visudhiphan P, Chiemchanya S, Somburanasin R, Dheandhanoo D. Torticollis as the presenting sign in cervical spine infection and tumor. Clin Pediatr 1982;21:71–76.
11. Shafir Y, Kaufman BA. Quadriplegia after chiropractic manipulation in an infant with congenital torticollis caused by a spinal cord astrocytome. J Pediatr 1992;120:266–269.

12. Merello M, Garcia H, Nogues M, Leiguarda R. Masticatory muscle spasm in a non-Japanese patient with Satoyoshi syndrome successfully treated with botulinum toxin. Mov Disord 1994;9:104–105.
13. Curtis BH, Blank S, Fisher RL. Atlantoaxial dislocation in Down's syndrome; report of two patients requiring surgical correction. JAMA 1968;205:464–465.
14. Brougham DI, Cole WG, Dickens DR, Menelaus MB. Torticollis due to a combination of sternomastoid contracture and congenital vertebral anomalies. J Bone Joint Surg Br 1987;71:404–407.
15. Kiwak KJ, Deray MJ, Shields WD. Torticollis in three children with syringomyelia and spinal cord tumor. Neurology 1983;33:946–948.
16. Grogaard B, Dullerud R, Magnaes B. Acute torticollis in children due to atlanto-axial rotary fixation. Arch Orthop Trauma Surg 1993;112(4):185–188.
17. Subach BR, McLaughlin MR, Albright AL, Pollack IF. Current management of pediatric atlantoaxial rotatory subluxation. Spine 1998;23(20):2174–2179.
18. Schwarz N. The fate of missed atlanto-axial rotatory subluxation. Arch Orthop Trauma Surg 1998;117:288–289.
19. Jagoda A, Riggio S, Burguieres T. Cephalic tetanus: a case report and review of the literature. Am J Emerg Med 1988;6:128–130.

10

Tardive and Neuroleptic-Induced Emergencies

Paul E. Greene and Steven J. Frucht

PATIENT VIGNETTES

Patient 1: A 26-year-old man with severe juvenile parkinsonism was maintained on a regimen of levodopa and pergolide. He was admitted to the hospital in order to adjust his Parkinson's disease medications, and pergolide was tapered off. The neurologist was called to the bedside when he subsequently experienced an acute episode of painful turning of his neck to the right and elevation of the right arm, and dystonic posturing of the left leg. His eyes remained deviated up and to the right, although he could bring them into primary gaze with difficulty. A diagnosis of oculogyric crisis secondary to pergolide withdrawal was made, and treatment with intravenous diphenhydramine terminated the crisis.

Patient 2: A 92-year-old woman presented to a movement disorder clinic in the company of her daughter. For the last 3 years, her daughter had meticulously documented episodes, occurring every 3 days and lasting for hours, during which she would obsess about a thought or object, and subsequently experience rapid irregular breathing, posturing, and jerking of her limbs. Examination in the office revealed Hoehn and Yahr stage IV parkinsonism, with a magnetic resonance imaging consistent with vascular parkinsonism. She had been taking carbidopa/levodopa 25/100 three times daily. She was admitted to the hospital in order to observe and film an episode. During the event, she was awake, followed commands intermittently, and demonstrated respiratory dysrhythmias, myoclonic jerks, and a fixed forward gaze. A diagnosis of oculogyric crisis was made, and elimination of levodopa and introduction of 0.5 mg of benztropine mesylate three times a day terminated the events. She died 2 years later, and autopsy confirmed the diagnosis of vascular parkinsonism.

INTRODUCTION

Exposure to most centrally acting dopamine receptor-blocking agents (DRBAs) can cause a variety of movement disorders. Neurologists characterize the movement disorders according to their natural history when the causative agent is stopped: they can be self-limited and have short duration, or they can be long-lasting. The self-limited movement disorders usually appear shortly after exposure

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

to the DRBA and resolve quickly after the agent is stopped. The most common short duration disorders are acute dystonic reactions, including oculogyric crises and acute akathisia. The long duration movement disorders usually appear after chronic exposure to the DRBA and may last a lifetime or for many years after the DRBA is stopped. The long-duration disorders usually consist of dyskinesias, dystonia, or akathisia. Occasionally, other movement disorder symptoms, such as myoclonus, tics, or tremors, have been attributed to DRBA exposure.

Despite the usefulness of the distinction between acute and tardive drug-induced movement disorders, the line between the two is sometimes blurred, especially in the older literature. There have been reports of recurrent acute dystonic reactions *(1)*, and tardive movements that typically appear after prolonged exposure may appear after as little as 1 week of neuroleptic exposure. Whenever possible, we try to distinguish between acute and tardive symptoms. In addition, many patients with tardive syndromes have a combination of symptoms, and it can be difficult to separate the effects of dystonia, dyskinesias, and akathisia. It is also important to remember that other centrally acting dopamine receptor blockers besides neuroleptics may case tardive syndromes, including antinausea agents such as prochlorperazine *(2)* and metaclopramide *(3)*, and calcium channel blockers such as flunarizine and cinarizine *(4)*.

Tardive symptoms may be mild and barely bothersome to the sufferer (as is frequently the case with oral-buccal dyskinesias), or they may cause severe discomfort (as is often the case with DRBA-induced dystonia and akathisia). Occasionally, these movement disorders present as emergencies, sometimes as life-threatening events, hence their inclusion as movement disorder emergencies.

TARDIVE RESPIRATORY PHENOMENA

Respiratory compromise rarely occurs with idiopathic dystonia; rather, it generally occurs in the setting of a severe exacerbation of symptoms called dystonic storm *(5)*. Respiratory compromise probably occurs more commonly with DRBA-associated dystonia than with idiopathic dystonia. The majority of reported cases seem to be associated with acute dystonic reactions *(6)*. Several of these cases have been associated with stridor, and presumably most occur because of dystonia of the larynx and or pharynx *(6)*. However, in several cases, respiratory compromise with hypoxia occurred in the setting of chronic neuroleptic use, and tardive dystonia was the probable underlying condition *(7,8)*. Respiratory compromise may also occur from aspiration in the setting of dysphagia.

The prevalence of respiratory irregularity in patients with tardive syndromes was estimated as 7.4% *(9)*. Patients may have a variety of findings: irregular respiration, grunting, sighing, humming, gasping, and choking *(9)*. At the time of that study, dystonia was not widely recognized as a tardive symptom, so the exact underlying tardive symptoms cannot be known for certain. We have seen patients with respiratory irregularities that have had exclusively oral-buccal dyskinesias.

However, idiopathic cranial dystonia (Meige syndrome) is accompanied by respiratory irregularity in as many as 5% of patients *(10)*, so it is likely that patients with tardive dystonia may also have this problem. Patients may have irregular respirations and grunting. The irregularity appears to be asymptomatic in many cases, but it can also present emergently as shortness of breath *(11)*. Although some patients with symptomatic respiratory dysrhythmia may have normal blood gases *(11)*, some apparently develop hypoxia and cyanosis *(12)*. Although many of the reported cases involve chronic respiratory dysrhythmia, in some of these cases doses of neuroleptics were changed shortly before the acute episode, and respiratory involvement may have been related to an acute dystonic reaction *(12)*.

OTHER TARDIVE COMPLICATIONS

Dysphagia in varying degrees of severity has been reported in conjunction with tardive syndromes. Tardive dystonia of the pharynx has been the presumptive diagnosis in some of these patients *(13,14)* but some may have just had oral-buccal dyskinesias *(9)*. In some patients, drug-induced parkinsonism has been hypothesized to exacerbate dysphagia, or possibly be the sole cause *(14)*. Choking, regurgitation of food, and weight loss are the usual symptoms. In some cases, these symptoms are accompanied by aspiration and recurrent pneumonia *(9)*.

Since the early 1980s, there have been a series of case reports ascribing suicidal ideation, suicide attempts, or completed suicide in akathisia *(15)*. Some of these cases appear to occur in the setting of acute akathisia, whereas the akathisia in other cases persists for so long that tardive akathisia is probably the underlying condition *(15)*. Many of these patients have underlying psychiatric disorders, such as depression and schizophrenia, that may also be associated with suicidal ideation. Some authors have questioned the association between suicide and akathisia *(16)*. However, there are reports of suicidal ideation in patients with no psychiatric history who developed akathisia from gastrointestinal DRBAs *(17)*.

Tardive dystonia can be severe and interfere with functions normally performed by the affected body parts. Severe jaw-closing dystonia can make it difficult or impossible for patients to take oral food. Severe jaw-opening dystonia can make chewing impossible, limiting patients to liquid nutrition. Severe lingual dystonia can make it impossible for patients to pass the bolus of food to the posterior pharynx where swallowing can be initiated. These patients may be unable to eat solid food even when swallowing itself is normal. Dystonia or dyskinesias may make walking difficult and lead to falls and fractures, as has been reported several times *(18,19)*. The risk of fractures may be higher in the presence of osteoporosis. When severe, truncal dystonia can make sitting and lying difficult, which quickly leads to an emergency presentation. There is at least one report of a patient who developed myoglobinuria associated with severe tardive dystonia *(20)*. There are also rare patients who develop intractable vomiting as a result of air swallowing, presumably related to pharyngeal dystonia *(8)*.

OCULOGYRIC CRISIS

The phenomenon of oculogyric crisis was first described in patients with encephalitis lethargica. A form of acute dystonia, it takes its name from the tendency of the eyes to deviate, although eye movements are only part of the syndrome. Sacks *(21)* elegantly summarized the panoply of disturbances in postencephalitic crises: "among the common accompanying symptoms we have observed in oculogyric crises are the following: opisthotonus and generalized rigidity, intense terror or rage, thalamic pain and anguish, multiple autonomic symptoms (sometimes accompanied by conspicuous tachycardia and hypertension), hypervigilance, extreme motor urge, akathisia, complex reiterative movements and ticking, forced gasping and gagging, loud phonation, tachyphemia and tachypraxis, pallilalia and verbigeration, obsessional and sometimes delusional remuneration, and—in all crises—some degree, and in the worst crises a profound degree, of catalepsy and/or block."

Oculogyric crises are most commonly seen following exposure to neuroleptics, and crises may occur as acute or tardive phenomena *(1,11)*. The incidence of oculogyric crises in patients treated with chronic neuroleptics may be as high as 10% *(11)*, and in one report of 24 children accidentally exposed to haloperidol, 14 developed oculogyric crises *(22)*. Tetrabenazine *(23)*, gabapentin *(24)*, domperidone *(25)*, carbamazepine *(26)*, and lithium carbonate *(27)* have all been reported to trigger oculogyric crises. Sacks *(21)* reported that levodopa initially suppressed crises in postencephalitic patients, although it later enhanced their severity and intensity. Oculogyric crisis may occur in patients with dopa-responsive dystonia, and in one such patient, treatment with levodopa eliminated both dystonia and crises *(28)*. There are also credible reports of oculogyric crises associated with structural brain lesions, such as bilateral paramedian thalamic infarction *(29)*, herpes encephalitis, cystic glioma of the posterior third ventricle *(30)*; and as the initial manifestation of Wilson's disease *(31)*.

TREATMENT

The treatment of acute dystonic reactions is usually easy. Anticholinergics or antihistamines generally abort the dystonia within minutes when given by the intravenous route. Regardless of their cause, acute oculogyric crises can be terminated with injection of intravenous anticholinergics or diphenhydramine. Twenty-five or 50 mg of intravenous diphenhydramine is readily available in hospital emergency rooms and is probably the treatment of choice for this condition. Oral clonazepam may be effective for patients with chronic neuroleptic-induced oculogyric crises that are resistant to anticholinergics *(32)*.

Acute akathisia can also usually be controlled with propranolol or benzodiazepines until it resolves. It is much more difficult to treat tardive syndromes. Discontinuation of the DRBA, when possible, is sometimes—but not always—effective. When persistent, or when the DRBA cannot be stopped, treatment of tardive syndromes is difficult and beyond the scope of this review. Atypical neuroleptics, such as clozapine, may allow symptoms to abate with continued

therapy. Dopamine depletors, such as reserpine or the investigational medication tetrabenazine, are probably the most effective agents, but they can cause depression, hypotension, and drug-induced parkinsonism *(33–35)*.

REFERENCES

1. FitzGerald PM, Jankovic J. Tardive oculogyric crises. Neurology 1989;39:1434–1437.
2. Alberts VA, Catalano G, Poole MA. Tardive dyskinesia as a result of long-term prochlorperazine use. South Med J 1996;89:989–991.
3. Ganzini L, Casey DE, Hoffman WF, McCall AL. The prevalence of metoclopramide-induced tardive dyskinesia and acute extrapyramidal movement disorders. Arch Int Med 1993;153:1469–1475.
4. Micheli FE, Pardal MM, Giannaula R, et al. Movement disorders and depression due to flunarizine and cinnarizine. Mov Disord 1989;4:139–146.
5. Manji H, Howard RS, Miller DH, et al. Status dystonicus: the syndrome and its management. Brain 1998;121:243–252.
6. Koek RJ, Pi EH. Acute laryngeal dystonic reactions to neuroleptics. Psychosomatics 1989;30:359–364.
7. Rowley H, Lynch T, Keogh I, Russell J. Tardive dystonia of the larynx in a quadriplegic patient: an unusual cause of stridor. J Laryngol Otol 2001;115:918–919.
8. Casey DE, Rabins P. Tardive dyskinesias as a life-threatening illness. Am J Psychiatry 1978;135:486–488.
9. Yassa R, Lal S. Respiratory irregularity and tardive dyskinesia. Acta Psychiatr Scand 1986;73:506–510.
10. Greene PE, Kang UJ, Fahn S. Spread of symptoms in idiopathic torsion dystonia. Mov Disord 1995;10:143–152.
11. Sachdev PS, Singh S. Dyskinesia presenting as a respiratory emergency. Med J Australia 1994;161:726–727.
12. Nishikawa T, Kaneda W, Uegaki A, Koga I, Uchida Y, Tanaka M. Respiratory dyskinesia: a variety of clincial forms differentially diagnosed by using a spirograph. Clin Neuropharmacol 1992;15:315–321.
13. Gregory RP, Smith PT, Rudge P. Tardive dyskinesia presenting as severe dysphagia. J Neurol Neurosurg Psychiatry 1992;55:1203–1204.
14. Hayashi T, Nishikawa T, Koga I, Uchida Y, Yamawaki S. Life-threatening dysphagia following prolonged neuroleptic therapy. Clin Neuropharmacol 1997;20:77–81.
15. Kasantikul D. Drug-induced akathisia and suicidal tendencies in psychotic patients. J Med Assoc Thai 1998;81:551–553.
16. Ayd FJ Jr. Akathisia and suicide: fact or myth? Int Drug Ther Newsl 1988;23:37–39.
17. Yassa R, Jones BD. Complications of tardive dyskinesia: a review. Psychosomatics 1985;26:305–313.
18. Szymanski S, Lieberman JA, Safferman A, Galkowski B. Rib fractures as an unusual complications of severe tardive dystonia. J Clin Psychiatry 1993;54:160.
19. Leung C, Chung DW, Kam IW, Wat KH. Multiple rib fractures secondary to severe tardive dystonia and respiratory dyskinesia. J Clin Psychiatry 2000;61:215–216.
20. Lazarus AL, Toglia JU. Fatal myoglobinuric renal failure in a patient with tardive dyskinesia. Neurology 1985;35:1055–1057.
21. Sacks OW, Kohl M. L-dopa and oculogyric crises. Lancet 1970:215–216.
22. Yoshida I, Sakaguchi Y, Matsuishi T, et al. Acute accidental overdosage of haloperidol in children. Acta Paediatr 1993;82:877–880.
23. Burke RE, Reches A, Traub MM, Ilson J, Swash M, Fahn S. Tetrabenazine induces acute dystonic reactions. Ann Neurol 1985;17:200–202.
24. Reeves AL, So EL, Sharbrough FW, Krahn LE. Movement disorders associated with the use of gabapentin. Epilepsia 1996;37:988–990.

25. Shafrir Y, Levy Y, Ben-Amital D, Nitzan M, Steinherz R. Oculogyric crisis due to domperidone therapy. Helv Paediat Acta 1985;40:95.
26. Gorman M, Barkley GL. Oculogyric crisis induced by carbamazepine. Epilepsia 1995;36:1158–1160.
27. Sandyk R. Oculogyric crisis induced by lithium carbonate. Eur Neurol 1984;23:92–94.
28. Lamberti P, de Mari M, Iliceto G, Caldarola M, Serlenga L. Effect of l-dopa on oculogyric crises in a case of dopa-responsive dystonia. Mov Disord 1993;8:236–237.
29. Kakigi R, Shibasaki H, Katafuchi Y, Iyatomi I, Kuroda Y. The syndrome of bilateral paramedian thalamic infarction associated with oculogyric crisis. Clin Neurol 1986;26:1100–1105.
30. Heimburger RF. Positional oculogyric crises. J Neurosurg 1988;69:951–953.
31. Lee MS, Kim YD, Lyoo CH. Oculogyric crisis as an initial manifestation of Wilson's disease. Neurology 1999;52:1714–1715.
32. Horiguchi J, Inami Y. Effect of clonazepam on neuroleptic-induced oculogyric crisis. Acta Psychiatr Scand 1989;80:521–523.
33. Burke RE, Kang U, Jankovic J, Miller LG, Fahn S. Tardive akathisia: an analysis of clinical features and response to open therapeutic trials. Mov Disord 1989;4:157–175.
34. Kang UJ, Fahn S. Management of tardive dyskinesia. Ration Drug Ther 1988;22:1–7.
35. Kang UJ, Burke RE, Fahn S. Natural history and treatment of tardive dystonia. Mov Disord 1986;1:193–208.

11
Hemiballism–Hemichorea

Ronald B. Postuma and Anthony E. Lang

PATIENT VIGNETTES

Patient 1: A 69-year-old man was followed at the Toronto Western Hospital with a 7-year history of Parkinson's disease (PD). Other past medical history included diabetes, coronary artery disease, and a previous stroke involving the right frontal lobe. Two weeks before presentation, he noticed the acute onset of involuntary movements of the left side, predominantly affecting the arm but also involving the leg and face. They tended to worsen soon after taking his levodopa. Clinical examination showed choreic movements of the left arm. Interestingly, the bradykinesia and rigidity were significantly ameliorated on the left side. Magnetic resonance imaging (MRI) examination demonstrated an infarction of the posterior putamen and globus pallidus, extending upwards into the periventricular white matter (*see* Fig. 1). Dopaminergic medications were decreased, resulting in improvement of his symptoms. During his admission, he began to have spontaneous improvement in symptoms, and did not require therapy.

This case illustrates several points. The first is that although stroke is the most common single cause of hemiballism, lesions are often outside of the subthalamic nucleus. The second is that prognosis is often benign. The third is that dopaminergic medications (in this case, levodopa) worsen hemiballism, just as dopamine antagonists treat it. Finally, we note the fortuitous effect of his stroke on his PD, perhaps as a result of infarction of the motor globus pallidus interna.

Patient 2: A 24-year-old woman had a 5-year history of multiple sclerosis with frequent relapses. She presented with parasthesias and left-sided incoordination associated with mild involuntary movements. As her sensory symptoms and coordination improved, involuntary movements increased in amplitude and became more violent, predominantly in the left arm and leg. Over time, smaller amplitude movements became evident on the right side, and these also progressed over time. MRI examination demonstrated numerous white matter lesions, including a large plaque in the area of the right subthalamic nucleus (Fig. 2). The ballismus persisted despite trials of pimozide, trifluoperazine, haloperidol, tetrabenazine, bromocriptine, sodium valproate, diazepam, and carbamazepine. A stereotactic thalamotomy provided no benefit, and was complicated by transient hemiparesis and postoperative epilepsy.

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

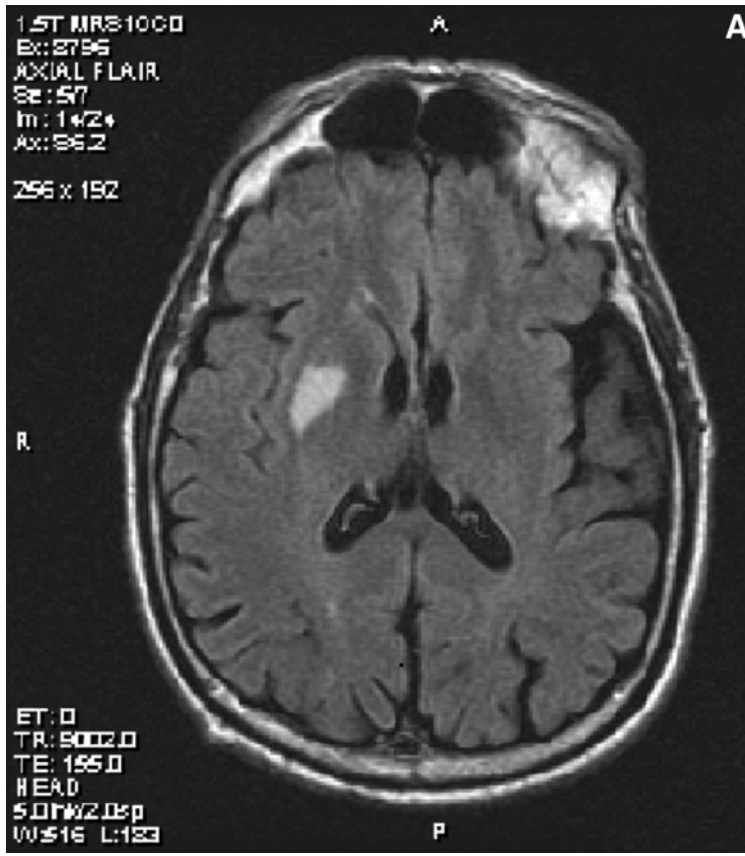


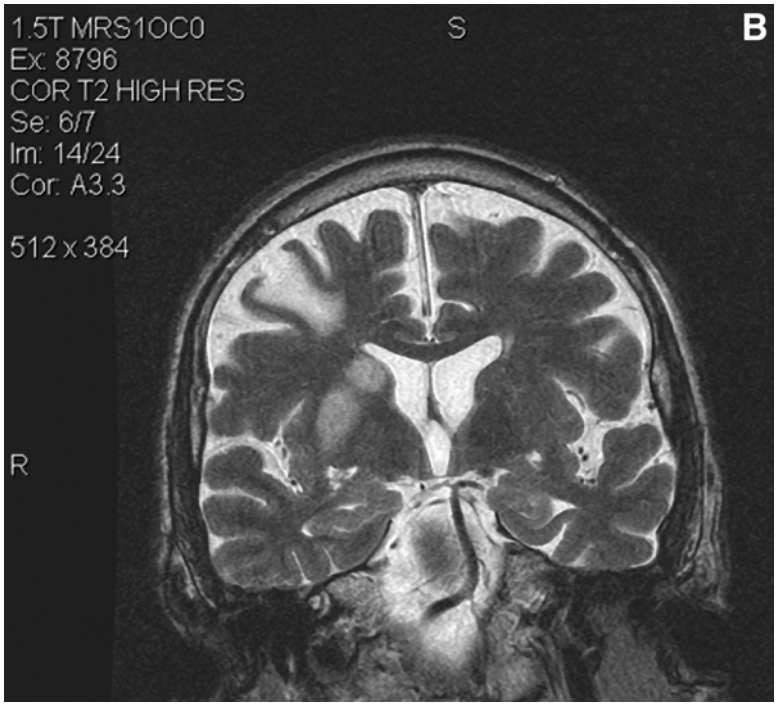
Fig. 1. Axial fluid-attenuated inversion-recovery **(A)** and high-resolution coronal T2-weighted **(B)** 1.5 Tesla magnetic resonance images of a 69-year-old man 2 weeks after the sudden development of hemiballism. An infarct is visible in the right striatum. On coronal images, an old right frontal infarct is also visible.

Over the next 5 years, she developed severe dystonia and athetosis of the left side. As the dystonia developed, the ballistic movements diminished.

This patient illustrates the more severe end of the spectrum of hemiballismus, with complete resistance to treatment. Hemiballism can be caused by any type of focal basal ganglia lesion, in this case a demyelinating plaque.

CLINICAL DESCRIPTION AND EPIDEMIOLOGY

Hemiballism is one of the most dramatic disorders in neurology. Because of its acute onset, it is frequently seen in the emergency room. Typically, the patient presents with an acute or subacute onset of flinging movements of one side of the body. These tend to occur both in the arm and leg, with variable involvement of the face. Movements often have a rotatory component and usually predominantly af-



fect proximal muscles. They can be severe enough to cause the patient to strike walls and bedrails, causing bruising and lacerations of the limb. Movements increase with action and stress, and are only rarely suppressible for more than a few seconds. They disappear in sleep. Hemichorea refers to movements that are similar in character but lower in amplitude, affecting both the distal and proximal limb. There is probably little pathophysiologic difference between the two movement disorders, as they share common etiologies, prognosis, and treatment. In fact, they can often be present in the same patient, with hemiballism more prominent early, and the lower amplitude hemichorea emerging as the disorder resolves. Therefore, for the purposes of this chapter, we consider them to be the same disorder, and use the terms interchangeably. Bilateral ballistic movement ("bi-ballism," or "para-ballism" if lower limbs are predominantly involved) is very uncommon, and occurs with bilateral central nervous system lesions.

Hemiballism is an uncommon disorder, and most general neurologists would not expect to see more than a handful of cases in their career. Dewey and Jankovic reported 21 patients with hemiballism out of 3084 patients evaluated in a specialty movement disorder clinic *(1)*. Of 2000 strokes in the Lausanne stroke registry, 550 involved basal ganglia structures, but only 11 caused hemiballism *(2)*. In most series, the mean age of onset is between 55 and 75 years, although many series are derived from subspecialty clinics, which may be biased because they generally see younger, more atypical patients. There is no clear gender predominance.

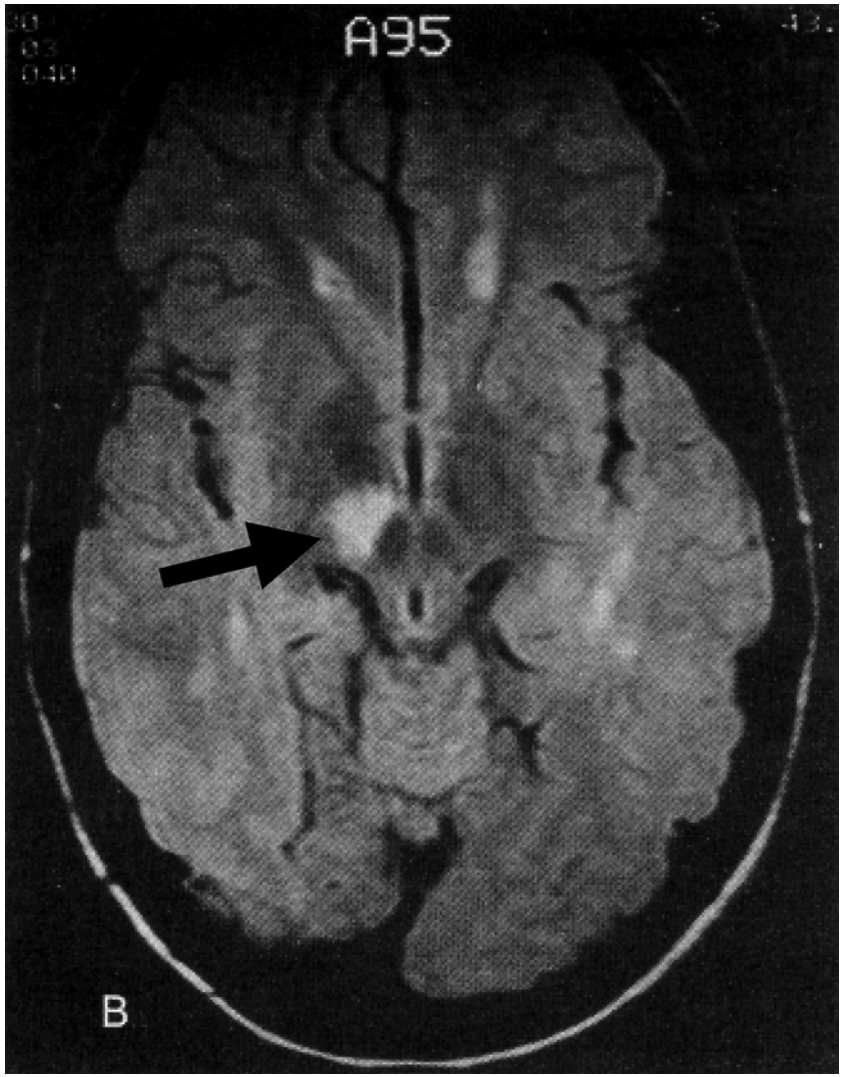


Fig. 2. Axial fluid-attenuated inversion-recovery sequence magnetic resonance image of a 24-year-old woman with multiple sclerosis demonstrating a plaque (arrow) in the area of the right subthalamic nucleus. (Reprinted with permission from ref. *15*.)

ETIOLOGY

Historically, hemiballism has been considered one of the most localizable symptoms in neurology—pathognomonic of a lesion of the subthalamic nucleus (STN). This thinking has been based on animal research, which suggested that hemiballism was reliably evoked by ablation of at least 20% of the STN (see "Pathophysi-

ology"). Review of the more recent literature, however, suggests that the STN is not the site of the lesion in the majority of cases.

Stroke is without question the single most common cause of hemiballism. In most cases, these are small-vessel lacunar infarcts commonly associated with diabetes or hypertension. However, conditions such as vasculitis and hypercoagulable states are other causes. In early series of patients with hemiballism, the STN was considered the most common site of stroke. In most of these cases, however, autopsy was not performed, and modern neuroimaging was not available. More recently, it has become clear that hemiballism can be caused by infarcts or hemorrhages in a variety of locations both inside and outside the basal ganglia. Stroke causing hemiballism was localized to the STN in only 4 of 27 cases reported by Ristic *(3)*, 4 of 11 cases in the Lausanne stroke registry *(2)*, and 4 of 11 cases reported by Dewey and Jankovic *(1)*. However, for some of these patients, only computed tomography imaging was performed, and STN lesions could have been missed. In sum, although stroke is the most common cause of hemiballism, the minority of these infarcts involve the STN directly.

More recent attention has been drawn to hemiballism associated with nonketotic hyperglycemia. With more than 60 reported cases, it may be the second most common cause worldwide. The condition has been described most in the Asian population. A typical patient is elderly, female, and presents with hemiballism and severe nonketotic hyperosmolar hyperglycemia *(4)*. As the blood glucose is corrected, the disorder usually resolves completely, although in 20% of patients mild symptoms persist for more than 3 months. Neuroimaging findings in these patients are striking. In all reported cases, high signal is seen on T1-weighted images in the putamen, with similar signal occasionally found in the globus pallidus and remainder of the striatum *(4)*. This finding usually clears when the movements subside. Two-thirds of patients also have high signal abnormalities on T2-weighted sequences, and some have corresponding abnormalities on diffusion-weighted imaging *(4,5)*. Pathological studies in two patients several months after symptoms resolved demonstrated significant gliosis, predominantly with gemistocytic astrocytes *(6,7)*. This might represent a reaction to microinfarction, although no blood vessel abnormalities were visualized and prominent gemistocytic infiltration would be an atypical response to infarction. The cause of this striking condition remains unknown.

Numerous other causes of hemiballism have been reported and are summarized in Table 1. These include mass lesions involving the basal ganglia or STN, medical diseases that predispose to infarction or hemorrhage, medications, and surgical lesions of either the STN or other basal ganglia structures.

PATHOPHYSIOLOGY

Much of our understanding of the pathophysiology of hemiballism derives from classic animal models of lesions of the STN. The original experiments were carried out by Whittier and Carpenter in 1949 and 1950 *(8)*. In these experiments, numerous lesions of the basal ganglia were created in primates, and their behavioral ef-

Table 1
Causes of Hemiballism

Common
Stroke (ischemic or hemorrhagic) in basal ganglia structures, most commonly lacunar
Nonketotic hyperglycemia
Uncommon or single case reports
Focal lesions in basal ganglia
Neoplastic
Metastases
Primary central nervous system tumors
Infectious
Cryptococcal granuloma
Toxoplasmosis
Tuberculoma
Vascular
Cavernous angioma
Postsurgical complications
Inflammatory
Multiple sclerosis
Iatrogenic
Subthalmotomy
Thalamotomy
Other mass lesions
Cerebellar metastases
Strokes in nonbasal ganglia areas
Subcortical white matter
Middle cerebral artery territory
Immunologic disorders/vasculitis
Systemic lupus erythematosus–often with anticardiolipin antibodies
Scleroderma
Bechet's disease
Hypoglycemia
Meningitis/encephalitis
Cryptococcal
Tuberculous
Sydenham's chorea
Head injury
Medications (usually superimposed on pre-existing basal ganglia lesion)
Anticonvulsants
Oral contraceptives
Levodopa
Ibuprofen

fects monitored. Contralateral hemiballism could be reliably produced only by lesions that destroyed more than 20% of the STN. Lesions in some areas of the globus pallidus were occasionally associated with hemiballism, and it was postulated

that these were the result of a disruption of connections to the STN. A second lesion to some areas of the globus pallidus interna (GPi) could abolish the movements. Crossman injected γ-aminobutyric acid antagonists, which affect neuronal cell bodies but not axons, into various basal ganglia locations in alert monkeys *(9)*. Again, only STN injections were capable of reliably causing hemiballism, confirming that the effects are caused by lesioning of neuronal cell bodies and not by white matter tracts in the region. Injections in the lateral globus pallidus were occasionally associated with slower hemichoreic/hemiathetoid movements. This may be analagous to hyperglycemic hemichorea, in which the areas predominantly affected are the putamen and GPi, and movements tend to be slower than those after a lesion of the STN. As a result of these and other investigations, it has been postulated that STN lesions interrupt the excitatory connections to the GPi, resulting in hypoactivity of the GPi. This disinhibits the motor thalamus, which in turn drives the motor cortex, resulting in excessive movement *(10)*. This simple model, which is based predominantly on neuronal firing rates, does not explain the mechanism of hemiballism caused by lesions outside of the STN, why movements are ballistic and intermittent, and why lesioning of the apparently hypoactive GPi is capable of abolishing hemiballism. Nor does it adequately explain why dopamine antagonists, which are generally believed to have their major effect at the level of the striatum, are especially effective in ameliorating hemiballism (see "Management"). Finally, it does not explain why subthalamotomy and subthalamic nucleus stimulation for Parkinson's disease are only very uncommonly complicated by hemiballism *(11)*.

Some additional recent insights have come from electrophysiological studies of three patients undergoing pallidotomy for hemiballism, in which microrecording of individual GPi neurons was obtained. All three patients had a vascular lesion as the presumed cause, two of these localized to the STN and one with a much more extensive infarct *(12–14)*. The two cases with STN lesions had firing rates of GPi neurons that were lower than expected normal values, whereas the third had a rate probably within the normal range. However, all three demonstrated an altered firing *pattern*, with intermittent bursts followed by pauses. Electromyogram examination of one case demonstrated that for some individual GPi neurons, ballistic movements correlated with pauses in firing. This suggests that the temporal pattern of GPi neuronal activity rather than the overall rate of firing is important in hemiballism, and that brief pauses in GPi firing may be responsible for the generation of ballistic movements.

PROGNOSIS

In the early literature, hemiballism was thought to carry a grave prognosis. Exhaustion and self-injury could cause significant morbidity, and at a time when medical therapy was unavailable, measures as extreme as limb amputation were sometimes considered. However, it has become clear that the natural history of hemiballism is much more benign than previously thought, and numerous effective treatments are now available. Because most cases are treated medically, the natural

history of hemiballism is unknown. Most cases will resolve spontaneously, usually in a few months to a year. Hyland and Foreman presented 14 patients with hemichorea, 12 of whom had spontaneous resolution within 3 months *(16)*. In the series by Johnson and Fahn, six patients stopped treatment after mean treatment duration of 27 days, and only two had a recurrence of movements *(17)*. Finally, in a series by Klawans, only 3 of 11 patients required long-term perphenazine therapy *(17,18)*. As mentioned previously, hemiballism associated with hyperglycemia usually improves over hours to days. The tendency for hemiballism to spontaneously improve should be considered when planning treatment, and also when interpreting reports of responses to treatment in the literature.

Although the prognosis of hemiballism is relatively benign, recent findings have raised concern about the long-term prognosis related to recurrent cerebrovascular disease. Ristic found a 50% mortality rate at 18 months in patients who had developed hemiballism from a stroke *(3)*. This is compared with an expected mortality rate after lacunar infarction of approx 15% at 5 years. Other series, although not directly examining mortality, did not seem to find a similar outcome.

MANAGEMENT

An algorithm for treating hemiballism is presented in Fig. 3. The first priority in the management of hemiballism is to look for reversible causes. Hyperglycemia and infectious and neoplastic lesions of the basal ganglia should be excluded. Treatment of the underlying cause may resolve the hemiballism, although severely affected patients may still require concomitant pharmacologic therapy. If stroke is the cause, standard stroke management such as antiplatelet therapy and secondary preventive measures such as blood pressure control and normalization of blood sugar must be implemented. The next step is to decide whether hemiballism is severe enough to warrant therapy. As mentioned previously, many cases will be mild and the majority of these will improve spontaneously. If therapy is required, nonpharmacological therapy, such as padding of the affected limb, should be considered. Attention should be paid to systemic complications such as exhaustion, dehydration, and rhabdomyolysis. In the very rare case of extremely severe hemiballism causing dangerous complications, patients may require sedation or even intubation with neuromuscular blockade as a temporary bridge until effective pharmacological therapy is instituted.

Antidopaminergic therapy is the mainstay of treatment for hemiballism. The best studied medications are typical neuroleptics such as haloperidol, perphenazine, pimozide, and chlorpromazine *(8,19,20)*. However, dopamine-depleting drugs, particularly tetrabenazine, can also produce marked benefit similar to that obtained with neuroleptics *(20)*. Given the minimal risk of tardive dyskinesia or acute dystonic reactions associated with its use, tetrabenazine is our preferred treatment for patients with persistent hemiballism who require ongoing dopaminergic blockade. Dosage can start at 12.5 mg two or three times daily and be titrated upward to a maximum of 250 mg per day. The speed of the titration and the maximum dose

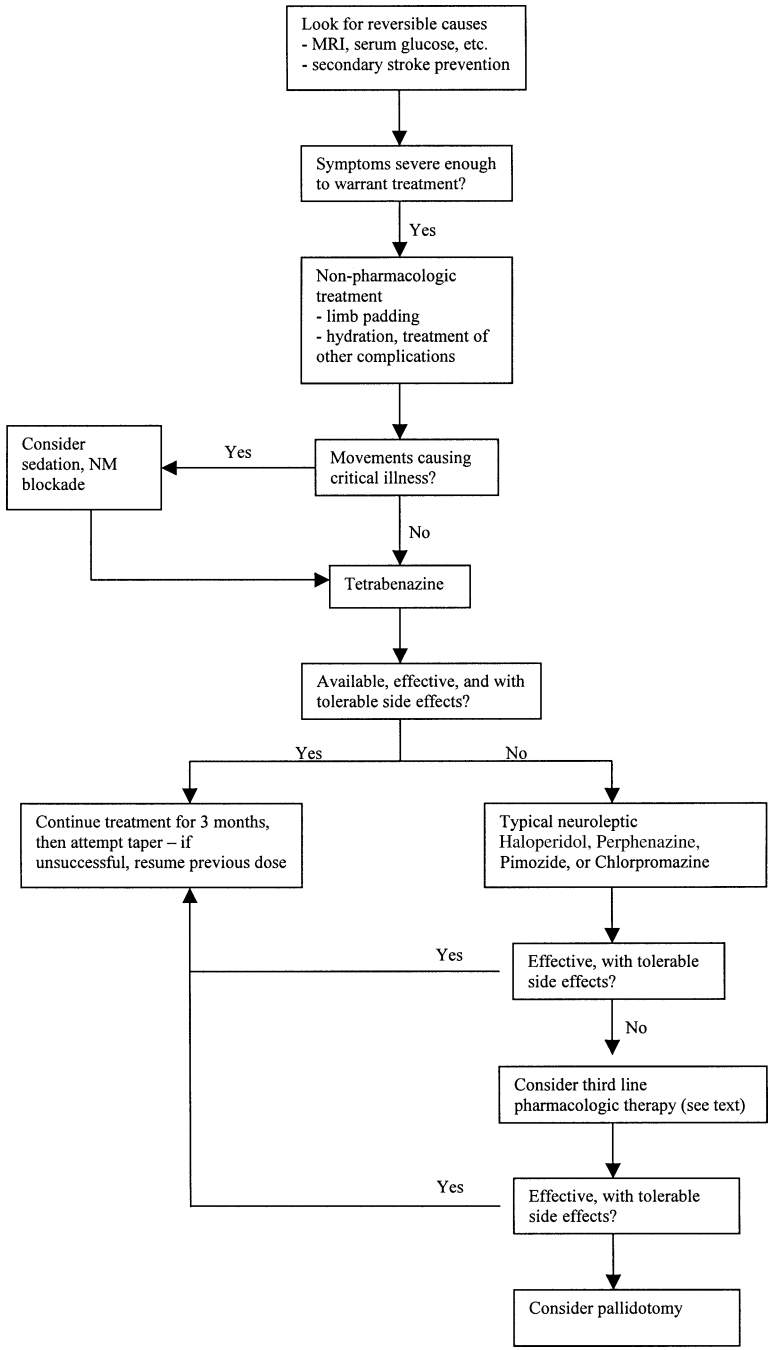


Fig. 3. Treatment algorithm.

depends on the severity of symptoms and the initial response to therapy. Clinicians should remain vigilant for the emergence of depression and orthostatic hypotension as side effects of tetrabenazine (in addition to drug-induced parkinsonism and akathisia). Blood pressure reduction may be a dose-limiting side effect if rapid titration is required for severe hemiballism.

If tetrabenazine is unavailable, ineffective, or causes severe side effects, or if the patient has a history of severe depression, typical neuroleptics should be tried. Although there are a wide variety of neuroleptics that may work, we favor haloperidol, starting at a dose of 0.5 to 1 mg twice daily, and titrating upwards as needed. In emergency situations, this can be given as an intramuscular dose of 1 mg and, if ineffective, 2 mg can be given 4 hours later. If there is still no improvement, 4 mg every 4 hours or even higher doses can be used, with subsequent attempts at downward titration if movements are successfully suppressed *(21)*. In urgent situations, tetrabenazine and haloperidol can be given together, to take advantage of their different mechanisms of action. The side effects of typical neuroleptics are well known, and will not be elaborated on further. However, one somewhat unique problem encountered with dopamine antagonists in hemiballism, especially in the elderly, is the development of drug-induced parkinsonism on the nonhemiballistic side. When this problem occurs before substantial benefit to the hyperkinetic movements, one may see an impressive combination of persistent hemiballism and contralateral parkinsonism, both causing disability. Conversely, in the case of rapid medication titration for severe hemiballismus, one can see a delayed-onset parkinsonism that may require subsequent downward titration of antidopaminergic therapy.

Response rates to dopamine-antagonist drugs are on the order of 90%, with quite dramatic reductions often achieved *(2,17,18)*. If typical neuroleptics fail, it is unlikely that other medications will have a dramatic effect. However, positive results have also been obtained with atypical neuroleptics such as risperidone, olanzapine, and clozapine, and with other presynaptic dopamine-depletors such as reserpine *(8,19,20)*. In addition, there have been reports of effective treatment with clonazepam, valproic acid, trihexyphenidyl, and amitriptyline *(8,19,20)*.

If effective, treatment should be maintained for a period of approx 3 months after which the medication should be gradually withdrawn. It is likely that the majority of patients will not have a significant recurrence. If pharmacological therapy is ineffective and patients have severe unremitting hemiballism for at least 3 months (or shorter, if symptoms have life-threatening consequences), surgical intervention may be appropriate. The procedure with the greatest reported experience is ventrolateral nucleus thalamotomy, with slightly fewer than 30 patients reported. Here the lesion is placed in the ventral anterior/ventral lateral thalamus, which is the region that receives basal ganglia (GPi, substantial nigra pars reticulata) outflow, in contrast to the ventral intermedial thalamotomy used for tremor, which is directed more posteriorly to the area that receives cerebellar input. Krauss and Mundinger have reported the largest series, with 13 patients followed for more than 3 years *(22)*. Of these 13 patients, 11 had significant improvement in their hemiballism. Side effects were few, with one patient suffering a transient hemiparesis, and two

with mild persistent dystonia. Another good option is GPi pallidotomy, with numerous case reports of successful treatment *(12–14,22)*. No large-scale series to date have thoroughly evaluated the efficacy of this approach. Finally, with the development of deep brain stimulation (DBS) of the pallidum or thalamus, this approach has become an option for the treatment of hemiballism. This is anticipated to have clinical effects similar to lesioning. However, many of the advantages of DBS, such as the greater safety of bilateral procedures (obviously irrelevant in hemiballism), and the ability to change stimulation parameters as the disease progresses (less crucial for static processes, such as those that cause hemiballism) are less important than for other conditions such as Parkinson's disease. This, in addition to the potential for long-term DBS hardware complications such as infection, breakage, and battery failure, argue for lesioning as the surgical treatment of choice in those rare patients who require surgery. Although no studies comparing thalamotomy to pallidotomy have been performed (and given the rarity of persistent hemiballism, it is very unlikely that they ever will be), based on our experience with modern pallidotomy for movement disorders we would favor pallidotomy directed at the sensorimotor ventroposterior medial pallidum as the surgical treatment of choice.

CONCLUSION

In summary, the view of hemiballism as a disorder localized to the STN carrying a grave prognosis is incorrect. Hemiballism has a variety of causes, most commonly basal ganglia stroke and hyperglycemia. Although impressive, it is generally benign and usually responds well to neuroleptic treatment. Treatment complications and drug-resistant cases do occur, representing important therapeutic challenges.

REFERENCES

1. Dewey RB, Jankovic J. Hemiballism-hemichorea. Clinical and pharmacologic findings in 21 patients. Arch Neurol 1989;46:862–867.
2. Ghika-Schmid F, Ghika J, Regli F, Bogousslavsky J. Hyperkinetic movement disorders during and after acute stroke: the Lausanne Stroke Registry. J Neurol Sci 1997;146:109–116.
3. Ristic A, Marinkovic J, Dragasevic N, Stanisavljevic D, Kostic V. Long-term prognosis of vascular hemiballismus. Stroke 2002;33:2109–2111.
4. Oh SH, Lee KY, Im JH, Lee MS. Chorea associated with non-ketotic hyperglycemia and hyperintensity basal ganglia lesion on T1-weighted brain MRI study: a meta-analysis of 53 cases including four present cases. J Neurol Sci 2002;200:57–62.
5. Chu K, Kang DW, Kim DE, Park SH, Roh JK. Diffusion-weighted and gradient echo magnetic resonance findings of hemichorea-hemiballismus associated with diabetic hyperglycemia: a hyperviscosity syndrome? Arch Neurol 2002;59:448–452.
6. Shan DE, Ho DM, Chang C, Pan HC, Teng MM. Hemichorea-hemiballism: an explanation for MR signal changes. AJNR 1998;19:863–870.
7. Ohara S, Nakagawa S, Tabata K, Hashimoto T. Hemiballism with hyperglycemia and striatal T1-MRI hyperintensity: an autopsy report. Mov Disord 2001;16:521–525.
8. Shefner J. Ballism. In: Joseph A, Young R, eds. Movement Disorders in Neurology and Neuropsychiatry. Blackwell Science, Malden, Mass: 1999;475–480.

9. Crossman AR, Sambrook MA, Jackson A. Experimental hemichorea/hemiballismus in the monkey. Studies on the intracerebral site of action in a drug-induced dyskinesia. Brain 1984;107(Pt 2):579–596.
10. DeLong MR. Primate models of movement disorders of basal ganglia origin. Trends Neurosci 1990;13:281–285.
11. Guridi J, Obeso JA. The subthalamic nucleus, hemiballismus and Parkinson's disease: reappraisal of a neurosurgical dogma. Brain 2001;124:5–19.
12. Lenz FA, Suarez JI, Metman LV, et al. Pallidal activity during dystonia: somatosensory reorganisation and changes with severity. J Neurol Neurosurg Psychiatry 1998;65:767–770.
13. Suarez JI, Metman LV, Reich SG, Dougherty PM, Hallett M, Lenz FA. Pallidotomy for hemiballismus: efficacy and characteristics of neuronal activity. Ann Neurol 1997;42:807–811.
14. Vitek JL, Chockkan V, Zhang JY, et al. Neuronal activity in the basal ganglia in patients with generalized dystonia and hemiballismus. Ann Neurol 1999;46:22–35.
15. Riley D, Lang AE. Hemiballism in multiple sclerosis. Mov Disord 1988;3:88–94.
16. Hyland H, Foreman D. Prognosis in hemiballismus. Neurology 1957;7:381–391.
17. Johnson WG, Fahn S. Treatment of vascular hemiballism and hemichorea. Neurology 1977;27:634–636.
18. Klawans HL, Moses H, III, Nausieda PA, Bergen D, Weiner WJ. Treatment and prognosis of hemiballismus. N Engl J Med 1976;295:1348–1350.
19. Shannon K. Ballism. In: Jankovic J, Tolosa E, eds. Parkinson's Disease and Movement Disorders. Williams and Wilkins, Baltimore: 1998;365–375.
20. Grandas F. Ballism. In: Jankovic J, Tolosa E, eds. Parkinson's Disease and other Movement Disorders. Lippincott Williams and Wilkins, Philadelphia: 2002;234–239.
21. Ranawaya R, Lang AE. Neurological Emergencies in Movement Disorders. In: Weiner W, ed. Emergent and Urgent Neurology. J.B. Lippincott, Philadelphia: 1992;277–319.
22. Krauss JK, Mundinger F. Functional stereotactic surgery for hemiballism. J Neurosurg 1996;85:278–286.

12

Sydenham's Chorea, PANDAS, and Other Poststreptococcal Neurological Disorders

Roser Pons

PATIENT VIGNETTE

A 12-year-old boy developed hyperthyroidism secondary to Grave's disease, which was successfully treated with I-131 treatment. Several months later, pharyngeal infection with group A β-hemolytic *Streptococcus* was documented by throat culture and subsequent rise in antistreptolysin O titer. He was treated with oral antibiotics, and 2 weeks later developed insidious, progressive chorea, incoordination with right hemibody, and imbalance. Examination revealed moderate chorea affecting the eyes, arms, and legs, incoordination of fine hand movements, motor impersistence on hand grip and tongue protrusion, and near inability to walk. He was treated with valproic acid, and his symptoms resolved within 3 weeks.

INTRODUCTION

In 1686, Thomas Sydenham described the entity that bears his name as a syndrome of involuntary, purposeless, rapid movements of the limbs accompanied by muscular weakness and emotional lability. Bouteille in 1810 and Bright in 1831 later recognized the association of chorea with rheumatic fever (RF) *(1)*. In 1889, Cheadle described the full rheumatic syndrome of carditis, polyarthritis, chorea, subcutaneous nodules, and erythema marginatum. Subsequent epidemiological and microbiological studies confirmed the link between *Streptococcus*, Sydenham's chorea, and RF. Since 1944, chorea has been included as one of the major criteria in the diagnosis of RF *(2)*.

During the second half of the 20th century, behavioral and emotional difficulties in patients with Sydenham's chorea were increasingly recognized *(3,4)*. In the 1980s, in the setting of an outbreak of group A streptococcal infection, a group of patients with acute, explosive tics and psychiatric disorders were recognized. The clinical phenotype of postinfectious immune-mediated neurobehavioral syndromes mimicking Tourette's syndrome was termed pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS) *(5)*.

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

Recent reports have suggested that the spectrum of poststreptococcal central nervous system (CNS) disease is broad, including a number of hyperkinetic movements and behavioral abnormalities. A subgroup of patients with acute disseminated encephalomyelitis with basal ganglia lesions, dystonia, and emotional lability associated with streptococcal infection was identified *(6)*. Other reports of poststreptococcal CNS disorders include acute myoclonus *(7)*, dystonia with isolated striatal necrosis *(8)*, and paroxysmal dystonic choreoathetosis *(9)*. These reports, together with the finding of antineuronal antibodies in many of these diseases, have raised the hypothesis of a common autoimmune pathophysiological mechanism *(10)*.

CLINICAL FEATURES AND DIAGNOSIS

Sydenham's Chorea

Sydenham's chorea is the neurological manifestation of RF. A major criterion for the diagnosis of acute RF, chorea alone is sufficient to make this diagnosis *(2)*. The portion of patients with RF who develop chorea and their associated clinical features vary according to temporal and geographic factors *(11–13)*. Usually Sydenham's chorea begins after a prolonged latent period following group A streptococcal infection. Patients develop chorea 4 to 8 weeks after an episode of streptococcal pharyngitis *(14)*, but a delay of several months has also been described *(15)*. Chorea may begin acutely or subacutely. The age of presentation ranges from 5 to 15 years, and there is a female preponderance *(11–17)* (Table 1).

The main features of Sydenham's chorea are involuntary, random, purposeless, nonrhythmic, sudden, brief movements. They flow from one body part to another, and patients often appear restless. Chorea spreads rapidly, although in 20–30% of cases it remains unilateral *(11,14,16,17)*. Chorea is often severe enough to be disabling, and in rare cases may prevent the patient from walking *(11,16)*. Patients display motor impersistence, noticeable during tongue protrusion or when sustaining muscle contraction. Muscle tone is usually decreased. In rare cases, symptoms are so severe that the patient becomes bedridden (so-called "paralytic chorea"). Other neurological features include dysarthria, weakness, clumsy gait, hypometric saccades, and hung-up reflexes *(11,15)*. Motor and vocal tics can also occur, and oculogyric crises have been reported *(11)* (Table 1).

Psychiatric symptoms are common in Sydenham's chorea. These include obsessive-compulsive symptoms, attention deficit hyperactivity disorder (ADHD), major depressive disorder, and separation anxiety *(3,18,19)* (Table 1). Clinical features of RF accompanying chorea, such as cardiac involvement, have been reported in 10 to 84% of patients *(11,12,24)*. Arthritis is seen in up to 30% *(11)* (Table 1). Sydenham's chorea is a self-limited condition, usually spontaneously remitting after 2 to 6 months *(15,16)*. In some patients it may last up to 2 years, and in rare cases it persists *(12,20)*. Chorea may recur, and the incidence of recurrences may be as high as 20 to 60% *(12–16)*. Recurrences may be induced by re-infection with *Streptococcus*, birth control pills, and pregnancy ("chorea gravidarum") (Table 1).

Diagnosis relies on clinical findings of acute chorea with a history of prior *Streptococcus* infection. Because chorea is generally a late manifestation of RF, it is

Table 1
Clinical Spectrum of Poststreptococcal Central Nervous System Disorders

	Sydenham's chorea	PANDAS	Poststreptococcal acute disseminated encephalomyelitis *(6)*	Poststreptococcal myoclonus *(7)*	Poststreptococcal isolated bilateral striatal necrosis *(8)*	Poststreptococcal paroxysmal dystonic choreoathetosis *(9)*
Age	5–15 years	3–8 years	3–14 years	5–12 years	1–4 years	8 years
Gender	F > M	M > F	M > F	M	M	M
Onset	Acute/ subacute	Acute	Acute	Acute	Acute	Acute paroxysmal
Movement disorder	Chorea	Tics	Dystonia Tremor Rigidity Paroxysmal dystonia	Myoclonus	Dystonia Rigidity Tremor Chorea	Chorea Dystonia
Psychiatric disorders	OCD, anxiety, major depression, ADHD	OCD, anxiety, major depression, ADHD	Emotional lability, disinhibition, perseverations, inattention, separation anxiety, confusion	Aggression, hyperactivity	Emotional lability	Immature behavior Separation anxiety Depression
↓Level of consciousness	–	–	50%	–	50%	–
Exacerbation/ recurrences	20–60%	100%	20%	33%	–	+
Heart involvement	+ (up to 84%)	–	–	–	–	–
↑ASO, ↑antiDNAse	±	+	+	+	+	+
Antineuronal antibodies	+	+	+	NR	+	+
Brain MRI	Normal Increased BG signal Enlarged BG	Normal Enlarged BG	Basal ganglia Demyelinating lesions	Normal	Striatal abnormalities	Normal

PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; F, female; M, Male; OCD, obsessive compulsive symptoms; ADHD, attention deficit hyperactivity disorder; ASO, antistreptolysin O titers; NR, not reported; BG, basal ganglia; MRI, magnetic resonance imaging.

unusual to find clinical evidence of acute streptococcal infection *(2)*. Elevated acute-phase reactants and antistreptoccocal antibodies (antistreptolysin O, antiDNAse-B antibodies) may be absent in patients with isolated chorea *(13,16)*. The electroencephalogram may show nonspecific abnormalities *(17)*, and brain magnetic resonance imaing (MRI) is usually normal, although reversible hyperintensities in the basal ganglia have been reported *(21,22)* (Table 1).

PANDAS

PANDAS is a contested diagnostic entity applied to children with tics and/or obsessive-compulsive symptoms temporally linked to prior streptococcal infection. These patients show a relapsing remitting course, often with significant psychiatric comorbidity. Clinical criteria for this condition include the following: (1) presence of tics and/or obsessive-compulsive disorder; (2) prepubertal symptom onset; (3) episodic course of symptom severity; (4) association with group A streptococcal infections; and (5) association with neurological abnormalities *(5)*.

In 1998, Swedo *(5)* reported clinical features of the first 50 patients diagnosed with PANDAS. The age of presentation ranged from 3 to 10 years, with a male preponderance. Forty-eight percent of the patients presented with acute obsessive-compulsive symptoms, and 52% presented primarily with motor and vocal tics. The severity of obsessive-compulsive symptoms and tics was moderate on average, and comorbid psychiatric symptoms were common. Patients typically presented abruptly, with significant distress. The most prevalent psychiatric diagnoses were ADHD, affective disorders, and anxiety disorders. Choreiform movements described as small, jerky movements occurring irregularly and arrhythmically in different muscles were noted in half of the patients. No child had overt chorea *(5)* (Table 1). The clinical course was episodic, characterized by a waxing and waning course and abrupt onset of symptoms. Symptom onset and exacerbations were temporally related to preceding streptococcal infection. Such infection was not always proven, although each child had at least one symptom exacerbation that was preceded by a documented streptococcal infection within the prior 6 weeks *(5)* (Table 1).

The diagnosis of PANDAS is based on the five inclusion criteria mentioned above. In order to prove the temporal association with *Streptococcus*, elevation of antistreptoccocal titers with onset and exacerbations, followed by falling titers with symptom remission, is required *(5)*.

Poststreptococcal Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis is a postinfectious or postvaccination inflammatory disease of the CNS. The pathological hallmark is scattered foci of demyelination throughout the brain and spinal cord. Various viral and bacterial pathogens have been associated with this condition *(23)*. A subgroup of patients with acute disseminated encephalomyelitis associated with streptococcal infections had been reported *(6)*. Recently, Dale *(6)* presented 10 patients with poststreptococcal acute disseminated encephalomyelitis. Extrapyramidal manifestations were present in 50% of the patients: four had dystonia, three had axial and

limb rigidity, and two had resting tremor. Behavioral problems were seen in seven patients. Streptococcal serologies were significantly elevated in all patients, and 80% showed basal ganglia lesions on neuroimaging. Thalamus, subthalamus, and substantia nigra were also involved in 60, 30, and 50% of the cases, respectively (Table 1).

Poststreptococcal Acute Myoclonus

In 1998, three patients with acute-onset myoclonus following streptococcal infection were reported *(7)*. Myoclonus was generalized in two patients and segmental in another. In one patient, myoclonus was associated with behavioral change, including aggression and hyperactivity. Streptococcal serologies were elevated in all patients (Table 1).

Poststreptococcal Autoimmune Dystonia With Isolated Striatal Necrosis

Bilateral striatal necrosis is an acute onset extrapyramidal disorder that may occur following a variety of infections. Neuroimaging shows symmetric lesions in the striatum *(24)*. Two patients with isolated striatal necrosis occurring shortly after a streptococcal pharyngitis were reported *(8)*. One patient presented with an acute neurological illness, with weakness, ataxia, and dystonic posturing followed by rigidity and tremor, oropharyngeal incoordination, and generalized chorea. The second patient presented with lethargy, episodic dystonic posturing, ataxia, and emotional lability. Cerebrospinal fluid protein concentration was elevated in both patients. Brain MRI showed selective striatal abnormalities. Streptococcal serologies were elevated and convalescent serology showed a reduction in titers (Table 1).

Poststreptococcal Paroxysmal Dystonic Choreoathetosis

There is one reported case of paroxysmal dystonic choreoathetosis occurring one week after a streptococcal pharyngitis *(9)*. This patient presented with acute onset of paroxysmal episodes of dystonic posturing, choreoathetosis, visual hallucinations, and immature behavior lasting minutes to hours. The episodes occurred several times day, and symptoms fluctuated, lasting 6 months. Streptococcal serologies were elevated, and convalescent serologies showed a reduction in titers (Table 1).

PATHOPHYSIOLOGY

The basal ganglia is believed to be the source of the problem in Sydenham's chorea and other poststreptoccocal movement disorders. This is supported by the known role of the basal ganglia in motor and behavior control, and by postmortem and neuroimaging studies in patients with Sydenham's chorea. Early pathological reports of Sydenham's chorea showed inflammatory changes involving the basal ganglia and, to a lesser extent, the cortex *(1)*. MRI has shown signal abnormalities in the striatum in some patients with Sydenham's chorea *(21,22)*. Abnormal striatal spectra consistent with neuronal damage have been reported in one patient with

Sydenham's chorea *(22)*. Volumetric studies have demonstrated enlargement of the caudate, putamen, and pallidum in patients with Sydenham's chorea and PANDAS *(21,25)*. Furthermore, patients with poststreptococcal acute disseminated encephalomyelitis showed basal ganglia lesions in 80% of the cases *(6)* and bilateral striatal lesions were noted in the two patients previously mentioned with poststreptococcal autoimmune dystonia with isolated striatal necrosis *(8)*. Single-photon emission computed tomography studies have also revealed hyperperfusion of the basal ganglia in some patients with Sydenham's chorea *(26)*.

Particular serotypes of the group A β-hemolytic *Streptococcus* are involved in RF and poststreptococcal disorders. The likely mechanism involves induction of antibodies to the infection that crossreact with the basal ganglia. This is supported by the induction of such antibodies when rats are immunized with the major virulence factor of group A *Streptococci* (surface M protein) *(10)*. Antibasal ganglia antibodies have been found in 45–100% of patients with Sydenham's chorea, and their levels correlate with disease activity *(27,28)*. A recent study showed that these antibodies possessed specific immunoglobulin binding sites for large striatal neurons, and that the binding was confined to tracts of neurons in the caudate head *(29)*. Antibasal ganglia antibodies have also been reported in other poststreptococcal disorders, including PANDAS, acute disseminated encephalomyelitis, paroxysmal dyskinesias, and striatal necrosis *(6,8,9,30)*.

The autoimmune mimicry hypothesis is further supported by reports of benefit from immunomodulatory treatment in some of these patients *(6,31,32)*, and a recent report of induction of hyperkinetic movements in rats after intrastriatal infusion of serum with antibasal ganglia antibodies *(33)*. However, this latter report has not been confirmed.

Given the fact that RF and Sydenham's chorea are more common in first-degree relatives of affected patients *(10)*, and the fact that obsessive-compulsive disorder and tics are more common in family members of PANDAS patients *(34)*, an underlying genetic predisposition has been proposed. The B-lymphocyte marker D8/D17 has been detected in high levels in patients with RF, Sydenham's chorea, and PANDAS supporting this concept *(35,36)*. The biological function of this marker remains undefined. In fact, it is fair to say that the relationship of streptococcal infection with poststreptococcal CNS syndromes other than Sydenham's is controversial. Evidence of current or recent streptococcal infection in school children in winter is common, and symptom exacerbations related to streptococcal or other infections may represent a nonspecific response to stress *(37)*. In addition, unlike Sydenham's chorea, no correlation between the production of autoantibodies and severity of symptoms has been demonstrated, and no features of RF have been reported to date.

TREATMENT

The symptoms of Sydenham's chorea, PANDAS, and other poststreptococcal CNS disorders can evolve rapidly, often requiring prompt intervention. Management of poststreptococcal CNS disorders are discussed in these settings (Table 2):

Table 2

Treatment Options Reported[a] in Poststreptococcal Central Nervous System Disorders

	Sydenham's chorea	PANDAS	Poststreptococcal acute disseminated encephalomyelitis *(6)*	Poststreptococcal myoclonus *(7)*	Poststreptococcal solated bilateral striatal necrosis *(8)*	Poststreptococcal paroxysmal dystonic choreoathetosis *(9)*
Symptomatic treatment	First line: Valproic acid Carbamazepine Second line: Pimozide Haloperidol	Serotonin reuptake inhibitors Clonidine Neuroleptics	NR	NR	NR	Carbamazepine
Antibiotic therapy for streptococcal acute infection		Penicillins Cephalosporins		+	+	
Antibiotic therapy for prophylaxis	B Penicillin Penicillin V Sulfadiazine	Penicillins	Penicillins		+	+
Immunotherapy	Steroids	Plasma exchange Immunoglobulins	Steroids	NR	Steroids	NR

[a]Except for antibiotic prophylaxis in Sydenhams' chorea, there are no routine treatment guidelines for the management of poststreptococcal central nervous system disorders. NR, not reported; +, antibiotic treatment was not specified in these reports; PANDAS, pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections.

(1) symptomatic treatment of the acute movement disorder and/or psychiatric problem; (2) antibiotic therapy; and (3) immunotherapy.

Sydenham's Chorea

Symptomatic Treatment

Sedatives, anticonvulsants, and neuroleptics have been used in the symptomatic management of Sydenham's chorea. Valproic acid is the anticonvulsant most widely used for the treatment of Sydenham's chorea. Several reports have shown that valproic acid is effective for the treatment of Sydenham's chorea, at doses of 10–25 mg/kg/day *(17,38,39)*. Patients who respond to valproic acid may show a marked reduction of involuntary movements within 1 week of treatment, although slower onset of action has also been reported *(38)*. Treatment is usually given for 4 to 8 weeks, although in cases where symptoms recur, patients may need to be treated for a longer period *(38)*. Carbamazepine has also been reported as a successful treatment for Sydenham's chorea *(40)*. A noncontrolled study of low-dose carbamazepine (4–10 mg/kg/day) showed improvement of chorea in 2 to 14 days. Treatment was continued for 1 to 15 months *(41)*. Recently, two prospective studies suggested that valproic acid and carbamazepine have similar efficacy and safety in this patient population *(17,39)*.

Because of the potential risk of tardive dyskinesias, dopamine receptor blockers are typically reserved for situations when chorea is severe and refractory to other treatments. Pimozide (1–2 mg twice a day) has been very effective, often controlling chorea within a few days *(42,43)*. Haloperidol has also been used successfully, although a recent study comparing valproic acid, carbamazepine, and haloperidol suggested that haloperidol was the least effective of the three agents *(39)*. Tetrabenazine, a dopamine receptor blocker and monoaminergic depletory, may also be useful, and has the advantage of carrying little to no risk of engendering tardive syndromes.

Antibiotic Treatment

For prevention of rheumatic recurrences, continuous antibiotic prophylaxis against further streptococcal infections is recommended. Monthly injections of 1.2 million U of benzathine penicillin G are recommended, although in populations where the prevalence of rheumatic fever is high, injections every 3 weeks are indicated. In areas where RF is no longer prevalent, 600,000 U of oral penicillin V twice a day or 0.5 g of sulfadiazine twice a day will suffice. Treatment is maintained for several years, and the decision to discontinue depends on the community's rheumatogenic characteristics *(44)*.

Immunotherapy

Immunomodulatory treatment is not routinely used in patients with Sydenham's chorea. However, corticosteroids have been successfully used in severe cases *(31,38)*. One noncontrolled prospective study showed marked improvement of chorea within a few days of treatment. The duration of treatment ranged from a few

days to 1 month. One patient experienced a recurrence of chorea after discontinuation of treatment, requiring a total of 3 months of steroid therapy *(31)*. Although there are no guidelines for immunotherapy in Sydenham's chorea, it is reasonable to try a short course of steroids in severe cases in which symptoms fail to respond to conventional treatment.

PANDAS

Symptomatic treatment

The neurospychiatric symptoms of PANDAS at onset or during acute exacerbations may be severe *(45)*. Symptomatic treatments include serotonin-specific reuptake inhibitors for obsessive-compulsive symptoms, and clonidine and neuroleptics for tics. However, often patients are refractory to treatment with standard agents *(32)*.

Antibiotic Treatment

A recent, prospective study of patients with new-onset PANDAS and documented streptococcal infection (using penicillins or cephalosporins) produced improvement of the neuropsychiatric symptoms within 5 to 21 days *(45)*. A double-blind crossover study comparing penicillin prophylaxis to placebo in patients with PANDAS failed, however, to show any change in symptom severity. The authors raised the possibility that failure to achieve acceptable antibiotic prophylaxis may have explained the negative results *(46)*.

Immunotherapy

A double-blind, randomized, placebo-controlled study compared either plasma exchange or intravenous immunoglobulins with placebo in a group of 30 patients with severe neuropsychiatric symptoms meeting criteria for PANDAS *(32)*. One month after treatment, patients who received plasma exchange or intravenous immunoglobulins showed significant improvement in obsessive-compulsive symptoms and psychosocial functioning. The plasma exchange group showed significant improvements in tic severity, whereas the intravenous immunoglobulins group did not. The beneficial effect was noted at the end of the first week in patients who received plasma exchange and at 3 weeks in the patients receiving intravenous immunoglobulins. Benefits of treatment were maintained at 1 year in both groups. Based on this single study, it appears that immunotherapy may be beneficial in select cases. The authors were careful to stress that their study did not provide support for generalized routine use. The decision to use immunomodulatory therapy in children must be balanced with the potential immediate and long-term risks of treatment.

Poststreptococcal Acute Disseminated Encephalomyelitis

Of the 10 patients, 9 reported with poststreptococcal acute disseminated encephalomyelitis were treated with intravenous methylprednisolone for 3 days. This was followed by rapid clinical improvement, and subsequent relapse in two patients

several months after presentation. Patients who relapsed were given penicillin prophylaxis to minimize the occurrence of further relapses *(6)*.

Poststreptococcal Acute Myoclonus

Two patients with post-streptococcal myoclonus showed resolution of their symptoms within several weeks of administration of antibiotics for streptococcal pharyngitis. A third patient did not respond to antistreptoccocal antibiotic therapy or conventional treatment for myoclonus *(7)*.

Poststreptococcal Autoimmune Dystonia With Isolated Striatal Necrosis

One patient was treated with antibiotic prophylaxis and oral prednisolone with significant improvement over several weeks. The second patient was treated with antibiotics, with improvement of symptoms within a few days *(8)*.

Poststreptococcal Paroxysmal Dystonic Choreoathetosis

In the reported patient with paroxysmal dystonic choreoathetosis associated with streptococcal infection, there was no response to antibiotic prophylaxis. Chlorpromazine also failed, whereas carbamazepine decreased the number of attacks.

CONCLUSION

Poststreptococcal movement disorders are phenomenologically varied. These illnesses often present suddenly, and it is not uncommon for there to be significant disability. With proper management, including pharmacological intervention, most patients can be effectively treated.

REFERENCES

1. Jummani R, Okun M. Sydenham chorea. Neurology 2001;58:311–313.
2. Shiffman RN. Guideline maintenance and revision. 50 years of the Jones criteria for diagnosis of rheumatic fever. Arch Pediatr Adolesc Med 1995;149:727–732.
3. Swedo SE, Rapoport JL, Cheslow DL, et al. High prevalence of obsessive-compulsive symptoms in patients with Sydenham's chorea. Am J Psychiatry 1989;146:246–249.
4. Swedo SE. Sydenham's chorea. A model for childhood autoimmune neuropsychiatric disorders. JAMA 1994;272:1788–1791.
5. Swedo SE, Leonard HL, Garvey M, et al. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections: clinical description of the first 50 cases. Am J Psychiatry 1998;155:264–271.
6. Dale RC, Church AJ, Cardoso F, et al. Poststreptococcal acute disseminated encephalomyelitis with basal ganglia involvement and auto-reactive antibasal ganglia antibodies. Ann Neurol 2001;50:588–595.
7. DiFazio MP, Morales J, Davis R. Acute myoclonus secondary to group A beta-hemolytic streptococcus infection: a PANDAS variant. J Child Neurol 1998;13:516–518.
8. Dale RC, Church AJ, Benton S, et al. Post-streptococcal autoimmune dystonia with isolated bilateral striatal necrosis. Dev Med Child Neurol 2002;44:485–489.
9. Dale RC, Church AJ, Surtees RA, Thompson EJ, Giovannoni G, Neville BGR. Post-streptococcal autoimmune neuropsychiatric disease presenting as paroxysmal dystonic choreoathetosis. Mov Disord 2002;17:817–820.
10. Dale RC. Autoimmunity and the basal ganglia: new insights into old diseases. QJM 2003;96:183–191.
11. Cardoso F, Eduardo C, Silva AP, Mota CC. Chorea in fifty consecutive patients with rheumatic fever. Mov Disord 1997;12:701–703.

12. Carapetis JR, Currie BJ. Rheumatic fever in a high incidence population: the importance of monoarthritis and low grade fever. Arch Dis Child 2001;85:223–227.
13. Terreri MT, Roja SC, Len CA, Faustino PC, Roberto AM, Hilario MO. Sydenham's chorea—clinical and evolutive characteristics. Sao Paulo Med J 2002;120:16–19.
14. Ghram N, Allani C, Oudali B, Fitouri Z, Ben Becher S. Sydenham's chorea in children. Arch Pediatr 1999;6:1048–1052.
15. Nausieda PA, Grossman BJ, Koller WC, Weiner WJ, Klawans HL. Sydenham chorea: an update. Neurology 1980;30:331–334.
16. Al-Eissa A. Sydenham's chorea: a new look at an old disease. Br J Clin Pract 1993;47:14–16.
17. Genel F, Arslanoglu S, Uran N, Saylan B. Sydenham's chorea: clinical findings and comparison of the efficacies of sodium valproate and carbamazepine regimens. Brain Dev 2002;24:73–76
18. Asbahr FR, Negrao AB, Gentil V, et al. Obsessive-compulsive and related symptoms in children and adolescents with rheumatic fever with and without chorea: a prospective 6-month study. Am J Psychiatry 1998;155:1122–1124.
19. Mercadante MT, Busatto GF, Lombroso PJ, et al. The psychiatric symptoms of rheumatic fever. Am J Psychiatry 2000;157:2036–2038.
20. Cardoso F, Vargas AP, Oliveira LD, Guerra AA, Amaral SV. Persistent Sydenham's chorea. Mov Disord 1999;14:805–807.
21. Giedd JN, Rapoport JL, Kruesi MJ, et al. Sydenham's chorea: magnetic resonance imaging of the basal ganglia. Neurology 1995;45:2199–2202.
22. Castillo M, Kwock L, Arbelaez A. Sydenham's chorea: MRI and proton spectroscopy. Neuroradiology 1999;41:943–945.
23. Dale RC, de Sousa C, Chong WK, Cox TC, Harding B, Neville BG. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain 2000;123:2407–2422.
24. Leuzzi V, Bertini E, De Negri AM, Gallucci M, Garavaglia B. Bilateral striatal necrosis, dystonia and optic atrophy in two siblings. J Neurol Neurosurg Psychiatry 1992;55:16–19.
25. Giedd JN, Rapoport JL, Garvey MA, Perlmutter S, Swedo SE. MRI assessment of children with obsessive-compulsive disorder or tics associated with streptococcal infection. Am J Psychiatry 2000;157:281–283.
26. Barsottini OGP, Ferraz HB, Seviliano MM, Barbieri A. Brain SPECT imaging in Sydenham's chorea. Braz J Med Biol Res 2002;35:431–436.
27. Husby G, van de Rijn I, Zabriskie JB, Abdin ZH, Williams RC Jr. Antibodies reacting with cytoplasm of subthalamic and caudate nuclei neurons in chorea and acute rheumatic fever. J Exp Med 1976;144:1094–1110.
28. Kotby AA, El Badawy N, El Sokkary S, Moawad H, El Shawarby M. Antineuronal antibodies in rheumatic chorea. Clin Diagn Lab Immunol 1998;5:836–839.
29. Church AJ, Cardoso F, Dale RC, Lees AJ, Thompson EJ, Giovannoni G. Anti-basal ganglia antibodies in acute and persistent Sydenham's chorea. Neurology 2002;59:227–231.
30. Church AJ, Dale RC, Lees AJ, Giovannoni G, Robertson MM. Tourette's syndrome: a cross sectional study to examine the PANDAS hypothesis. J Neurol Neurosurg Psychiatry 2003;74:602–607.
31. Green LN. Corticosteroids in the treatment of Sydenham's chorea. Arch Neurol 1978;35:53–54.
32. Perlmutter SJ, Leitman SF, Garvey MA, et al. Therapeutic plasma exchange and intravenous immunoglobulin for obsessive-compulsive disorder and tic disorders in childhood. Lancet 1999;354:1153–1158.
33. Taylor JR, Morshed SA, Parveen S, et al. An animal model of Tourette's syndrome. Am J Psychiatry 2002;159:657–660.
34. Swedo SE. Pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections (PANDAS). Mol Psychiatry 2002;7:S24–S25.
35. Khanna AK, Buskirk DR, Williams RC Jr, et al. Presence of a non-HLA B cell antigen in rheumatic fever patients and their families as defined by a monoclonal antibody. J Clin Invest 1989;83:1710–1716.

36. Swedo SE, Leonard HL, Mittleman BB, et al. Identification of children with pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections by a marker associated with rheumatic fever. Am J Psychiatry 1997;154:110–112.
37. Kurlan R. Tourette's syndrome and 'PANDAS': will the relation bear out? Neurology 1998;50:1530–1534.
38. Daoud AS, Zaki M, Shakir R, Al-Saleh Q. Effectiveness of sodium valproate in the treatment of Sydenham's chorea. Neurology 1990;40:1140–1141.
39. Pena J, Mora E, Cardozo J, Molina O, Montiel C. Comparison of the efficacy of carbamazepine, haloperidol and valproic acid in the treatment of children with Sydenham's chorea: clinical follow-up of 18 patients. Arq Neuropsiquiatr 2002;60:374–377.
40. Roig M, Montserrat L, Gallart A. Carbamazepine: an alternative drug for the treatment of nonhereditary chorea. Pediatrics 1988;82:492–495.
41. Harel L, Zecharia A, Straussberg R, Volovitz B, Amir J. Successful treatment of rheumatic chorea with carbamazepine. Pediatr Neurol 2000;23:147–151.
42. Harries-Jones R, Gibson JG. Successful treatment of refractory Sydenham's chorea with pimozide. J Neurol Neurosurg Psychiatry 1985;48:390.
43. Shannon KM, Fenichel GM. Pimozide treatment of Sydenham's chorea. Neurology 1990;40:186.
44. Stollerman GH. Rheumatic fever in the 21st century. Clin Infect Dis 2001;33:806–814.
45. Murphy ML, Pichichero ME. Prospective identification and treatment of children with pediatric autoimmune neuropsychiatric disorder associated with group A streptococcal infection (PANDAS). Arch Pediatr Adolesc Med 2002;156:356–361.
46. Garvey MA, Perlmutter SJ, Allen AJ, et al. A pilot study of penicillin prophylaxis for neuropsychiatric exacerbations triggered by streptococcal infections. Biol Psychiatry 1999;45:1564–1571.

13
Acute Spinal Rigidity

P. D. Thompson

PATIENT VIGNETTE

A 69-year-old woman presented with a 1-year history of low back and leg pain accompanied by progressive difficulty walking. Lumbar surgery was undertaken for spondylolisthesis and canal stenosis. Postoperatively, the pain improved but her walking continued to deteriorate. She then developed spasms of the back and right leg causing flexion of the trunk, hip, and knee. Her mobility deteriorated further. Examination at this time revealed a rigid right leg with palpable muscle activity in all muscle groups, brisk tendon reflexes, and an extensor plantar response. There was no truncal rigidity. There was no sensory loss, but sensory stimulation elicited a brisk flexion withdrawal movement of the whole leg. Similar flexion spasms of the leg and hip were evident while walking and severely restricted her gait. Further imaging of the whole spinal cord was normal. A glucose tolerance test was abnormal, but anti-glutamic acid dehydrogenase (anti-GAD) antibodies were not detected. Baclofen was prescribed with some improvement in the rigidity and mobility. One year later, her mobility declined again. Examination on this occasion revealed abdominal wall and lumbar paraspinal rigidity along with bilateral leg rigidity. The clinical picture was now that of the stiff-person syndrome, although anti-GAD antibodies remained negative.

This case illustrates the onset and early evolution of the distribution of rigidity in the stiff-person syndrome which, although rare, is a more common cause of segmental rigidity than spinal lesions. In each section of this chapter, relevant case histories from the literature illustrating structural, inflammatory, or paraneoplastic causes of spinal rigidity are discussed to highlight the presenting and diagnostic features. Such cases are rare, and the importance of imaging cannot be overemphasized in cases of segmental rigidity where a spinal origin is suspected. Modern imaging techniques permit detailed anatomical examination of the spinal cord, making such diagnoses much simpler than in the past.

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

THE DIFFERENTIAL DIAGNOSIS OF RIGIDITY

Rigidity and Basal Ganglia Disease

Basal ganglia rigidity in Parkinson's disease (PD), the striatonigral form of multiple system atrophy or neuroleptic-induced parkinsonism, is characterized by a uniform increase in muscle tone, and detected as a continuous "lead pipe" resistance to passive movement of a limb. When there is superimposed tremor, the rigidity is described as "cogwheeling." The mechanisms of this increase in tone are poorly understood. Increased muscle tone in dystonia is typically variable and related to action or movement. During movement, co-contraction of antagonist muscle pairs and overflow of muscle activity leads to an increase in muscle tone and twisted or dystonic postures of the limbs. The dystonic postures and excessive muscle contraction subside during rest, although in advanced primary and secondary dystonia, there may be a sustained increase in muscle tone which persists in repose.

Increased Tone in Spasticity and the Upper Motor Neuron Syndrome

Hypertonia in spasticity is associated with enhanced monosynaptic stretch reflexes and is typically velocity dependent. The increased tone is detected as a "catch" or an abrupt increase in tone felt upon rapid limb manipulation, followed by a reduction in tone (the "clasp-knife" phenomenon). The latter is best appreciated in the lower limbs. Spasticity and the upper motor neuron syndrome also include brisk tendon reflexes and altered cutaneous reflexes, including loss of superficial abdominal reflexes and extensor plantar responses.

Frontal Lobe Rigidity

The distinguishing characteristic of frontal rigidity is a progressive increase in muscle tone, or the resistance to movement, during limb manipulation. As the examiner applies increasing force to move the limb, the amount of resistance encountered increases. The examiner may suspect that the patient is not fully relaxed or is voluntarily opposing the movement (gegenhalten). Frontal lobe signs, including grasp reflexes, are useful adjuncts to recognizing frontal rigidity.

Muscle Stiffness and Peripheral Nerve Hyperexcitability

Hypertonia may be caused by continuous muscle activity resulting from peripheral neuromuscular hyperexcitability in Isaacs' syndrome or neuromyotonia. Widespread muscle rippling as a result of fasciculations and myokymia are accompanied by delayed muscle relaxation. Tendon reflexes may be absent, and in some cases other signs of neuropathy are an important clue to the peripheral origin of the syndrome.

Primary Muscle Disease and Muscle Stiffness

Myotonia and delayed muscle relaxation in primary muscle disease may present with complaints of muscle stiffness during voluntary movement, although muscle tone and resistance to passive movement are normal. Some congenital myopathies,

muscular dystrophies, and inflammatory myopathies are associated with muscle contractures limiting the range of limb movement, which may be misinterpreted as rigidity.

Clinical Features of Spinal Rigidity

Rigidity of spinal origin is characterised by a continuous and marked increase in muscle tone that is more or less uniform throughout the range of movement. The rigidity may be so intense that manipulation of the affected limb is difficult or impossible. Rigidity of this severity frequently is accompanied by abnormal limb posturing. Persistent muscle contraction also leads to contracture, and fixed deformities of the limb soon develop. Another characteristic feature is the superimposition of spasms, which can be prolonged and painful, segmental myoclonus and a jerky tremor.

In most examples of spinal rigidity in man, other signs of spinal cord disease are present. These include segmental muscle wasting and weakness, absent tendon reflexes at the level of the spinal lesion, brisk reflexes below the lesion, and extensor plantar responses. Segmental radicular and tract sensory disturbances complete the clinical picture of a myelopathy. Spinal rigidity and spasms have been described in a variety of diseases of the spinal cord including traumatic spinal injury, tumours, multiple sclerosis, paraneoplastic myelopathy, arteriovenous malformations, ischemia, and syringomyelia. The common pathological feature in these examples is predominant and selective involvement of the central spinal cord affecting spinal interneurons within the spinal grey matter.

Spinal rigidity is an uncommon clinical phenomenon. Accordingly, recognizing spinal rigidity can be a difficult clinical task, and differentiating spinal rigidity from other causes of hypertonia is often influenced by the presence of other clinical signs. The physiology of spinal rigidity has been studied in an experimental canine model, produced by ischemia of the central and posterior spinal grey matter damaging spinal interneurons and sparing anterior horn cells *(1)*. Loss of inhibitory (and excitatory) interneuronal activity resulted in enhanced motoneuronal excitability with continuous spontaneous discharge of spinal motoneurons. The resulting continuous muscle contraction lead to rigidity and was followed by muscle contracture after a few days. The posture of the rigid hindlimbs resembled decerebrate rigidity but was not influenced by posture. Rigidity was continuous without phasic exacerbations and was uninfluenced by cutaneous or noxious stimuli, although primary afferent input increased the activity recorded directly from motoneurons. Dorsal root section did not abolish or prevent the development of spinal rigidity, indicating that the rigidity was not primarily driven by afferent feedback *(1)*.

Accordingly, spinal or "α-"rigidity is attributed to the unrestrained discharge of alpha motor neurones isolated from normal inhibitory interneuron control *(1–3)*. The rigidity is caused by continuous muscle activity in antagonist muscle groups. Antagonist muscles co-contract because of the loss of interneuronal mediated reciprocal inhibition. The motor activity is barely influenced by voluntary effort or

stimulation of reflex pathways, indicating isolation of the spinal motoneurons from segmental reflex and descending supraspinal influences. Some modification of the pattern of discharge may be evidenced by an increase in spasms during traction or passive limb manipulation.

DISORDERS OF SPINAL RIGIDITY IN MAN

Structural Lesions of the Spinal Cord

Rushworth *(3)* reported a patient in whom a cervical intramedullary astrocytoma infiltrated the central grey matter throughout the cervical cord between C2 and C6. The patient presented with neck pain, a wasted left arm, and a Brown-Sequard syndrome. Right-sided involvement ensued over the following months and both arms became weak and stiff. Both arms were areflexic, rigid, adducted, and extended. Spontaneous electromyogram (EMG) activity was recorded in deltoid, pectoralis major, biceps, and triceps. Stretching these muscles evoked an increase in their activity and also that of the antagonist. Reciprocal innervation during voluntary shoulder abduction was impaired but was preserved between biceps and triceps. The authors concluded this "α-rigidity" was caused by spontaneous discharge of motoneurones isolated from interneuronal inhibitory control, and therefore insensitive to reflex or voluntary inputs.

Tarlov *(4)* described a 38-year-old woman with an intrinsic spinal cyst at the level of T12 who developed the gradual onset of painful flexor spasms over the 8 years following surgical drainage of the cyst. The hips and knees were flexed as a result of a combination of rigidity and contracture. She was able to flex the hips voluntarily but there was little distal voluntary leg movement. All modalities of sensation were impaired in the legs. Dorsal root section from L2-L5 produced only a transient reduction in rigidity and spasm.

In a later patient with posttraumatic hydromyelia, dorsal rhizotomy (T11–L1) and subsequently T12–L1 spinal cord section also failed to relieve painful flexor spasms and rigidity of the legs *(5)*. Removal of the isolated segment of the spinal cord and the associated ventral roots reduced the muscle activity. Pathological examination of the excised spinal cord revealed a reduced number of interneurons in the intermediate zone of the cord at L5. Lourie *(6)* described a 55-year-old man who presented with a history of stiffness of the hips, pain and numbness of the lower back, a scoliosis, board-like rigidity of the abdomen, persistent contraction of lumbar paraspinal muscles, and "plastic" rigidity of the legs with slow leg movements. A spinothalamic sensory loss with sacral sparing suggested an intramedullary lesion. Spontaneous rhythmic contractions of the hip adductor, external oblique, and paraspinal muscles occurred and persisted during sleep.

Necrotizing Myelopathy

Penry *(2)* described a patient with "subacute necrotizing myelopathy" and extensive gliosis with destruction of the posterolateral central grey and white matter

in the posterolateral regions of the spinal cord between C3 and T8. The initial clinical presentation was of a cervical myelopathy evolving over weeks with flaccid weakness of the left arm and an asymmetric quadriplegia. Five months later, rigidity and spasm developed in the left arm. The arm was held in a posture of shoulder abduction and internal rotation, elbow flexion, dorsiflexion of the wrists, and finger flexion. Intense EMG discharges in muscles of the left arm were not influenced by muscle stretch or tendon taps. A curious and distinctive finding was the inability to activate voluntarily the muscles in spasm.

Tetanus and Strychnine

The rigidity accompanying tetanus may be localized to the site of infection, but there is often facial (risus sardonicus) and jaw spasm (trismus or lock jaw). Spasms occur spontaneously or are induced by sound and touch, spreading throughout the body and producing abdominal rigidity and opisthotonic spasms. These may be dramatic. Spasms and rigidity build in a crescendo fashion over several seconds. They may last for minutes and spread from one site to another. Profound autonomic features including hypertension, tachycardia, and sweating frequently accompany the spasms. Myoclonus and tremor may also occur *(7)*. Similar spasms occur in strychnine poisoning *(8)*. Tendon reflexes are brisk. An encephalopathy with decreased conscious state accompany the spasms of strychnine poisoning. Both tetanus and strychnine disrupt inhibitory glycinergic and γ-aminobutyric acid release, blocking interneuronal inhibition of motoneurons in the spinal cord, brainstem, and possibly the cortex. Prolonged rigidity and spasm can lead to fever, rhabdomyolysis, and acute renal failure.

Spinal Segmental Rigidity and Myoclonus

The capacity of the isolated spinal cord to produce a range of rhythmic activities was documented in traumatic spinal injuries during World War I *(9)*. These included jerks and spasms with phasic and tonic elements that resulted in multisegmented movements of the abdomen, pelvis, and legs and coordinated locomotor-like activities of the legs *(9,10)*. Similar rhythmic activities in complete paraplegia have recently been described in traumatic paraplegia *(11)* and spina bifida *(12)*. Luttrell *(13)* demonstrated that Newcastle disease encephalomyelitis could trigger intrinsic spinal generators of myoclonic activity that were independent of afferent and descending inputs. The spinal cord also exhibited the capacity to recruit activity at more distal sites through propriospinal neural pathways linking the lumbar and cervical networks. It is not clear whether this experimental model also caused rigidity.

Varying combinations of spontaneous motor activities including rigidity and jerky, myoclonic, or tremulous involuntary movements have also been described in many reports of "spinal myoclonus." In these cases, the emphasis was placed on the jerky elements of the movement disorder. As is evident from the cases described above, jerky myoclonic movements may also accompany spinal rigidity.

Segmental rigidity and myoclonus affecting one leg were the presenting features of a paraneoplastic syndrome in a 68-year-old woman reported by Roobol *(14)*. The rigidity produced a posture of flexion of the leg at the knee, plantar flexion of the foot, and extension of the great toe. Thoracic radicular sensory symptoms and signs also were present. Microscopic examination of the spinal cord revealed a reduction in the number of anterior horn cells, and interneurons could not be identified in the lumbar region.

Involvement of the central spinal grey matter in ischemic myelopathy may lead to a similar clinical picture. Davis *(15)* reported the case of a 75-year-old man who presented with bilateral spontaneous and stimulus-sensitive myoclonus of the legs. The myoclonus produced movement of the whole leg involving hip, knee, and plantar flexion. Intermittent with the myoclonus, muscle tone in the legs was increased with spasticity and plastic rigidity. Fasciculations were recorded on surface EMG between spasms but there was no mention of continuous motor activity to explain the rigidity. Pathological examination of the lumbar and sacral spinal segments revealed a selective reduction in the number of small and medium-sized interneurons, with relative sparing of the large anterior horn cells. The anterior spinal artery was virtually occluded at the mid-thoracic level. Extensor jerks resulting from contraction of the paraspinal muscles when sitting and standing were described in an ischemic myelopathy *(16)*.

Spasms of upper and lower limb extension precipitated by touch and limb movement and accompanied by autonomic features were symptoms of an inflammatory myelopathy presenting with a mild quadriparesis and sensory signs *(17)*. Leg rigidity, a flexed posture of one leg, and spasms developed 6 months or so after transverse myelitis in a 35-year-old woman *(18)*. Jerky spasms occurred both spontaneously and during voluntary and passive movements of the legs. Tendon reflexes were brisk and there was a mid-thoracic sensory level. Continuous motor unit activity was detected in leg muscles and cutaneomuscular reflexes were enhanced. Although the precise origin of the movements could not be determined, the authors postulated a disorder of spinal interneurons.

Rigidity in the Stiff-Person Syndrome

The precise nature and anatomical location of the disturbance causing the stiff-person syndrome is not known *(19)*. The distribution of rigidity in the stiff-person syndrome is frequently confined to the lower trunk and the legs, mimicking segmental rigidity of spinal origin. Continuous motor unit activity in thoracolumbar paraspinal and abdominal muscles leads to axial stiffness and rigidity in the stiff-person syndrome. The abdominal wall rigidity is described as "board-like," and paraspinal muscle contraction rigidity may result in an exaggerated lumbar lordosis. The lower limbs are frequently involved, particularly proximal muscles. Voluntary movement is restricted because of the rigidity.

Stimulus-sensitive spasms resulting from enhanced cutaneo-muscular reflexes may be superimposed on the rigidity and are a characteristic finding *(19)*. These begin with a myoclonic burst followed by a tonic phase of muscle contraction representing the "spasm."

Electrophysiological studies demonstrating continuous muscle contraction and enhanced cutaneo-muscular reflexes along with serological testing for antibodies to glutamic acid dehydrogenase (anti-GAD antibodies) may be helpful in diagnosis *(19)*. Repeated spasms in the stiff-person syndrome may be accompanied hypertension, tachycardia, and sweating, leading to an acute autonomic crisis. This clinical picture may be precipitated by the inadvertent abrupt withdrawal of treatment, such as may occur with disruption of intrathecal baclofen administration *(20)*.

Progressive Encephalomyelitis With Rigidity and Myoclonus

The relationship of progressive encephalomyelitis with rigidity and myoclonus to the stiff-person syndrome is unclear *(19,21)*. The distribution and characteristics of the rigidity may be very similar, involving axial and proximal limb muscles with superimposed spasms and myoclonus. From a clinical point of view, a diagnosis of this condition is suggested by a subacute onset with a fluctuating, often progressive course and the presence of sensory symptoms and brainstem dysfunction *(21,22)*. Signs of the latter include ophthalmoplegia, nystagmus, ataxia, and dysphagia *(22,23)*. In addition, there may be segmental muscle-wasting and areflexia *(21)*. The extent of overlap between these two conditions is further evident in pathological studies that show perivascular inflammatory change in both stiff-person syndrome and progressive encephalomyelitis with rigidity and myoclonus *(19)*. The relationship of these cases to apparently isolated inflammatory myelopathies with rigidity *(17)* is uncertain.

Rigidity in Spinal Interneuronitis and the Stiff-Leg Syndrome

Isolated rigidity of one leg was described as the "stiff-leg syndrome" by Brown *(24)*. These authors reported four cases in which co-contraction of leg muscles with spasms and rigidity was caused by segmental motoneuronal disinhibition. The disorder remained static over a number of years and it was postulated that a localized form of chronic spinal interneuronitis caused the syndrome. Segmental or focal limb rigidity resulting from continuous motor unit activity may be the first sign of the stiff-person syndrome, and of progressive encephalomyelitis with rigidity and myoclonus *(19)*. Leg rigidity and difficulty walking is the most common focal presentation, with progression of rigidity to a more generalized distribution occurring after a variable interval. The onset of arm rigidity in a woman should prompt a search for breast malignancy *(25)*. Follow-up examinations are important in these situations.

MANAGEMENT

The management of acute spinal rigidity and any associated movement disorders relies on the recognition of the spinal origin and identification of the underlying cause. This will usually require appropriate imaging of the spinal cord. In the case of identifiable structural or inflammatory disease of the spinal cord, treatment revolves around management of the underlying cause. Serological studies for anti-GAD antibodies and electrophysiological testing for enhanced cutaneo-muscular

Table 1
Drugs That May be Useful in Treatment of Spinal Rigidity and Spasms

Benzodiazepines: diazepam, clonazepam
γ-Aminobutyric acid analogue: baclofen
Centrally acting anti-adrenergic: tizanidine, clonidine
Anticonvulsants (valproate, carbamazepine, gabapentin)
Botulinum toxin injections (for focal rigidity, spasm)

reflexes may be helpful when the stiff-person syndrome is suspected. Immunological therapies are increasingly being used in the stiff-person syndrome, including intravenous immunoglobulin *(26)*.

Drugs such as baclofen, tizanidine, and diazepam are useful in the treatment of spinal rigidity and spasms (Table 1). Large doses are often needed, and intrathecal baclofen may provide a more effective method of delivery. Caution is required, however, in order to avoid abrupt cessation of these drugs, as this may precipitate a severe exacerbation of rigidity accompanied by acute autonomic failure *(20)*.

REFERENCES

1. Gelfan S, Tarlov IM. Interneurones and rigidity of spinal origin. J Physiol (London) 1959;146:594–617.
2. Penry JK, Hoefnagel D, Noort S van den, Denny-Brown D. Muscle spasm and abnormal postures resulting from damage to interneurones in spinal cord. Arch Neurol 1960;3:500–512.
3. Rushworth G, Lishman WA, Hughes TJ, Oppenheimer DR. Intense rigidity of the arms due to isolation of motor neurones by a spinal tumour. J Neurol Neurosurg Psychiatry 1961;24:132–142.
4. Tarlov IM. Rigidity in man due to spinal interneuron loss. Arch Neurol 1967;16:536–543.
5. Tarlov IM. Deafferentation to relieve spasticity or rigidity: reasons for failure in some cases of paraplegia. J Neurosurg 1966;25:270–274.
6. Lourie H. Spontaneous activity of alpha motor neurons in intramedullary spinal cord tumor. J Neurosurg 1968;29:573–580.
7. Warren JD, Kimber TE, Thompson PD. Brainstem myoclonus in generalized tetanus. Mov Disord 2003;18:1204–1206.
8. Case records of the Massachusetts General Hospital. N Engl J Med 2001;344:1232–1239.
9. Riddoch G. The reflex functions of the completely divided spinal cord in man, compared with those associated with less severe lesions. Brain 1917;40:264–401.
10. Pollock LJ, Boshes B, Finkelman I, Chor H, Brown M. Spasticity, pseudospasms and other reflex activities later after injury to the spinal cord. Arch Neurol Psychiatry 1951;66:537–560.
11. Bussell B, Roby-Brami A, Azouvi P, Biraben A, Yakovleff A, Pierrot-Deselligny E. Myoclonus in a patient with spinal cord transection. Brain 1988;111:1235–1245.
12. Warren JE, Vidailhet M, Kneebone CS, Quinn NP, Thompson PD. Myoclonus in spinal dysraphism. Mov Disord 2003;18:961–964.
13. Lutterell CN, Bang FB, Luxenberg K. Newcastle disease encephalomyelitis in cats. II: physiological studies on rhythmic myoclonus. Arch Neurol Psychiatry 1959;81:285–291.
14. Roobol TH, Kazzazz BA, Vecht CHJ. Segmental rigidity and spinal myoclonus as a paraneoplastic syndrome. J Neurol Neurosurg Psychiatry 1987;50:628–631.
15. Davis SM, Murray NMF, Diengdoh JV, Galea-Debono A, Kocen RS. Stimulus-sensitive spinal myoclonus. J Neurol Neurosurg Psychiatry 1981;44:884–888.
16. Nogues M, Cammarota A, Sola C, Brown P. Propriospinal myoclonus in ischemic myelopathy secondary to a spinal dural arteriovenous fistula. Mov Disord 2000;15:355–358.

17. McCombe PA, Chalk JB, Searle JW, Tannenberg AEG, Smith JJ, Pender MP. Progressive encephalomyelitis with rigidity: a case report with magnetic resonance imaging findings. J Neurol Neurosurg Psychiatry 1989;52:1429–1431.
18. Brown P, Quinn NP, Barnes D, Wren DR, Marsden CD. Spinal rigidity following acute myelitis. Mov Disord 1997;12:1056–1059.
19. Meinck H-M, Thompson PD. The stiff-man syndrome and related conditions. Mov Disord 2002;17:853–866.
20. Stayer C, Tronnier V, Dressnandt J, et al. Intrathecal baclofen therapy for stiff-man syndrome and progressive encephalomyelopathy with rigidity and myoclonus. Neurology 1997;49:1519–1597.
21. Kasperek S, Zebrowski S. Stiff man syndrome and encephalomyelitis. Arch Neurol 1971;24:22–31.
22. Howell DA, Lees AJ, Toghill PJ. Spinal internuncial neurones in progressive encephalomyelitis with rigidity. J Neurol Neurosurg Psychiatry 1979;42:773–785.
23. Whiteley AM, Swash M, Urich H. Progressive encephalomyelitis with rigidity. Brain 1976;99:27–42.
24. Brown P, Rothwell JC, Marsden CD. The stiff leg syndrome. J Neurol Neurosurg Psychiatry 1997;62:31–37.
25. Rosin L, De Camilli P, Butler M, et al. Stiff man syndrome in a woman with breast cancer: an uncommon central nervous system paraneoplastic syndrome. Neurology 1998;50:94–98.
26. Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome. N Engl J Med 2001;345:1870–1876.

14
Tic Emergencies

Vanessa K. Hinson and Christopher G. Goetz

PATIENT VIGNETTES

Patient 1: The parents of a 16-year-old boy ask that their son be urgently evaluated for an exacerbation of his tics. He was diagnosed with Gilles de la Tourette's syndrome (GTS) at age 5 years and never required pharmacotherapy for his tics. Since the start of the school year and the transition to junior high school, he has developed frequent grunting, coughing, and shouting. These vocal tics are extremely disruptive and socially embarrassing. Classmates have commented, some heckling him, and one concerned student asked him if he was taking illicit drugs. The boy refuses to go to school and his grades are dropping. He recently had a bad cold, and started taking pseudonephrine, and feels his tics are even worse. On examination, there are mild multifocal motor tics, and severe repetitive vocal tics. The remainder of the examination is normal.

Patient 2: A 16-year-old girl presents with the chief complaint of neck pain and left-handed weakness. She was diagnosed with GTS at age 13. Her tics involve repeated backward jerks of her head, as well as nose twitching, eye blinking, leg jerking, grunting and throat clearing. She first noticed tingling sensations radiating from her neck into the left arm and hand associated with her neck tics 6 months prior to evaluation. On examination, wasting of the first dorsal interosseus and weakness of the abductor pollicis brevis and intrinsic hand muscles on the left was present. Diminished sensation over the left little finger and hypothenar region extended slightly above the wrist. Cervical spine films were normal. An electromyogram study of the affected limb was recommended but refused.

Patient 3: A 9-year-old girl presents with a 3-week history of facial grimacing, abdominal flexion, and finger curling. She describes a sensation in her abdomen preceding the involuntary movements, and she is able to temporarily suppress the facial and abdominal movements. Simultaneously, she developed mild confusion and headaches. Laboratory work-up through the pediatrician's office is significant for a positive strep throat culture and an elevated anti-streptolysin O titer. On examination, there are fine, random choreic movements of hands and fingers but in addition, there are distinct motor tics of face, neck, shoulders, and abdomen.

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

Patient 4: A patient with a 10-year history of GTS presents with a complaint of worsening leg tics. He had been started on pimozide 3 weeks earlier and saw his pediatrician again 1 week later who further increased the pimozide because of the patient's complaint of leg movements. On examination, multifocal motor tics affecting eyes, face, neck, and shoulder, as well as complex phonic tics, were present. In addition, marked rhythmic leg movements and rocking motions typical of akathisia were accompanied by a subjective sense of inner restlessness and an inability to sit still.

INTRODUCTION

Tics are sudden involuntary stereotypic movements or sounds that emerge out of a normal background. Tic disorders usually start in childhood and typically wax and wane over many years. In our tertiary care center, only one-third of subjects require medical therapy for tics. For most subjects, education of the patients, their families, and school and work personnel is sufficient. When medications are needed, tics can be controlled in most patients, although side effects can be problematic. The identification of comorbid conditions such as attention deficit hyperactivity disorder (ADHD) or obsessive-compulsive disorder are important, because these disorders often cause more disruption than tics themselves. Because the long-term history of tics is generally benign, the primary aim of treatment is to maintain a child in the school environment so that normal or near-normal socialization and school achievement occurs during formative years.

In rare instances, tics are severe enough to cause a neurologic emergency, and these fall into several categories (Table 1). First, intense exacerbations may occur in the normal context of the waxing and waning course of tic disorders. On occasion, these exacerbations can frighten patients and their families and limit social or academic integration. Second, tics can cause secondary neurological impairment that may result in permanent disability. Third, a series of severe pain syndromes have been described in some tic subjects that can be highly disabling. Fourth, sudden and unusual tics can emerge in the context of disorders of global neurologic injury, and therapies aimed at the primary disorder need to be started promptly. Finally, the pharmacological treatment of tics can cause sudden adverse events. In this chapter, each of these tic emergencies is discussed with patient vignettes, and the diagnosis and treatment are reviewed.

TIC EXACERBATIONS

The natural history of chronic childhood-onset tic disorders is well described. Typically, symptoms start at age 5 or 6 years, often with simple motor tics such as frequent eye blinking. Tics tend to peak in severity between 7 and 15 years of age, followed by a steady decline *(1,2)*. Tics wax and wane in frequency and severity, and the tic repertoire varies. Simple motor tics (only affecting one muscle group) may migrate or become more complex (coordinated, sequenced movements). Complex tics often resemble normal movements or gestures, but they occur at an inappropriate time or with exaggerated intensity. Gestures may be obscene or provocative and are often socially embarrassing. Phonic tics might appear in form

Table 1
Tic Emergencies

Tic exacerbations
Neurological impairment secondary to tics
Pain syndromes caused by tics
Sudden and unusual tics in the context of global neurological injury
New abnormal movements caused by anti-tic medications

Table 2
Tics: Exacerbating Factors

Internal
Fatigue
Hormone status
Level of perceived stress
External
Diet
Drugs
Infections

of simple noises (e.g., throat clearing, sniffing, humming), or complex words or phrases. Complex phonic tics containing profanities are referred to as *coprolalia*, repetitions of someone else's words *echolalia*, and repetitions of the subject's own words *palilalia*. Tics are temporarily suppressible, often preceded by a premonitory sensation or an urge to perform them, and usually produce a sense of relief. Tics can persist in adulthood *(2)*, but are usually mild or well suppressed and do not cause disability.

Because tics occur in bouts, and the course of chronic tic disorders waxes and wanes, exacerbations are common. Factors that influence tic severity and may trigger exacerbations can be divided in *internal* and *external* factors (Table 2). An individual's susceptibility to these factors varies greatly. Internal factors include fatigue, hormone status, and levels of perceived stress. Children commonly experience exacerbations of tics at the beginning of the school year and at the time of return from school holidays. Tics also may increase during relaxation after a period of stress. Lack of sleep has been well documented to cause tic exacerbations. Late or night-shift work may not be advisable in a professional with problematic tics. Hormonal fluctuations during teenage years have been implicated in worsening tics. Some patients also report fluctuations with their monthly menstrual cycles *(3)*.

External factors that may exacerbate tics include diet, stress, drugs, and concurrent infections. Even though there is no proven link between dietary products and tic severity, some patients report symptom exacerbations associated with the consumption of certain foods. Numerous drugs have been reported to exacerbate tics (Table 3). The most commonly encountered scenario occurs with stimulant drugs

Table 3
Drugs Implicated in Tic Exacerbations

Methylphenidate
Pemoline
Dexedrine
Decongestants
Levodopa
Phenytoin
Carbamazepine
Lamotrigine
Phenobarbital
Imipramine
Clomipramine
Fluoxetine
Sertraline
Fluvoxamine
Bupropion
Amphetamine
Cocaine

for the treatment of comorbid ADHD *(4,5)* and over-the-counter drugs used to treat common colds *(6)*. Anticonvulsants *(7)*, tricyclic antidepressants *(8)*, selective serotonin reuptake inhibitors *(9)*, and certain illicit drugs *(10)* have also been reported to exacerbate tics. A patient suffering from a concurrent infection may experience a tic exacerbation related either to the drugs used to treat the infection, or to compromised general health.

During these periods, tics may become disabling, requiring urgent management, as illustrated with patient 1. In the case of an external provoking factor, the elimination of the latter (e.g., discontinuation of the offending drug) may reverse the problem. The CD shows a patient's tics at baseline and the tic exacerbation provoked by exposure to scopolamine used to treat a viral vestibulopathy. If there is no reversible causative agent, drugs for tic suppression may be warranted (Table 4). At present, the only agents approved for treatment of tics by the US Food and Drug Administration are haloperidol and pimozide. There is evidence that pimozide is more effective and better tolerated than haloperidol *(11)*. Pimozide is our first choice for the treatment of acute, disabling tics. Because of the potential side effects of typical neuroleptics (extrapyramidal symptoms, sedation, weight gain), the lowest possible dose should be used, and the need for treatment needs to be critically reviewed on a regular basis. Other neuroleptics used to treat tics are fluphenazine and risperidal. There is little experience with newer atypical neuroleptics. The dopamine depletors tetrabenazine (not available in the United States) *(12)* and reserpine are effective anti-tic agents, but the patient needs to be carefully watched for signs of depression. If there are prominent associated problems with restlessness or ADHD, the α-adrenergic receptor agonists clonidine and guanfacine are

Table 4
Selected Drugs to Treat Tics

Drug	Usual starting dose	Usual maximum dose/day
Pimozide	1 mg at bedtime	10 mg
Haloperidol	0.25 mg at bedtime	20 mg
Fluphenazine	0.5 mg at bedtime	5 mg
Risperidone	0.25 mg at bedtime	4 mg
Tetrabenazine	12.5 mg at bedtime	200 mg
Reserpine	0.1 mg at bedtime	1 mg
Clonidine	0.05 mg at bedtime	0.8 mg
Guanfacine	0.5 mg at bedtime	3 mg
Botulinum toxin	Varies with injected muscle	Varies with injected muscle

useful, although less potent. Selected patients with prominent, disabling focal tics may benefit from botulinum toxin injections. This form of treatment is best suited for patients whose tics can be readily targeted for treatment with the toxin. Several case series and one double-blind, placebo-controlled trial demonstrates reduction of motor tics and the premonitory urge *(13,14)*. The double-blind trial studied relatively mild patients with multifocal tics, and failed to show a change in the indices of overall patient well-being. Other case reports have described the improvement of disruptive vocal tics with intralaryngeal botulium toxin injections *(15,16)*. Education is an important arm of intervention, and the Tourette Syndrome Association has special programs that can be organized to inform teachers and students about tic disorders. These programs aim to defuse misunderstanding and stigmatization related to tic exacerbations.

In the case of patient 1, the exacerbating influences included the new school situation, the cold medication, and poor sleep. The cold medication was stopped, but tics remained problematic. The parents and patient were adamant that no educational program be organized on behalf of the student, so the neurologist opted to start 2 mg of pimozide each evening after checking an electrocardiogram and verifying that the QT interval was normal. They agreed that if the physician prescribed medication treatment, the boy also had to agree to return to school immediately. The pimozide was helpful in promoting sleep the first night and tics improved slightly. Over a 2-week period, the tics improved substantially and although they are still present, the emergency situation was considered by all parties to have passed.

ACUTE NEUROLOGICAL COMPLICATIONS FROM TICS

Occasionally, violent motor tics can result in secondary neurological injury, particularly radiculopathy or compressive neuropathy. In a previous report of two cases of secondary compressive neuropathies in patients with Gilles de la Tourette's Syndrome *(17)*, both patients developed peripheral nerve or radicular injury within the area involved by violent tics. In the first case (patient 2), neck tics led to a C8-T1

radiculopathy; the second case was one of a compressive neuropathy at the sciatic notch caused by a hip-thrusting tic (*see* CD). Severe motor tics have also been reported to cause cervical myelopathy *(18)*. Rapid recognition and treatment of the tic disorder is essential to prevent permanent neurological deficits. The tics should be treated according to the treatment principles outlined in the previous section. In addition, physical therapy can often facilitate recovery from the neurologic injury. Patient 2 was taking haloperidol (1 mg/day) at the time of her presentation. The dose was gradually increased to 4 mg/day, with improvement of her neck tics. She was also referred to the occupational therapy department for rehabilitation of her left hand function.

PAIN RELATED TO TICS

Tic disorders can cause acute pain syndromes that require urgent management. Riley and Lang reviewed pain in tic disorders *(19)* and classified these conditions into four categories: (1) pain resulting from the actual performance of the tic (such as neck pain caused by sudden neck movements); (2) pain resulting from a traumatic injury from being struck by a body part involved in a tic, or pain to a body part striking against nearby objects; (3) pain caused by the effort of tic suppression (excessive isometric muscle contraction), or self-inflicted pain in order to reduce tic expression; and (4) pain caused by behavioral abnormalities accompanying the tic disorder such as self-mutilating compulsions. Pain caused by tic disorders may be a source of significant disability for patients, and the same treatment principles discussed in management of tic exacerbations apply.

ABRUPT TICS SECONDARY TO CENTRAL NERVOUS SYSTEM DISORDERS

The abrupt onset of new tics in a patient with other neurological signs, particularly at an atypical age for first presentation of tics, warrants the careful search for an underlying cause. Numerous acquired and genetic conditions as well as exposure to various drugs and toxins may cause secondary tics *(20)*. Central nervous system infections, autoimmune disorders, metabolic and toxic encephalopathies, stroke, head trauma, and psychogenic disorders all have been implicated in triggering tics. During the pandemic of encephalitis lethargica (1926–1927), tics were frequently observed as one of a variety of different movement disorders secondary to the infection *(21)*. This disorder is now rarely seen, but tics have been described in encephalitis secondary to other infective agents such as herpes simplex virus *(22,23)* and human immunodeficiency virus *(24)*. The other infection-related phenomenon is that of tic disorders caused by an autoimmune response triggered by the underlying infection. Sydenham's chorea is the prototype example, following β-hemolytic streptococcal infection. Tics have been reported to occur at the onset, or following Sydenham's chorea *(25,26)* as in the case of patient 3, a clinical presentation showing encephalopathy and chorea along with motor tics. There is an ongoing debate whether streptococcal infection and rheumatic fever can not only

lead to Sydenham's chorea, but also trigger pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) *(27)*. Treatment of these cases includes antibiotics and appropriate tic treatment as necessary. Patient 3 was started on amoxicillin by the infectious disease specialists, and clonidine by the treating neurologist with good response of her movements and behavioral changes.

Cases of tics occurring after carbon monoxide poisoning have also been described *(28)*. The documentation of tics attributable to metabolic disturbances such as hypoglycemia is questionable. Strokes can cause the abrupt onset of a tic disorder. Most documented cases describe multifocal or facial tics following cerebral infarction, but unilateral tics in the distribution of the accompanying neurological deficit have also been reported *(29)*. In one instance, magnetic resonance imaging findings linked an anatomic region to a case of post-stroke tics *(30)*. An 8-year-old boy suffered a left hemiparesis, followed by the development of hemidystonia and facial tics. The MRI scan demonstrated a lesion in the right middle cerebral artery territory including the head of the caudate nucleus. A few cases of tics following or exacerbated by head trauma have also been reported *(31)*. Even though it is conceivable that traumatic brain injury induces tics, pathophysiological mechanisms remain unknown, and neuroimaging studies of affected patients have been unrevealing. Psychogenic tics can be seen in somatoform disorders, factitious disorders, and malingering *(20)*. They can be hard to diagnose because they share common characteristics with organic tics, namely suppressibility, distractibility, and variability. Certain atypical features evoke a diagnosis of psychogenic tics. Abrupt onset in context of a life stressor, entrainment of tics with synkinetic hand movements, lack of response to antidopaminergic therapy, resolution with suggestion/placebo/psychotherapy or financial settlement, association with other false neurological signs (such as give-way weakness), and psychiatric comorbidity. In these cases, the underlying psychiatric disorder needs to be treated in order to ameliorate the tics.

These examples underscore the importance of careful differential diagnosis in the consideration of a tic disorder. When tics occur in a typical pattern and context, follow the expected waxing and waning natural history, are not associated with other neurological signs, and a family history of tics is clear, additional work-up is not generally required. In other instances, further evaluation is required, because a treatable neurologic condition may underlie the tics, and standard tic treatment, although potentially beneficial in controlling the tics, misses the etiological source.

NEW INVOLUNTARY MOVEMENTS FROM TIC DRUGS

The chronic tic patient may present for an urgent consultation because of the onset of new abnormal movements. In this context, it is important to differentiate tic exacerbations from new movement disorders secondary to anti-tic medications. Kompoliti and Goetz *(32)* reported 12 tic patients with treatment-induced movement disorders. Both acute (akathisia, acute dystonia) and tardive (tardive dysto-

nia, tardive chorea, withdrawal-emergent chorea) phenomena were observed during treatment with typical neuroleptics (pimozide, haloperidol, fluphenazine). All patients had been misdiagnosed as having tic exacerbations by the referring physicians. Akathisia was the most common phenomenon in this series (also demonstrated by patient 4). Akathisia affects trunk and leg muscles, is associated with an inner feeling of restlessness, and typically starts shortly after neuroleptic initiation or dose increase (*see* CD). Usually, a significant decrease in the neuroleptic medication is required to achieve relief of akathisia. If the neuroleptic dose cannot be reduced, the addition of anticholinergics, amantadine, or β-blockers may be helpful. In patient 4, the neuroleptic dose could not be decreased because of the severe complex vocal tics, and the patient was treated successfully with benztropine.

Acute dystonia, especially oculogyric crisis, can also occur in association with the start of a neuroleptic or an increase in dosage. This frightening and often painful disorder requires addition of an anticholinergic agent to the neuroleptic, usually in the form of an intramuscular or intravenous dose (e.g., trihexyphenidyl) followed by an oral anticholinergic, often for the duration of neuroleptic therapy. Reports of tardive syndromes in tic patients are few *(33,34)*, but the phenomenon needs to be recognized and appropriately managed (*see* CD). As opposed to tics that are generally perceived as "voluntary" and suppressible, patients usually perceive tardive dystonic or choreic movements as "involuntary" and not suppressible *(35)*. Unlike tics, dystonic or choreic movements remain unchanged or even increase during distraction or the performance of skilled tasks. The management of these tardive syndromes consists of withdrawal of the neuroleptic if possible. If the tardive movements are primarily dystonic, oral anticholinergic drugs can be used, but these drugs often increase choreic movements. Tardive dystonia may be amenable to treatment with botulinum toxin if specifically problematic muscles groups are targeted.

REFERENCES

1. Leckman JF, Zhang H, Vitale A, et al. Course of tic severity in Tourette's syndrome: the first two decades. Pediatrics 1998;102:14–19.
2. Goetz CG, Tanner CM, Stebbins GT, et al. Adult tics in Gilles de la Tourette's syndrome: description and risk factors. Neurology 1992;42:784–788.
3. Kompoliti K, Goetz CG, Leurgans S, et al. Estrogen, Progesterone, and tic severity in woman with Gilles de la Tourette syndrome. Neurology 2001;57(8):1519.
4. Erenberg G, Cruse RP, Rothner AD. Gilles de la Tourette's syndrome: effect of stimulant drugs. Neurology 1985;35:1346–1348.
5. Price RA, Leckman JF, Pauls DL, et al. Gilles de la Tourette syndrome: tics and central nervous system stimulants in twins and non-twins. Neurology 1986;36:232–237.
6. Shafii M. The effects of sympathomimetic and antihistaminic agents on chronic motor tics and Tourette's disorder. N Engl J Med 1986;315:1228–1229.
7. Burd L, Kerbeshian J Fisher W, Gascon G. Anticonvulsant medications: an iatrogenic cause of tic disorders. Can J Psychiatry 1986;31:419–423.
8. Fras I. Gilles de la Tourette's syndrome: effects of tricyclic antidepressants. NY State J Med 1978;78:1230–1232.

9. Gatto E, Pikielny R, Micheli F. Fluoxetine in Tourette's syndrome. Am J Psychiatry 1994;151:946–947.
10. Mesulam M. Cocaine and Tourette's syndrome. N Engl J Med 1986;315:389.
11. Sallee FR, Nesbitt L, Jackson C, et al. Relative efficacy of haloperidol and pimozide in children and adolescents with Tourette's disorder. Am J Psychiatry 1997;154:1057–1062.
12. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. Neurology 1997;48:358–362.
13. Jankovic J. Botulinum toxin in the treatment of dystonic tics. Mov Disord 1994;9:347–349.
14. Marras C, Andrews, Sime E, Lang AE. Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. Neurology 2001;56(5):605–610.
15. Scott BL, Jankovic J, Donovan DT. Botulinum toxin injection into vocal cord in the treatment of malignant coprolalia associated with Tourette's syndrome. Mov Disord 1996;11:431–433.
16. Salloway S, Stewart CF, Israeli L, et al. Botulinum toxin for refractory vocal tics. Mov Disord 1996;11:746–748.
17. Goetz CG, Klawans HL. Gilles de la Tourette syndrome and compressive neuropathies. Ann Neurol 1980;8:453.
18. Krauss JK, Jankovic J. Severe motor tics causing cervical myelopathy in Tourette's syndrome. Mov Disord 1996;11(5):563–566.
19. Riley DE, Lang AE. Pain in Gilles de la Tourette syndrome and related tic disorders. Le Journal Canadien Des Sciences Neurologiques 1989;16:439–441.
20. Kumar R, Lang AE. Secondary Tic Disorders. Neurol Clin 1997;15(2):309–331.
21. von Economo C. Encephalitis Lethargica: Its Sequelae and Treatment. Oxford University Press, London: 1931.
22. Turley JM. Tourette-like disorder after herpes simplex encephalitis. Am J Psychiatry 1988;145:1604–1605.
23. Northam RS, Singer HS. Postencephalitic Tourette-like syndrome in a child. Neurology 1991;4:592–593.
24. McDaniel JS, Summerville. Tic disorder associated with encephalopathy in advanced HIV disease. Gen Hosp Psychiat 1974;125:593–594.
25. Behan P, Geschwind N, Quadfase FA. Coprolalia in Sydenham's chorea. Abstract. First International Gilles de la Tourette Syndrome Meeting, New York: 1981.
26. Lees AJ. Tics occurring in association with neurological disorders. In: Tics and Related Disorders. Churchill Livingstone, New York: 1985:70–82.
27. Swedo SE. Sydenham's chorea: a model for childhood autoimmune psychiatric disorders. JAMA 1994; 272:1788–1791.
28. Pulst S, Walshe TM, Romero JA. Carbon Monoxide Poisoning with Features of Gilles de la Tourette's Syndrome. Arch Neurol 1983; 40: 443-444.
29. Sacks OW. Tourettism in strokes. Tourette Syndrome Association Newsletter 1980 (VII:4:7).
30. Jankovic J. Tics in other neurologic disorders. In: Kurlan R, ed. Handbook of Tourette's syndrome and related tic and behavioral disorders. Marcell Dekker, New York: 1993:167–182.
31. Krauss JK, Jankovic J. Tics secondary to craniocerebral trauma. Mov Disord 1997;12(5):776–782.
32. Kompoliti K, Goetz CG. Hyperkinetic movement disorders misdiagnosed as tics in Gilles de la Tourette syndrome. Mov Disord 1998;13(3):477–480.
33. Bruun RD. Subtle and under-recognized side effects of neuroleptic treatment in children with Tourette's disorder. Am J Psychiatry 1988;145:621–624.
34. Shapiro E, Shapiro AK. Tardive dyskinesia and chronic neuroleptic treatment of Tourette patients. In: Friedhoff AJ, Chase TN, eds. Gilles de la Tourette Syndrome. Adv Neurol, Vol. 35. Raven, New York: 1982;413.
35. Lang A. Patient perception of tics and other movement disorders. Neurology 1991;41:223–228.

15
Malignant Phonic Tics

Carolyn Kwak and Joseph Jankovic

PATIENT VIGNETTES

The following five patients illustrate the problem of malignant motor tics.

Patient 1: Patient with Gilles de la Tourette's syndrome (GTS) who, in addition to motor tics, exhibits loud vocalizations and screams which have markedly impaired his quality of life. His mother has only blinking tics.

Patient 2: Patient with severe GTS and complex tics, one of which is manifested by severe Valsalva maneuver and loud noise imitating "monsters."

Patient 3: Adult patient with GTS and severe obsessive-compulsive disorder (OCD). He had to stop working because of the loud screaming vocalizations.

Patient 4: A 46-year-old professor referred to our clinic with uncontrollable phonic tics such as bursts of screaming and obscene words. He developed phonic tics of coughing and wheezing, which was diagnosed as a "psychogenic motor disorder." He had other phonic tics of sniffing, sudden outbursts of laughing, and meaningful phrases such as "shut up" and "help." He then developed severe coprolalia. His motor tics presented in adulthood including facial grimacing, head jerking, and complex maneuvers of slapping his right upper extremity and knee. Because of the persistent and severe nature of his phonic tics, the patient resigned from lecturing at the university and now teaches classes on-line through Internet-based learning.

Patient 5: This youngster, a subject of our initial report of treatment of malignant coprolalia with botulinum toxin (BTX) *(12)*, reported to have the initial onset of motor tics at age 2 years with facial grimacing, nose twitching, snorting, and sniffing. He also exhibited bulimic eating patterns, with a compulsion to vomit because it "felt good." He later developed severe coprolalia, frequently blurting words like "bitch," "mother fucker," and "asshole." He described an urge to have to make the movements and shout the obscenities. He reported that he was able to suppress his tics and vocalizations transiently, until he "let it all out" in the bathroom. His vocalizations resulted in several fights, social stigmitization from his peers, poor academic performance, depression, and anxiety. The phonic tics and coprolalia were initially well controlled with pimozide, approx 6 mg/day and fluphenazine, approx 5 mg/day. However, his symptoms became very severe and a trial of BTX type A (BTX-A) injection,

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

30 U into the left vocal cord resulted in drastic improvement of his vocal symptoms. The patient received four treatment sessions over a period of 15 months. He reported a mean beneficial response of 2.3 at peak effect on a 0–4-point scale (0, *no effect*; 1, *mild effect but no functional improvement*; 2, *moderate improvement but no change in functional disability*; 3, *moderate change in both severity and function*; 4, *marked improvement in both severity and function*). A mean dose of 25 mouse U was injected, and mean duration of response was 20 weeks. He had no response (peak effect score 0) with a low dose of 20 U. However he reported a mean peak effect score of 3.3 with dosages of 25–30 U. He noted that BTX-A injections drastically improved his quality of life, allowing him to socialize and secure employment. His phonic tics improved during young adulthood, and he is currently not taking any anti-tic medications. His last BTX-A injection for the phonic tics was 7 years ago.

INTRODUCTION

Motor tics are among the most common, childhood-onset, genetic movement disorders, affecting about 20% of all school children, 3–6% of whom have persistent tics and satisfy the diagnostic criteria for Tourette syndrome (TS) *(1,2)*. Tics, the clinical hallmark of TS, are relatively brief, intermittent movements (motor tics) or sounds (vocal or phonic tics) *(3,5)*. Motor tics typically consist of sudden, abrupt, transient, often repetitive and coordinated (stereotypical) movements that may resemble gestures and mimic fragments of normal behavior. They typically vary in intensity and are repeated at irregular intervals. Although the diagnostic criteria for definite TS require the presence of "vocal tics" *(6)*, we believe that because the sounds that patients with TS make do not always involve the vocal cords, the term "phonic tic" is preferable and will be used in this review. Phonic tics are actually motor tics involving respiratory, laryngeal, pharyngeal, oral, or nasal musculature. Contractions of these muscles may produce sounds, such as barking, excessive throat clearing, grunting, inhaling, sniffing, yelping, clicking of the teeth, and other noises. Phonic tics are often the most distressing and debilitating symptoms of TS. Complex vocal phenomenon include echolalia (repetition of others' words), palilalia (repetition of one's own words), and coprolalia (socially inappropriate words or phrases, obscene utterances, shouting of profanities) *(7,8)*. The latter phenomenon usually leads to the most troublesome social, and sometimes legal, problems.

CLINICAL SYMPTOMS

Patients with TS rarely present with an emergency complication of their disease. Nevertheless, we have seen patients who sustained life-threatening injuries such as evulsing their own cornea or the entire eye, or evisceration by cutting an abdominal wall with a razor in response to an inner obsession and the need to satisfy a sexual urge. Some of our patients have become quadriparetic as a result of compressive myelopathy caused by repetitive, violent "whiplash" tics of the neck *(9)*. Others may present because of severe scratches or other self-injurious behaviors *(10)*. Some TS patients may present to the emergency room or clinic with loud, uncontrollable barking, yelping, shouting of obscenities, or other vocal utterances. Understanding

the phenomenology and recognizing associated symptoms of tic disorders allows correct diagnosis and treatment. Often misconstrued as a disorder of psychological origin as a result of its peculiar behavioral and vocal spectrum, TS has frequently been misdiagnosed as a "mental illness," and patients were historically confined to psychiatric institutions. The discovery in the 1960s that dopamine receptor-blocking drugs (neuroleptics) markedly improve tics helped change the image of TS from a bizarre psychiatric disorder to a neurobiological and neurobehavioral condition *(11)*.

In previous studies, 8–60% of TS patients exhibited coprolalia, inappropriate obscene utterances, or profanities *(7,8)* (patients 1–5,Video). The severity of phonic tics may be measured by the volume of voice projection, the effect on respiration, frequency of tics, and their social impact. One study showed coprolalia persisting throughout adulthood in 4% of TS cases *(8)*. A few cases of refractory coprolalia, severe and frequent vocal outbursts unresponsive to conventional anti-tic medications, have been reported *(12–14)*. Scott et al. *(12)* described a TS patient who exhibited severe coprolalia with racial slurs, sniffing, and grunting refractory to treatment with fluoxetine, fluphenazine, guanfacine, pimozide, and tetrabenazine (patient 5, Video). He blurted out obscenities and profanities while riding the school bus, resulting in school absences owing to embarrassment. A stranger in a public bathroom also attacked him after he blurted out a racial slur. He expressed a need to repeat his vocal utterances until they seemed "just right." Salloway also reported a refractory case of phonic tics responsive to botulinum toxin type A (BTX-A) injections *(13)*. Trimble *(14)* described a TS patient with coprolalia refractory to behavioral therapy, clonidine, and neuroleptics. The patient's coprolalia was so severe that he was threatened with eviction from his residence. The patient also reported strong premonitory "feelings in the brain," rather than in the throat.

Disinhibition resulting from a dysfunction of the cortico-striato-thalamo-cortical circuits has been implicated in the pathophysiology of phonic tics, coprolalia, and other complex vocalizations *(15–17)*. Motor and phonic tics have been classified as "unvoluntary" movements, with a semi-volitional component and underlying sensory phenomenon *(3,18)*. Motor and phonic tics are preceded by premonitory sensations, and patients commonly report that they perform the movements voluntarily in response to an involuntary sensory urge *(3–5,19–22)*. TS subjects receiving BTX-A injections for motor and phonic tics report not only a reduction in the tics, but also improvement in the premonitory sensory perception and local urge that frequently precedes the tic *(23–25)*. The limbic system and ventral basal ganglia may be involved in generating aberrant impulses to the motor cortex *(19–22,26–28)*.

TREATMENT

Several behavioral and pharmacological treatments have been used to treat severe phonic tics (Fig. 1). Dopamine receptor-blocking drugs are often tried first for moderate to severe motor tics *(29–33)*. Haloperidol and pimozode are the two medications approved for the treatment of tics by the US Food and Drug Administration (FDA). We prefer fluphenazine and risperidone, although the atypical neuroleptics

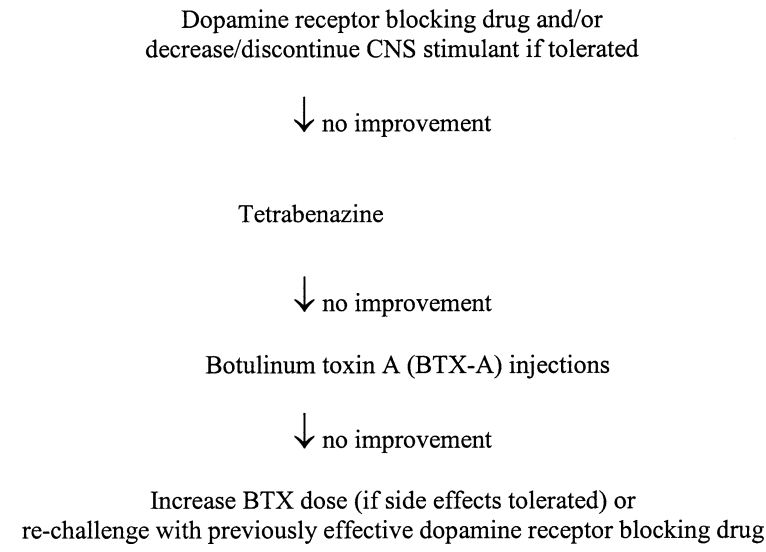


Fig. 1. Treatment algorithm for severe phonic tics.

olanzapine and ziprasidone may also be helpful *(31–33)*. Tetrabenazine, a synthetic benzoquinolone that presynaptically depletes monoamines and possesses D2 blocking activity, has also shown to reduce tic severity without incurring the risk of tardive dyskinesia *(34,35)*. A recent review of our center's experience shows that 76% of 77 TS patients reported complete abolishment or marked improvement of their tics during a 2-year follow-up *(35)*. Antiadrenergic drugs such as clonidine and guanfacine possess moderate benefit for tics *(36,37)*. A small double-blind trial of δ-9-tetrahydrocannabinol (δ [9]-THC) also showed significant improvement of motor tics, with a trend towards improvement for "vocal tics," as well ($p = 0.09$) *(38)*.

Behavioral techniques utilizing habit-reversal training and distraction tasks may provide some benefit, but few studies have systematically examined these approaches. Many reports are hampered by small sample size and limited follow-up *(39–41)*. Overall, case studies using behavior reinforcement-based interventions are disappointing in reducing tic severity.

BTX-A injections have shown to be particularly useful in treating focal motor and phonic tics *(12–14,23–25)* (Table 1). BTX injections are routinely used in the treatment of focal dystonia, hemifacial spasm, and tremor *(42,43)*. Scott et al. *(12)* was the first to report a patient with TS whose severe coprolalia markedly improved with unilateral vocal cord injection of BTX. After injection of 30 mouse U of BTX-A into the left vocal cord under electromyographic guidance, the patient reported reduction of coprolalia by "at least 75%," with only moderate hoarseness and hypophonia (*see* CD). The premonitory urge to shout was also markedly decreased. A repeat injection of 25 U produced similar benefit, and the patient was able to return to school. Trimble et al. *(14)* later reported a patient with refractory

Table 1
Case Reports of Botulinum Toxin Injections for Phonic Tics

Study (*references*)	Number of patients	Site of injection	Response	Premonitory	Side effects
Kwak et al. 2000 *(24)*	4	Thyroarytenoid muscle	Marked reduction in frequency	Reduced	Hypophonia, mild dysphagia and intensity
Trimble et al. 1998 *(14)*	1	Thyroarytenoid muscle	Excellent response	Unchanged	Hypophonia, mild aspiration
Salloway et al. 1996 *(13)*	1	Thyroarytenoid muscle	Improvement	Not specified	Hypophonia
Scott et al. 1996 *(12)*	1	Thyroarytenoid muscle	Decreased markedly	Reduced	Hypophonia, moderate hoarseness

vocal tics and coprolalia who also responded to BTX-A. Selective serotonin reuptake inhibitors, neuroleptics, and behavior therapy failed to improve his severe coprolalia, echolalia, and vocalizations of bird-like noises. Both thyroarytenoid muscles were injected under local anesthesia and electromyogram with 3.75 mouse U of Dysport. He reported an excellent response, with reduction in intensity of obscene outbursts. Mild side effects included a breathy, weak voice (hypophonia), and slight aspiration of liquids. The severity of the premonitory sensation remained unchanged after the injection. Kwak et al. *(24)* reported four patients with vocal tics in a large series of various motor tics treated with BTX. The mean dose given to the vocal cords was 17.8 ± 6.5 mouse U (range 10–23.8). Transient side effects included mild dysphagia and hypophonia. The study reported a global response score of 2.7 ± 1.5 in 35 patients injected with BTX in various muscle sites.

BTX injections have thus become an effective treatment option for patients with severe, loud, and disabling involuntary vocalizations.

CONCLUSION

Malignant phonic tics are a severe, incapacitating movement disorder emergency. With appropriate interventions, including careful application of neuroleptics or tetrabenazine, and skilled injection of vocal cord botulinum toxin, patients can be effectively managed through this crisis.

REFERENCES

1. Kurlan R, Como PG, Miller B, et al. The behavioral spectrum of tic disorders: a community-based study. Neurology 2002;59:414–420.
2. Snider LA, Seligman LD, Ketchen BR, et al. Tics and problem behaviors in schoolchildren: prevalence, characterization, and associations. Pediatrics 2002;110:331–336.

3. Jankovic J. Phenomenology and classification of tics. In: Jankovic J, ed. Tourette Syndrome. Neurol Cl N Am, Vol 15. WB Saunders, Philadelphia: 1997;267–275.
4. Jankovic J. Tourette's syndrome. N Engl J Med 2001;345:1184–1192.
5. Leckman J. Tourette's syndrome. Lancet 2002;360:1577–1586.
6. The Tourette Syndrome Classification Study Group. Definitions and classification of tic disorders. Arch Neurol 1993;50:1013–1016.
7. Singer C. Tourette syndrome. Coprolalia and other coprophenomena. Neurol Clin 1997;15:299–308.
8. Goldenberg J, Brown S, Weiner W. Coprolalia in younger patients with Gilles de la Tourette's syndrome: description and risk factors. Neurology 1992;42:784–788.
9. Krauss JK, Jankovic J. Severe motor tics causing cervical myelopathy in Tourette's syndrome. Mov Disord 1996;11:563–566.
10. Jankovic J, Sekula SL, Milas D. Dermatological manifestations of Tourette's syndrome and obsessive-compulsive disorder. Arch Dermatol 1998;134:113–114.
11. Shapiro A, Shaprio E. Treatment of Gilles de la Tourette's syndrome with haloperidol. Br J Psychiatry 1968;114:345–350.
12. Scott B, Jankovic J, Donovan D. Botulinum toxin into vocal cord in the treatment of malignant coprolalia associated with Tourette's syndrome. Mov Disord 1996;11:431–433.
13. Salloway S, Stewart C, Israeli L. Botulinum toxin for refractory vocal tics. Mov Disord 1996;11:746–748.
14. Trimble M, Whurr R, Brookes F, Robertson M. Vocal tics in Gilles de la Tourette syndrome treated with botulinum toxin injections. Mov Disord 1998;13:617–619.
15. Mink J. Neurobiology of basal ganglia circuits in Tourette syndrome: faulty inhibition of unwanted motor patterns? In: Cohen D, Jankovic J, Goetz C, eds. Tourette Syndrome, Advances in Neurology, Vol. 85. Lippincott Williams and Wilkins, Philadelphia: 2001;113–122.
16. Jeffries K, Schooler C, Schoenbach C, Herscovitch P, Chase T, Braun A. The functional neuroanatomy of Tourette's syndrome: an FDG PET study III: functional coupling of regional cerebral metabolic rates. Neuropsychopharmacology 2002; 27:92–104.
17. Peterson B, Staib L, Scahill L, et al. Regional brain and ventricular volumes in Tourette syndrome. Arch Gen Psychiatry 2001;58:427–440.
18. Lang A. Patient perception of tics and other movement disorders. Neurology 1991;41:223–228.
19. Leckman J, Walker D, Cohen D. Premonitory urges in Tourette's syndrome. Am J Psychiatry 1993;150:98–102.
20. Scahill L, Leckman J, Marek K. Sensory phenomenon in Tourette's syndrome. Behavioral Neurology of Movement Disorders. In: Weiner W, Lang A, eds. Advances in Neurology, Vol. 65. Raven, New York: 1995;273–280.
21. Cohen A, Leckman J. Sensory phenomenon associated with Gilles de la Tourette's syndrome. Clin Psychiatry 1992;53:319–323.
22. Kwak C, Vung KD, Jankovic J. Premonitory sensory phenomenon in Tourette syndrome. Mov Disord 2004 (in press).
23. Jankovic J. Botulinum toxin in the treatment of dystonic tics. Mov Disord 1994;9:347–349.
24. Kwak C, Hanna P, Jankovic J. Botulinum toxin in the treatment of tics. Arch Neurol 2000;57:1190–1193.
25. Marras C, Andrews D, Sime E, Lang A. Botulinum toxin for simple motor tics: a randomized, double-blind, controlled clinical trial. Neurology 2001;56:605–610.
26. Graybiel A, Aosaki T, Flaherty A. The basal ganglia and adaptive motor control. Science 1994;265:1826–1831.
27. Fried I, Katz A, McCarthy G, et al. Functional organization of human supplementary motor cortex studied by electrical stimulation. J Neurosci 1991;11:3656–3666.
28. Jimenez-Jimenez F, Garcia-Ruiz P. Pharmacological options for the treatment of Tourette's disorder. Drugs 2001;61:2207–2220.
29. Singer H. The treatment of tics. Curr Neurol Neurosci Rep 2001;1:195–202.

30. Robertson M, Stern J. Gilles de la Tourette syndrome: symptomatic treatment based on evidence. Eur Child Adolesc Psychiatry 2000;9(Suppl 1):160–175.
31. Onofrj M, Paci C, D'Andreamatteo G, Toma L. Olanzapine in severe Gilles de la Tourette syndrome: a 52-week double-blind cross-over study vs. low-dose pimozide. J Neurol 2000;247:443–446.
32. Bruggeman R, van der Linden C, Buitelaar J, Gericke G, Hawkridge S, Temlett J. Risperidone versus pimozide in Tourette's disorder: a comparative double-blind parallel-group study. J Clin Psychiatry 2001;62:50–56.
33. Sallee F, Kurlan R, Goetz C, et al. Ziprasidone treatment of children and adolescents with Tourette's syndrome: a pilot study. J Am Acad Child Adolesc Psychiatry 2000;29:292–299.
34. Jankovic J, Beach J. Long-term effects of tetrabenazine in hyperkinetic movement disorders. Neurology 1997;48:358–362.
35. Hunter CB, Wang A, Vuong KD, Jankovic J. Tetrabenazine in the treatment of Tourette syndrome. Mov Disord 2002;17(Suppl 5):S341.
36. Scahill L, Chappell P, Kim Y, Schultz R, et al. A placebo-controlled study of guanfacine in the treatment of children with tic disorders and attention deficit hyperactivity disorder. Am J Psychiatry 2001;158:1067–1074.
37. Gaffney G, Perry P, Lund B, Bever-Stille K, Arndt S, Kuperman S. Risperidone versus clonidine in the treatment of children and adolescents with Tourette's syndrome. J Am Acad Child Adolesc Psychiatry 2002;41:330–336.
38. Muller-Vahl K, Schneider U, Koblenz A, et al. Treatment of Tourette's syndrome with Delta 9-tetrahydrocannabinol (THC): A randomized crossover trial. Pharmacopsychiatry 2002;35:57–61.
39. Piacentini J, Chang S. Behavioral treatments for Tourette syndrome and tic disorders: state of the art. Adv Neurol 2001;85:319–331.
40. Bergin A, Waranch H, Borwn J, Carson K, Singer H. Relaxation therapy in Tourette syndrome: a pilot study. Pediatr Neurol 1998;18:136–142.
41. Evers R van de Wetering B. A treatment model for motor tics based on a specific tension-reduction technique. J Behav Ther Exp Psychiatry 1994;25:255–260.
42. Hsiung G, Das S, Ranawaya R, Lafontaine A, Suchowersky O. Long-term efficacy of botulinum toxin A in treatment of various movement disorders over a 10-year period. Mov Disord 2002;17:1288–1293.
43. Comella CL, Simpson L, Jankovic J. Botulinum toxins: transformation of a toxin into a treatment. In: Waxman SG, ed. Neuroscience, Molecular Medicine, and the Therapeutic Transformation of Neurology. Elsevier/Academic, 2004, in press.

16

Serotonin Syndrome

Mark Forrest Gordon and Adena Leder

PATIENT VIGNETTES

Patient 1: A 34-year-old woman had a history of migraine with aura since age 16 and recent postpartum depression. Approximately 6 months ago, she started fluoxetine for depression and migraine prophylaxis. At her most recent clinic appointment, she also started sumatriptan to abort her migraines. Two weeks later, 1 hour after her third subcutaneous 6-mg dose of sumatriptan, she presented to the emergency room. Her exam showed diaphoresis, agitation, confusion, dysarthria, staggering gait, and occasional myoclonic jerks in the legs.

Patient 2: A 73-year-old man with a 7-year history of Parkinson's disease, progressive motor impairment, and depression was taking carbidopa/levodopa (C/L) and selegiline. Sertraline was recently added. About three nights ago, he abruptly stopped his C/L and selegiline. On arrival in the emergency room, he was confused, shivering and stiff, with involuntary movements.

INTRODUCTION

In 1960, Oates and Sjoerdsma *(1)* first identified the serotonin syndrome in depressed patients. The patients exhibited diaphoresis, change in mental status, restlessness, ataxia, and lower extremity hyperreflexia. The authors attributed this syndrome to increased levels of serotonin from concurrent use of L-tryptophan and monoamine oxidase inhibitors (MAOIs). The serotonin syndrome has three manifestations: cognitive, autonomic, and neuromuscular, as outlined in Table 1 *(2)*. Each of these groups includes various features that may or may not be present. When diagnosing the serotonin syndrome, at least one feature from each group should be present. Rarely, the serotonin syndrome causes high fever, seizures, nystagmus, oculogyric crisis, opisthotonus, dysarthria, and parasthesias.

In 1991, Sternbach *(3)* proposed criteria for the diagnosis of serotonin syndrome: (a) coincident with the addition of or increase in a known serotonergic agent to an established medication regimen, at least three of the following clinical features are present: mental status changes; agitation; myoclonus; hyperreflexia; diaphoresis;

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

Table 1
Clinical Manifestations of the Serotonin Syndrome

(1) Cognitive and behavioral features:
- Confusion/disorientation
- Agitation/irritability
- Coma/unresponsiveness
- Anxiety
- Hallucinations (visual and auditory)

(2) Autonomic features:
- Hyperthermia
- Diaphoresis
- Sinus tachycardia
- Hypertension
- Dilated pupils
- Nausea
- Flushing

(3) Neuromuscular features:
- Myoclonus (especially in the legs)
- Hyperreflexia (in the legs more than the arms)
- Muscle rigidity
- Restlessness/hyperactivity
- Tremor
- Ataxia
- Extensor plantar responses

Adaped from ref. *2*.

shivering; tremor; diarrhea; incoordination; fever; (b) other etiologies (e.g., infectious, metabolic, substance abuse or withdrawal) have been ruled out; (c) a neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms listed.

NEUROCHEMISTRY AND NEUROANATOMY

Serotonin is synthesized from the amino acid tryptophan (Fig. 1). Tryptophan is transported into the brain from the plasma. Tryptophan is one of the eight essential amino acids, and the body cannot synthesize it—it must be ingested with foods. Foods that are high in tryptophan include dairy products, beef, poultry, barley, brown rice, fish, soybeans, legumes, and peanuts. Adults require 720–960 mg per day of tryptophan *(4)*.

Once tryptophan enters the serotonin neuron, the following conversion occurs:

Tryptophan → 5-hydroxytryptophan (5-HTP) using the enzyme *tryptophan hydroxylase.*

5-HTP → serotonin (5-HT) using the enzyme *aromatic amino acid decarboxylase.*

The rate-limiting step of the pathway is production of 5-HTP by tryptophan hydroxylase. Serotonin is a monoamine present throughout the body. Only 1 to 2% of

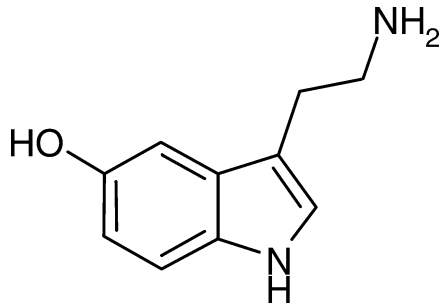


Fig. 1. Chemical structure of serotonin.

its entire body content is in the central nervous system (CNS). Serotonin is unable to cross the blood–brain barrier.

Many serotonin receptors have been identified. The 5-HT1A, 5-HT1B, 5-HT1C, 5-HT1D, and 5-HT2 receptors are single-subunit proteins that are members of the G protein-receptor superfamily. This receptor family is characterized by the presence of seven transmembrane domains, an intracellular carboxy-terminus, and an extracellular amino-terminus. It is the interaction of the receptor with the G protein that allows the receptor to modulate the activity of different effector systems, such as ion channels, phospholipase C, and adenyl cyclase *(5)*.

The 5HT-1 receptor family contains receptors that are negatively coupled to adenyl cyclase, and includes the 5-HT1A receptor. The 5-HT1A receptor is coupled via G proteins to two distinct effector systems: (1) the inhibition of adenyl cyclase activity, and (2) the opening of potassium channels, which results in neuronal hyperpolarization. Two serotonin receptors are presynaptic: 5-HT1A and 5-HT1D. These receptors act as auto-receptors and when they sense the presence of 5-HT, prevent further 5-HT release by a process called feedback inhibition.

Several serotonin receptors are postsynaptic, including 5-HT1A, 5-HT1D, and 5-HT2A (the latter one also known as the 5-HT2 receptor). These receptors are responsible for postsynaptic nerve stimulation or inhibition. The 5-HT1A and 5-HT2 have been implicated in the serotonin syndrome. The pathophysiology is presumed to involve hyperstimulation of the brainstem and spinal cord 5-HT1A receptors by combining serotonergic agents with MAOIs. The 5-HT2, β-adrenergic, and dopaminergic systems are also thought to play a role in the serotonin syndrome. Activation or modification of 5-HT1A in brainstem and spinal cord neurons with enhancement of overall neurotransmission may cause the serotonin syndrome.

The evidence implicating serotonin as the cause of the serotonin syndrome is largely based on animal models. Human studies have been anecdotal, and the mechanism of the serotonin syndrome remains unclear *(3)*. Serotonergic neurons are restricted to midline structures of the brainstem. Most serotonergic cells overlap with the distribution of the raphe nuclei in the brainstem. A rostral group (B6–8 neurons) projects to the thalamus, hypothalamus, amygdala, striatum, and cortex.

The largest group of serotonergic cells is B7, which is continuous with a smaller group of serotonergic cells, B6. Groups B6 and B7 together comprise the dorsal raphe nucleus. A more caudal group (B1–4 neurons) of serotonergic cells is found in the mid-pons to caudal medulla and projects to other brainstem neurons, the cerebellum, and the spinal cord. In the medulla, serotonergic neurons lie in the nuclei raphe magnus, raphe obscurus, and raphe pallidus, and give rise to descending spinal projections.

The principal ascending fibers arise from serotonin-containing cell bodies located in the dorsal (supratrochlear) and median (superior central) nucleus of the raphe nuclei. The major ascending pathway from the rostral raphe nuclei passes through the ventral tegmental area and joins the medial forebrain bundle in the lateral hypothalamus. The superior central nucleus is particularly associated with serotonergic fibers projecting to the interpeduncular nucleus, the mammillary bodies and the hippocampal formation. Ascending projections from the caudal raphe nuclei are less numerous and distribute to the superior colliculus, the pretectum, and the nuclei of the posterior commissure. Ascending serotonergic pathways from the superior central nucleus project mainly to mesolimbic structures, such as hippocampus and the septal nuclei, whereas the dorsal nucleus of the raphe has major projections to the neostriatum and substantia nigra.

Serotonin has been implicated in appetite, emotion, and motor, cognitive, and autonomic (sympathetic) function. Studies of the firing rate of serotonergic soma in the raphe nuclei suggest that serotonergic activity correlates with behavioral arousal, motor output, circadian rhythm, neuroendocrine function, eating, and sleeping. Precursors of 5-HT, releasing agents, reuptake inhibitors, and receptor agonists and antagonists have been used to assess serotonergic function *(5)*.

EPIDEMIOLOGY AND TRIGGERS

Serotonin syndrome is an iatrogenic disorder related to drugs that augment serotonin transmission. It occurs in patients treated for depression (most commonly), bipolar affective disorder, obsessive-compulsive disorder, eating disorder with depression, Parkinson's disease (PD), and even migraine. The patient's age and gender are not known predispositions to the development of serotonin syndrome. Serotonin syndrome generally occurs when two or more serotonergic drugs are taken concurrently, but it also occurs in cases with single drug exposures and overdoses. Antidepressants are the most common class of drugs to produce serotonin syndrome. Specifically, MAOIs, selective and nonselective serotonin reuptake inhibitors, and tricyclic antidepressants can cause the serotonin syndrome. There are many other serotonergic drugs reported to produce serotonin syndrome. Table 2, derived from Mills *(2)*, lists mechanisms of action and names of serotonergic drugs.

The serotonin syndrome is most commonly the result of the interaction between serotonergic agents and MAOIs. Monoamine oxidase (MAO)-A has greater affinity for serotonin, whereas MAO-B has a higher affinity for dopamine. Classical MAOIs produce irreversible inhibition of MAO enzyme activity. MAO enzyme activity is regenerated in approx 2 weeks as a result of the gradual production of

Table 2
Mechanisms of Action and Names of Serotonergic Drugs

Increase serotonin synthesis
L-tryptophan

Decrease serotonin metabolism
Isocarboxazid (Marplan)
Phenelzine (Nardil)
Selegiline (Eldepryl)
Tranylcypromine (Parnate)
Moclobemide

Increase serotonin release
Amphetamines
Cocaine
Fenfluramine (Pondimin)
Reserpine

Inhibit serotonin uptake
Tricyclic antidepressants
Selective serotonin reuptake inhibitors
Other uptake inhibitors
- Amphetamines
- Cocaine
- Dextromethorphan
- Tramadol (Ultram)
- Meperidine (Demerol)
- Venlafaxine (Effexor)
- Clomipramine

Direct serotonin receptor agonists
Buspirone (Buspar)
Lysergic acid diethylamide (LSD)
Sumatriptan (Imitrex)

Nonspecific increase in serotonin activity
Electroconvulsive therapy
Lithium

Dopamine agonists
Amantadine (Symmetrel)
Bromocriptine (Parlodel)
Bupropion (Wellbutrin)
Levodopa

Adapted from ref. *2*.

uninhibited MAO enzyme. Therefore, when a patient changes from an MAOI to a different class of serotonergic agent, a 2-week period must elapse between the two drugs. Serotonin syndrome may also occur with moclobemide, a reversible inhibitor of monoamine oxidase-A (RIMA *[6]*).

Increased concentrations of dopamine in the CNS can induce the serotonin syndrome by indirect serotonin release. Specifically, patients with PD are at risk to develop this syndrome. Levodopa, bromocriptine, and selegiline have all been associated with serotonin syndrome. The association of PD and serotonin syndrome is attributed to the high rate of depression among patients with PD, with many of these patients concurrently using an antidepressant and a dopaminergic agent. Toyama and Iacono *(7)* suggested that patients with PD might be protected from the serotonin syndrome by decreased serotonergic functioning, shown by loss of serotonergic neurons and decreased serotonin metabolites. A chart review by Waters *(8)* of 23 patients receiving combined fluoxetine and selegiline (an MAO-B inhibitor) and another chart review by Toyama *(7)* of 25 patients receiving combined serotonin-specific reuptake inhibitors (SSRIs) and selegiline both revealed no serious side effects. Nevertheless, it remains unclear how safe it is to use an SSRI.

Some narcotic analgesics, such as meperidine, dextromethorphan, and tramadol, are SSRIs (increase CNS serotonin) and may cause serotonin syndrome. Zornberg *(9)* described a patient taking meperidine and selegiline who developed possible serotonin syndrome. Meperidine, dextromethorphan, and tramadol are contraindicated in patients using MAOIs, including selegiline, and should be used with caution in patients using other serotonergic drugs. Fluoxetine has unique pharmacokinetics, which makes it prone to cause serotonin syndrome. The half-life of fluoxetine is 1 to 4 days, but its active metabolite has a half-life of 7 to 14 days. To decrease the risk of serotonin syndrome, when discontinuing fluoxetine, a patient should wait 5 weeks before starting another serotonergic agent. Durson *(10)* reported a patient who developed serotonin syndrome while taking carbamazepine and fluoxetine.

In addition to traditional prescription antidepressants, herbal antidepressants may also cause serotonin syndrome. The mechanism of St. John's Wort (*Hypericum perforatum*) is not entirely clear. It is hypothesized that it may reduce the expression of serotonin receptors, increase the numbers of 5HT-1A and 5-HT2A receptors, and inhibit synaptosomal serotonin uptake. Parker *(11)* reported a patient who developed cognitive and autonomic symptoms following ten days of monotherapy with St. John's Wort. Other herbal remedies that may also increase the activity of serotonin include ginseng, Brewer's yeast, and yohimbine.

SPECIFIC CLINICAL SETTINGS

Misdiagnosis of Serotonin Syndrome as Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is a potentially lethal disorder that is most often seen in psychiatric patients. NMS is also seen in patients with PD and is frequently triggered by withdrawing dopaminergic agents. The disorder likely occurs as a result of blockade of central dopamine receptors in the basal ganglia and hypothalamus, and blockade of peripheral postganglionic sympathetic neurons in

smooth muscle. The clinical picture may mimic serotonin syndrome. The fourth edition of American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV-TR*) *(12)* defines NMS as the development of severe muscle rigidity and elevated temperature in association with two or more of the following: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, and laboratory evidence of muscle injury (elevated creatinine phosphokinase). Table 3, derived from Mills *(2)*, compares the serotonin syndrome and the NMS. Distinguishing the two syndromes can be challenging.

Serotonin Syndrome in Migraine Patients

Classically, the serotonin syndrome was described in psychiatric patients and patients with PD, but more recently it has been identified in migraineurs as well. Patients with recurrent migraines have been hypothesized to have chronically low levels of systemic 5-HT. Agents that increase serotonin in the CNS have shown to be effective in treating migraine. Sumatriptan selectively activates the 5-HT1D receptor. Dihydroergotamine (DHE), another 5-HT agonist, is more potent at the 5-HT1A than the 5-HTD receptor. Additionally the SSRIs, which are used for migraine prophylaxis, inhibit serotonin reuptake. Several cases of serotonin syndrome were reported in migraine patients treated with prophylactic and/or abortive agents *(13,14)*. The responsible agents include sumatriptan with lithium, methysergide, sertraline, and DHE with lithium, imipramine and paroxetine. Other reported cases used a different combination of 5-HT1 agonist with a serotomimetic agent.

HIV-Positive Patients

Human immunodeficiency virus (HIV)-positive patients are at risk for developing the serotonin syndrome. Because depression is prevalent among HIV-positive patients, serotonin reuptake inhibitors are frequently prescribed in these patients. Antiretroviral agents inhibit serotonin metabolism via the cytochrome P450 system. Although ritonavir specifically inhibits the 2D6 isoenzyme, many other antiretrovirals inhibit the 3A4 enzyme. DeSilva *(15)* described five cases of serotonin syndrome in HIV-positive patients taking fluoxetine with protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Fluoxetine is metabolized by P450 2D6 to an active metabolite norfluoxetine, which is then further metabolized by 2D6. The long half-life of fluoxetine likely contributes to this problem.

Drugs of Abuse

3,4-Methylenedioxymethamphetamine (MDMA) or "Ecstasy" has become one of the most popular recreational drugs over the past 15 years. MDMA increases serotonin availability by stimulating its release from presynaptic terminals and preventing its reuptake. In addition to serotonin, MDMA is thought to affect other neurotransmitters, including dopamine. MDMA, a synthetic amphetamine, is re-

Table 3
Comparison of the Serotonin Syndrome and the Neuroleptic Malignant Syndrome

	Serotonin syndrome	Neuroleptic malignant syndrome
Cause of syndrome	Dopamine agonist Serotonin agonist	Dopamine antagonists Withdrawl of dopamine agonists
Onset of signs and symptoms	Within minutes to hours	Gradually in days to weeks
Resolution of symptoms	Improves in < 24 hours	Slower to resolve (average of 9 days)
Hyperthermia >38.0°C/100.4°F	45%	>90%
Altered level of consciousness	50%	>90%
Autonomic dysfunction	50–90%	>90%
Muscle rigidity	50%	>90%
Leukocytosis	11%	>90%
Increased creatinine phosphokinase level	15%	>90%
Elevated liver transaminase	8%	>75%
Metabolic acidosis	9%	Common
Hyperreflexia	Very common	Rare
Myoclonus	Very common	Rare
Therapy: dopamine agonists	Exacerbate condition	Improve
Therapy: serotonin antagonists	May improve condition	No effect

Adapted from ref. 2.

lated to mescaline, a hallucinogen. Initially in the 1980s, MDMA was used as a psychotherapeutic adjunct. Today MDMA is used in dance clubs, and its popularity is likely the result of its positive effect on mood and well being. The drug is used via several routes: oral, injection, smoking, and nasal. According to Parrot *(16)*, about 85 to 90% of recreational Ecstasy users ("ravers") reported an increase in body temperature, increase in sweating, and dehydration. Other physical reactions from MDMA include bruxism and trismus. Deaths in UK "rave" parties were attributed to serotonin syndrome following ingestion of MDMA *(17)*. The factors that contribute to death from MDMA ingestion may include dosage, individual sensitivity, tolerance, variability in drug metabolism, and concomitant use of antidepressants or other recreational drugs including cocaine, amphetamines, cannabis or alcohol.

Pediatric Population

Serotonin syndrome occurs in the pediatric population, and the syndrome is more frequently seen with the increased treatment of children with behavioral disorders

with serotonergic agents. Additionally, unintentional exposures of children to serotonergic drugs may occur as a result of the rising number of serotonergic antidepressants being prescribed to adults. Several case reports describe children who developed the serotonin syndrome after overdosing on serotonergic antidepressants, and even while on therapeutic doses of these drugs in combination with other serotonergic drugs *(18,19)*. Dextromethorphan, a widely used agent in cough syrups, should be given cautiously to children who take behavior-modifying medications because it may trigger the serotonin syndrome.

MANAGEMENT

Laboratory Studies

There are no specific laboratory tests that will help to positively identify the serotonin syndrome. Laboratory data are useful to eliminate other problems (infection, drug intoxication, etc.) and to identify any complications of serotonin syndrome. It is not necessary to demonstrate increased drug levels of the serotonergic agents. In fact, the majority of patients do not have elevated drug levels. The serotonin metabolite, 5-HIAA, can be measured, but this does not aid in diagnosis.

In NMS, serum creatinine kinase (CK) and polymorphonuclear leukocytes are generally increased, whereas in serotonin syndrome these levels are either normal or mildly increased. Carcinoid syndrome, which can mimic the serotonin syndrome, can be ruled out by checking 5-HIAA, the marker for carcinoid. An electroencephalogram may be necessary to rule out seizures. Complications of serotonin syndrome include rhabdomyolysis (with increased CK), hypoxia (resulting from respiratory muscle rigidity or coma), disseminated intravascular coagulation (from multiple organ failure), metabolic acidosis (from seizures or ventricular tachycardia), and aspiration pneumonia (from decreased level of consciousness).

Management

Serotonin syndrome must be promptly recognized, and supportive care is critical. All serotonergic agents must be immediately discontinued. Intensive care unit monitoring may be necessary. In severe cases, external cooling, muscular paralysis with neuromuscular blocking agents, mechanical ventilation, and sedation with an intravenous benzodiazepine may be necessary. Benzodiazepines may have a protective role as a result of nonspecific inhibitory effects on serotonergic transmission. The benzodiazepines also treat muscle hypertonia. Aside from benzodiazepines, other agents that may modify serotonergic excess include nonspecific serotonin receptor blockers, such as cyproheptadine, chlorpromazine, and methysergide. Table 4 reviews the management of serotonin syndrome. The prognosis of serotonin syndrome is generally good, with improvement generally within 24 hours of symptom onset. Cyproheptadine is a first-generation histamine-1 receptor-blocking agent with nonspecific antagonist properties at 5-HT1A and 5-HT2 receptors. Patients with the serotonin syndrome often respond within 1 to 2 hours of receiving 4–8 mg of cyproheptadine by mouth *(20)*. There is no parenteral formulation.

The treatment of serotonin syndrome in children is similar to that in adults. Recognition of the syndrome and discontinuation of the offending agent(s) are again

Table 4
Management of Serotonin Syndrome

–Prompt recognition
–Supportive care
–Discontinuation of all serotonergic agents
–Intensive care unit monitoring, if needed
–External cooling
–Muscular paralysis with neuromuscular blocking agents
–Mechanical ventilation
–Sedation and muscle relaxation with intravenous benzodiazepine
–Nonspecific serotonin receptor blockers, such as cyproheptadine, chlorpromazine, and methysergide
–Electroconvulsive therapy

critical. Supportive care, maintenance of high urine output, and prevention of rhabdomyolysis are key. Cyproheptadine is recommended in severe cases of serotonin syndrome in children. The pediatric dose is 0.25 mg/kg per day, with a maximum dose of 12 mg per day. A few case reports suggest that serotonin syndrome may also resolve with electroconvulsive therapy (ECT). For example, Nisijima *(21)* reported a depressed patient with diaphoresis, tremor, and myoclonus who was diagnosed with serotonin syndrome (by Sternbach's criteria). The patient was refractory to medical therapies, and the serotonin syndrome resolved and the depression lessened with ECT.

To decrease the risk of serotonin syndrome, it is important to avoid prescribing more than one serotonergic agent. If it becomes necessary to do so, the patient should be monitored closely for serotonin syndrome. MAOIs should not be used with other serotonergic agents. When switching agents, a 5-week washout period is necessary after discontinuing fluoxetine, and a 2-week washout period is necessary after discontinuing an MAOI. When prescribing a serotonergic agent, it is important to obtain a clear history of other drugs or herbs that the patient is currently taking or has recently discontinued (and record the date of cessation).

CONCLUSION

Serotonin syndrome is an uncommon but dangerous condition related to excess serotonergic activity. Fortunately, knowledge of drug mechanisms, pharmacodynamics, and interactions can help prevent this syndrome. Prompt identification and management will produce a satisfactory outcome in most cases.

REFERENCES

1. Oates JA, Sjoerdsma A. Neurologic effects of tryptophan in patients receiving a monoamine oxidase inhibitor. Neurology 1960;10:1076–1078.
2. Mills KC. Serotonin syndrome. American Family Physician 1995;52:1475–1482.
3. Sternbach H. The serotonin syndrome. Am J Psychiatry 1991;148:705–713.

4. Harrison's Principles of Internal Medicine. 15th edition. Braunwald E, Stone RM, Fauci AS, Hauser SL, Jameson JL, eds. McGraw-Hill, New York: 2001.
5. Siegel GJ, Albers RW, Agranoff BW, et al. Basic Neurochemistry: Molecular, Cellular, and Medical Aspects. 6th edition. Lippincott–Raven, Philadelphia: 1999.
6. Gillman, PK. Serotonin syndrome: clomipramine too soon after moclobemide. Int Clin Psychopharmacol 1997;12:339–342.
7. Toyama SC, Iacono RP. Is it safe to combine a selective serotonin reuptake inhibitor with selegiline? Ann Pharmacother 1994;28:405.
8. Waters CH. Fluoxetine and selegiline-lack of significant interaction. Can J Neurol Sci 1994;21:259–261.
9. Zornberg GL, Bodkin JA, Cohen BM. Severe adverse interaction between pethidine and selegiline. Lancet 1991;337:246.
10. Durson SM, Mathew VM, Reveley MA. Toxic serotonin syndrome after fluoxetine plus carbamazepine. Lancet 1993;342:442–443.
11. Parker V, Wong AHC, Boon HS, Seeman MV. Adverse reactions to St John's Wort. Can J Psychiatry 2001;46:77–79.
12. Task Force on DSM-IV. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR). American Psychiatric Association, 2000.
13. Gardner DM, Lynd LD. Sumatriptan contraindications and the serotonin syndrome. Ann Pharmacother 1998;32:33–38.
14. Mathew NT, Tietjen GE, Lucker C. Serotonin syndrome complicating migraine pharmacotherapy. Cephalalgia 1996;16:323–327.
15. DeSilva KE, Le Flore DB, Marston BJ, Rimland D. Serotonin syndrome in HIV-infected individuals receiving antiretroviral therapy and fluoxetine. AIDS 2001;15:1281–1285.
16. Parrott AC. Recreational Ecstasy/MDMA, the serotonin syndrome, and serotonergic neurotoxicity. Pharmacol Biochem Behav 2002;71:837–844.
17. Randall T. Ecstasy-fueled "rave" parties become dances of death for English youths JAMA 1992;268:1505–1506.
18. Gill M, Lo Vecchio F, Seldan B. Serotonin syndrome in a child after a single dose of fluvoxamine. Ann Emerg Med 1999;33:457–459.
19. Spirko BA, James FW. Serotonin syndrome: A new pediatric intoxication. Pediatr Emerg Care 1999;15(6):440–443.
20. Graudins A, Stearman, Chan B. Treatment of the serotonin syndrome with cyproheptadine. J Emerg Med 1998;16:615–619.
21. Nisijima K, Nibuya M, Kato S. Toxic serotonin syndrome successfully treated with electroconvulsive therapy. J Clin Psychopharmacol 2002;22:338–339.

17

Risks and Dangers From Hyperekplexia and Other Startle Disorders

Frederick Andermann and Eva Andermann

PATIENT VIGNETTE

A neurological consultation is requested in the neonatal intensive care unit for a newborn infant who is noted to be extremely jittery. On examination, the baby is neurologically normal except for exaggerated response to tactile and auditory stimuli, lack of habituation on nose tap, and an exaggerated and sustained Moro response. Resting tone is markedly increased, particularly in axial muscles. On one occasion, a flurry of monitor noises triggers jerks and sustained stiffening that produce a 30-second apneic pause. Based on the examination, hyperekplexia is diagnosed, and clonazepam markedly attenuates the startle and stiffening. Screen of the patient's family reveals one other affected child, who startles to loud noises.

INTRODUCTION

It is customary to start a presentation on startle by referring to the normal reflex, a common reaction in animals and humans, preparing the subject to respond by fighting or by escaping as quickly as possible *(1)*. Fatigue or stress predisposes to increased startle, and there is great variation of the tendency to startle in the population, with some individuals aptly described as hyperstartlers. Excessive startle is also a frequent but not an obligatory feature of people with tics or Tourette's syndrome.

The three main disorders manifesting with excessive startle are hyperekplexia, startle epilepsy, and jumping *(2)*. The early distinction between startle epilepsy and startle disease comes from the work of Alajounanine and Henry Gastaut, who used the terms "maladie du sursaut" for the nonepileptic process and "epilepsie sursaut" for persons in whom the excessive startle was coupled with epileptic clinical manifestations *(3)*. Although startle disorders are often benign, there are risks in some affected individuals including a danger of mortality in some affected individuals.

HYPEREKPLEXIA

Kirstein and Silverskjold were the first to report a family with several affected individuals. Although they considered this an unusual form of epilepsy, in retro-

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

spect these individuals were affected with startle disease *(4)*. Two major papers were then published by Kok and Bruyn *(5)* and by Suhren, Bruyn, and Tuynman *(6)*, and the clinical pattern of nonepileptic startle disease, or hyperekplexia, emerged *(7)*. Exaggerated and persistent startle to unexpected auditory, somatosensory, or visual stimuli is the defining feature of this syndrome. The disease usually presents in infancy, although presentations have been reported in the perinatal period *(8)*. Attacks of tonic stiffening may interfere with breathing, and affected children have been described with "stiff-baby syndrome" *(9)*. Recognition of these attacks and identification of children of affected parents who may be at risk is critical to prevent sudden death from stiffening leading to apnea. Associated clinical features include regurgitation, hiatal, inguinal, or umbilical hernias, and congenital dislocation of the hips (presumably as a result of rigidity).

Infants often experience delay in walking, and develop falling attacks as a result of brief generalized tonic spasms. These may occur in response to surprise, sensory stimuli, and strong emotions such as stress or fright. The child typically falls without being able to prevent him- or herself, but without loss of consciousness. Often the peculiarity of the stimuli and circumstances lead to the diagnosis. One of our patients carried a diagnosis of spastic quadriparesis, a common mistake because affected children are often rigid. The child collapsed like a log when he caught a small fish, which fell on to him as he pulled it out of the water.

In older children and occasionally in adults, a short period of generalized stiffness may follow the startle response. Voluntary movements become impossible, resulting in unprotected falls, fractures, and rare head injury. A diagnosis of epilepsy is usually entertained, and inappropriate overmedication with anti-epileptic drugs is not infrequent.

Excessive startle persists throughout life and is best elicited by gently tapping the tip of the nose or forehead. This response is similar to the McCarthy reflex. It may also be more apparent under stressful conditions. The hypertonia or generalized muscular rigidity gradually diminishes with time, but the exaggerated response to startle persists, leading to an unusual gait. Somewhat broad-based with a tendency to walk along and touch the wall, patients appear fearful in an attempt to anticipate abnormal stimuli. Considerable embarrassment and limitation of activity are common.

Hyperreflexia is sometimes present, particularly in the lower extremities. Nocturnal episodes of generalized clonus may develop, typically affecting the legs and lasting up to minutes. Fatigue, loss of sleep, or stress may precipitate these events. The attacks are generally well recognized by the families, but because they are unusual they may be inappropriately diagnosed as conversion reactions *(10)*. Sustained stiffness is seen in childhood or adults, occasionally involving one or more limbs. In the limited experience known, this has been associated with recurrences of symptoms related to cessation of medication *(11)*.

Affected individuals possess normal intelligence, but occasional patients have some degree of mental retardation and epileptogenic electroencephalogram (EEG)

abnormalities may be present *(6)*. This suggests more widespread cerebral involvement. Patients with hereditary hyperekplexia respond dramatically to clonazepam, which abolishes most clinical features except for head retraction on nose and forehead tapping *(7)*.

Because of intermittent excessive startle in family members of clearly affected individuals, we wondered about the possibility of a minor form of the disorder in addition to the full-blown or major form of startle disease *(6,7)*. The mother of two affected girls, while going through a difficult divorce, startled excessively and literally rose off the chair when the phone rang, but these features disappeared as her life settled down. Later studies by Tijssen and colleagues suggested that this minor form merely represents excessive physiological startle, because these individuals did not have the identified molecular mutation *(12)*.

Startle disease is inherited as an autosomal dominant, with a high penetrance of more than 90% and with variable expressivity. Sporadic and autosomal recessive forms have been described, and the familial and sporadic cases appear to have the same clinical phenotype. Sporadic cases may represent either a new mutation in the proband, autosomal recessive inheritance, germline mosaicism, or lack of penetrance in affected relatives *(7,13,14)*.

In the last decade, the molecular basis of startle disease has been linked to an abnormality of the inhibitory glycine receptor (GLYR) *(15)*. Two different missense mutations have been identified in the same base pair of exon 6 of the α1 subunit of the inhibitory glycine receptor GLRA1: G1192A and G1192T. These result in amino acid substitutions at codon 271 of arginine > leucine and arginine > glutamine, respectively. Mutations were found in four of seven families tested. The first mutation was confirmed in a Swiss family reported by Schorderet *(16)*, and in the original German Dutch family described by Suhren.

The finding of two point mutations at the same position suggested that the arginine at position 271 is critical for the function of the inhibitory GLYR. The mutation was not present in individuals in the German Dutch family affected with the minor form—that is, in individuals with only an excessive startle reaction to unexpected stimuli *(17)*. Functional studies of the inhibitory GLYR showed that picrotoxin is a competitive antagonist of the α1 subunit of the human GLYR. The two mutations described transform picrotoxin from an allosterically active competitive antagonist to an allosteric potentiator at low concentrations and to an uncompetitive antagonist at higher concentrations. Thus the allosteric transduction pathways of both agonists and antagonists converge at a common residue, suggesting that this residue may act as an integration point for information from various extracellular ligand-bindings sites *(18)*.

Functional studies have shown that agonist binding in the GLYR initiates opening of a chloride-selective channel that modulates the neuronal membrane potential. Missense mutations substituting arginine 271 with either leucine or glutamine change GLYR single-channel conductances to lower conductance levels. The binding of the glycinergic agonists β-alanine and taurine to mutated GLYRs does not

initiate chlorine current, but competitively antagonizes currents activated by glycine. Thus, arginine 271 mutations result in uncoupling of the agonist-binding process from the channel activation mechanism of the receptor.

In summary, there has been an enormous amount learned regarding the molecular basis of hyperekplexia during the last decade. Nine mutations of the GLYRA1 gene have been identified, five dominant and four recessive. One of the recessive mutations is a null mutation, and two others occurred in a compound heterozygote. In a number of familial cases, no mutation of GLYR has been identified. This suggests nonallelic genetic heterogeneity and the possibility of mutations in other GLYR subunits exists. Three mouse models of hyperekplexia have been identified, one with a missense mutation of GLYRA1, one with an insertion mutation at GLYRB, and one null allele at GLYRA1 *(19)*.

These molecular advances should lead to improved genetic counseling, prevention of neonatal deaths and complications, increased knowledge of the mechanisms involved in abnormal startle, and eventually rational therapy. For the time being, treatment with clonazepam or with valproic acid in low doses brings about adequate, although incomplete, improvement *(7,11,19)*. There are also patients with symptomatic hyperekplexia as a result of central nervous system pathology. Patients with static perinatal *(20)*, postanoxic *(1)*, posttraumatic encephalopathy *(2)*, sarcoidosis *(1)*, and paraneoplastic etiology *(2)* have been described. Brainstem lesions *(21,22)* may also produce this clinical picture. These various symptomatic startle abnormalities must be distinguished from startle epilepsy, which is sometimes difficult given the paucity of EEG abnormalities in some patients with frontal epilepsy. The prognosis of symptomatic hyperekplexia depends on the underlying cause.

STARTLE EPILEPSY

In startle epilepsy, auditory, tactile, or more rarely, visual stimuli trigger seizures. The coexistence of neurological abnormalities facilitates the diagnosis. Startle epilepsy may occur in patients with infantile hemiparesis, quadriparesis, diffuse encephalopathy, and secondary generalized epilepsy, Down syndrome and, very rarely, in patients with normal intelligence and normal neurological exams. The pathophysiology of startle epilepsy has been studied by Chauvel *(23)*. Seizures start in the muscles first involved in the startle reflex, and propagate to the contralateral limb and then to the ipsilateral side. The abnormality is usually frontal or frontoparietal, involving the supplementary motor area in the vicinity of the paracentral lobule *(24,25)*. Aguglia and Gastaut found mesial frontal atrophy in 40% of patients with startle epilepsy, frontocentral spikes in 50%, evoked frontocentral spikes in 33%, and frontal spike foci in all *(26)*.

Startle epilepsy is quite variable in its response to antiepileptic medication. Some patients are easily controlled and remain with only minor, although still abnormal, responses to startle. In others, the abnormal response progresses to falling with attendant risks of injury despite optimal anti-epileptic medication. In the presence of identifiable structural lesions, surgical treatment after appropriate localization studies is quite effective. In others, particularly in the absence of a visible lesion,

the potential for surgical treatment is low and occasional patients are confined to life in a wheelchair. Jimenez Roldan has suggested a specific response of startle epilepsy to clonazepam, but this has not been confirmed by himself or others *(27)*.

JUMPING AND OTHER CULTURE-BOUND SYNDROMES

Excessive startle is also a feature of the culture-bound syndromes first described in the late 1800s. The Jumping Frenchmen of Maine, loggers from the Beauce region of Quebec working in the Moosehead Lakes area of Maine, were described by Beard *(28)*. Their clinical features were excessive startle, echolalia, echopraxia, and forced obedience. Later studies by Kunkle have stressed the occasional late appearance of symptoms after a nonspecific illness *(29)*. The familial nature is obviously not compatible with a learned process, though good family studies are not available. Drs. Marie Helene and Jean Marc St. Hilaire described several jumpers who, in response to startle, adopted a fighting stance and swore *(30)*. They, like Rabinovitch *(31)*, assumed that this was a learned behavior designed to amuse bystanders by startling susceptible individuals, but this is unlikely to explain the genetic features.

In patients with the culture-bound syndromes, forced obedience to such orders as "throw it," "punch," or "hit" may bring about not only embarrassment, but also occasionally danger. An analogous disorder, Myriachit, Amurath, or Icotta, has been described in Siberia, the former by Hammond, then surgeon general of the United States *(32)*. Latah in Malaysia, Goosey in the United States, Jaun in Myanmar, Bah Tsche in Thailand, Mali Mali and Silok in the Philippines, and Panic in Lapland probably represent analogous, if not identical, disorders *(33)*. The studies of Simons *(34)* and Tanner *(35)* were carried out in Latah subjects in Malaysia. They stressed the behavioral features and the social utilization of such behaviors. Imu, a behavioral disorder in the Ainu of Hokkaido in Northern Japan, likely represents the same process. The early descriptions come from Uchimura, who also filmed affected persons *(36)*. The current perspective among Japanese neurologists on Hokkaido suggests that the process occurred mainly in women, and that it is currently dying out.

When one reviews the descriptions of these various disorders, a great similarity of the clinical features, with increased startle, echolalia, echopraxia, and, more rarely, forced obedience, is inescapable. It is the social superstructure that varies; the clinical features of startle epilepsy and of hyperekplexia are always absent. Most likely, these culture-bound startle disorders represent an unusual form of tics. Their molecular basis remains unknown, similar to that of Tourette's syndrome, with which they share many clinical features.

CONCLUSION

The differential diagnosis of startle disorders includes the three entities described here. In most individuals, awareness of the diagnostic possibilities should lead to recognition of the underlying process, and initiation of treatment.

REFERENCES

1. Brown P, Day BL, Rothwell JC, Thompson PD, Marsden CD. The effect of a posture on the normal and pathological auditory startle reflex. J Neurosurg Psychiatry 1991;54(10):892–897.
2. Andermann F, Andermann E. Excessive reflex syndromes: startle disease, jumping, and startle epilepsy. Adv Neurol 1986;43:321–338.
3. Alajouanine T, Gastaut H. La syncinésie-sursaut et l'épilépsie-sursaut à déclanchement sensoriel or sensitif inopiné. I . Les faits anatomo-cliniques (15 observations). Revue Neurologique 1955;93:29–41.
4. Kirstein L, Silfverskjold B. A family with emotionally precipitated drop seizures. Acta Psychiatr Scand 1958;33:417–476.
5. Kok O, Bruyn GW. An unidentified hereditary disease. Lancet 1962;I:1359.
6. Suhren O, Bruyen GW, Tuynman JA. Hyperekplexia: a hereditary startle syndrome. J Neurol Sci 1966;3:577–605.
7. Andermann F, Keene DL, Andermann E, Quesney LF. Startle disease or hyperekplexia: further delineation of the syndrome. Brain 1980;103:985–997.
8. Gordon N. Startle disease or hyperekplexia. Dev Med Child Neurol 1993;35(11):1015–1018.
9. Cioni G, Biagioni E, Bottaie P, Castellacci Am, Paolicelli PB. Hyperekplexia and stiff-baby syndrome: an identical neurological disorder? Ital J Neurol Sci 1993;14(2):145–152.
10. De Groen JH, Kamphuisen HA. Periodic nocturnal myoclonus in a patient with hyperekplexia (startle disease). J Neurol Sci 1978;38(2):207–213.
11. Dooley JM, Andermann F. Startle disease or hyperekplexia: adolescent onset and response to Valproate. Pediatr Neurol 1989;55(2):126–127.
12. Tijssen MAJ, Vergouwe MN, van Dijk GJ. Major and minor form of hereditary hyperekplexia. Mov Dis 2002;17(4):826–830.
13. Ryan SG, Dixon MJ, Nigro MA, et al. Genetic and radiation hybrid mapping of the hyperekplexia region on chromosome 5q. Am J Hum Genet 1992a;51(6):1334–1343.
14. Ryan SG., Sherman SL, Terry JC, Sparkes RS, Torres MC, Mackey RW. Startle disease, or hyperekplexia: response to Clonazepam and assignment of the gene (STHE) to chromosome 5q by linkage analysis. Ann Neurol 1992b;31(6):663–668.
15. Shiang R, Ryan SG, Zhu YZ, Hahn AF, O'Connell P, Wasmuth JJ. Mutations in the alpha 1 subunit of the inhibitory glycine receptor cause the dominant neurological disorder, hyperekplexia. Nat Genet 1993;5(4):351–358.
16. Schorderet DF, Pescia G, Bernasconi A, Regli F. An additional family with startle disease and G1192A mutation at the a1 subunit of the inhibitory glycine receptor gene. Hum Mol Genet 1994;3:1201.
17. Tijssen MA, Shiang R, van Deutekom J, et al. Molecular genetic reevaluation of the Dutch hyperekplexia family. Arch Neurol 1995;52(6):578–582.
18. Lynch JW, Rajendra S, Pierce KD, Handford CA, Barry PH, Schofield PR. Identification of intracellular and extracellular domains mediating signal transduction in the inhibitory glycine receptor chloride channel. EMBO J 1997;16(1):110–120.
19. Rajendra S, Lynch JW, Pierce KD, French CR, Barry PH, Schofield PR. Mutation of an arginine residue in the human glycine receptor transforms beta-alanine and taurine from agonist into competitive antagonists. Neuron 1995;14(1):169–175.
20. Shimamura M. Neural mechanisms of the startle reflex in cerebral palsy, with special reference to its relationship with spino-bulbo-spinal reflexes. In: Desmedt JE, ed. New Developments in Electromyography and Clinical Neurophysiology, Volume 3. Karger, Basel: 1995;761–766.
21. Duensing F. Schreckreflex und Schreckreaktion als hirnorganische Zeichen. Archiv für Psychiatrie und Nervenkrankheiten 1952;188:162–192.
22. Shibasaki H, Kakigi R, Oda K-I, Masukawa S-I. Somatosensory and acoustic brain stem reflex myoclonus. J Neurol Neurosurg Psychiatry 1988;51:572–575.

23. Chauvel P, Liègeois C, Chodkiewicz JP, Bancaud J, Talairach J. Startle epilepsy with infantile hemiplegia: the physiopathological data leading to surgical therapy. Abstracts of the 15th Epilepsy International Symposium 1983;180.
24. Bancaud J, Talairach J, Bonis A. Physiopathogénie des épilepsies-sursaut: (à propos d'une épilepsie de l'aire motrice supplémentaire). Revue Neurologique 1967;117:441–453.
25. Bancaud J, Talairach J, Lamarche M., Bonis A, Trottier S. Hypothèses neuro-physiopathologiques sur l'épilepsie-sursaut chez l'homme. Revue Neurologique 1975;131:559–571.
26. Aguglia U, Tinuper P, Gastaut H. Startle-induced epileptic seizures. Epilepsia 1984;25:712–720.
27. Gimenez-Roldan S, Martin M. Effectiveness of clonazepam in startle-induced seizures. Epilepsia 1979;20:555–561.
28. Beard GM. Remarks on "Jumpers" of Maine. The Popular Science Monthly 1878;5:526.
29. Stevens II. "Jumping Frenchmen of Maine". Archives of Neurology, Chicago 1965;12:311–314.
30. Saint-Hilaire MH, Saint-Hilaire JM, Granger L. Jumping Frenchmen of Maine. Neurology 1986;36:1269–1271.
31. Rabinovitch R. An exaggerated startle reflex resembling a kicking horse. Can Med Assoc J 1965;93:130.
32. Hammond W. Miryachit: a newly described disease of the nervous system, and its analogues. New York Med J 1884;39:191–192.
33. Andermann F, Andermann E. Startle disorders of man: hyperekplexia, jumping and startle epilepsy. Brain Dev 1988;10:213–222.
34. Simons RC. The resolution of the Latah paradox. J Nerv Ment Dis 1980;168(4):195–206.
35. Tanner CM, Chamberland J. Latah in Jakarta, Indonesia. Mov Disord 2001;16(3):526–529.
36. Uchimura Y. Imu, a psychoreactive manifestation in Ainu women. Nervenarzt 1956;27(12):535–540.

18

Wilson's Disease

George J. Brewer

PATIENT VIGNETTES

Patient 1: A 26-year-old man presented to a neurologist with a 6-month history of mild upper extremity tremor. He also felt that during the past year his memory was not as good as it used to be, and sometimes he had difficulty focusing mentally on tasks. Otherwise, the patient had been healthy. His family history revealed two ancestors on his mother's side who had had mild tremor. Physical and neurological examinations were negative except for tremor. Laboratory studies were confined to blood counts and a biochemistry panel, which came back normal.

The neurologist sat across the desk from the patient to discuss the diagnosis. Unbeknownst to either of them, the patient at this moment faced an emergency. Not an emergency-room emergency, but a diagnostic emergency. The correct line of thinking, including an appropriate differential diagnosis list, would lead to a work-up, the correct diagnosis, effective treatment, and prevention of further brain damage. Instead, the neurologist reassured the patient that he had essential tremor, and that it would likely be never more than a minor inconvenience. The family history supported the diagnosis, the neurologist said.

The tremor worsened and the patient sought a second opinion from a movement disorder specialist. Without work-up other than a neurological exam, this doctor confirmed the diagnosis of essential tremor. This neurologist followed the patient, and over a period of 2 years the patient's tremor worsened to the point of being partially disabling. In addition, he developed dysarthria, facial dystonia, drooling, and increasing generalized incoordination. Without further diagnostic work-up the diagnosis was modified to essential tremor with parkinson-like features. While seeing yet a third neurologist the patient, who had been educating himself about his symptoms, asked if he might have Wilson's disease. The presence of Kayser-Fleischer rings was then detected, and other tests confirmed Wilson's disease. Some of the patient's neurological damage was permanent, even after several years of effective anticopper therapy.

Patient 2: The diagnosis of Wilson's disease had been quickly established in a 23-year-old female graduate student. She had presented with mild dysarthria and mild

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

upper extremity tremor. She had been amenorrheic for about 1 year. The neurologist to whom the patient had been referred considered Wilson's disease as part of the differential and moved quickly to measure urine copper and blood ceruloplasmin, and ordered a slit lamp examination for Kayser-Fleischer rings. All tests came back positive.

The neurologist felt good about herself and her clinical acumen as she sat across her desk from the patient, explaining the diagnosis, and discussing therapy with penicillamine. Unbeknownst to either of them, the patient now faced an emergency. Not an emergency-room emergency, but a therapeutic emergency. Would she be a patient who would respond favorably to the anticopper drug, penicillamine? Or would she be one of the one in two patients who suffer further neurological deterioration from penicillamine? Or worse, one of the one in four patients who never recover from this worsening and end up with additional permanent neurological deterioration as a result of penicillamine therapy?

Unfortunately, she was one of the one in four. She deteriorated rapidly. Two weeks after therapy initiation the dose of penicillamine was increased from 1 g to 2 g and later to 4 g in an attempt to curb the storm. This seemed to accelerate the deterioration. By three months she was essentially anarthric and so dystonic that her face was locked in a continuous drooling grimace. She had severe, generalized tremor. Her back was twisted into a comma shape and she could walk only a short distance. She was so uncoordinated that she could not feed herself without flinging food around the room. She never recovered any of her neurological function despite years of anticopper therapy. She was not able to return to school or find employment. Meaningful life had all but been destroyed by penicillamine therapy.

INTRODUCTION

The clinical and pathological features of Wilson's disease were originally described by Wilson, an American neurologist working in England at the time *(1)*. He noted the combination of liver disease and degeneration of certain areas of the brain, particularly the lenticular nuclei that coordinate movement, and named the disorder hepatolenticular degeneration. Later, two ophthalmologists, working independently, identified the corneal copper deposits that now bear their names, the Kayser-Fleischer rings *(2,3)*. Still later, the causative role of copper accumulation was identified *(4–6)*. Further work established that the liver controlled copper balance by excretion of excess copper in the bile *(7)*, and that there was a failure of biliary copper excretion in Wilson's disease *(8)*. A low level of ceruloplasmin, a copper-containing serum protein, was found in most Wilson's disease patients *(9,10)*.

The causal involvement of copper led to a trial of anticopper therapy, first British Anti-Lewisite (BAL) given parenterally *(11)*, and later penicillamine *(12)* and trientine *(13)*, chelators that increase the urinary excretion of copper, given orally. Still later, zinc—which blocks the intestinal absorption of copper *(14–16)*—was developed, and then tetrathiomolybdate (TM), which not only blocks intestinal absorption of copper, but complexes serum copper with albumin and renders the copper nontoxic *(17,18)*.

Wilson's disease was established as an autosomal recessive disorder *(19)*, and the gene eventually cloned *(20–22)*. The gene is a copper-binding, membrane-bound

ATPase called ATP7B. It bears close homology to ATP7A, the causative gene for Menke's disease *(23–25)*. More than 200 causative mutations have already been described *(26)*. The frequency of the disease is believed to be about 1 in 40,000 in most populations.

CLINICAL PRESENTATIONS

Clinically, patients usually present in one of three ways *(27–31)*; note that these reviews and monographs support all the material in this section and the next. Approximately one-half of the patients are diagnosed because of liver disease, typically during the second to third decade of life, although the overall age of presentation is broader: ages 5–60 years. Patients may have an episode of hepatitis, with or without jaundice. This may spontaneously resolve, although serum transaminase enzymes tend to remain at least mildly elevated. Hepatitis may recur a few months or years later and repeatedly resolve, leading to an incorrect diagnosis of chronic active hepatitis. Other patients may come to medical attention because of the diagnosis of cirrhosis, perhaps because of the complications of portal hypertension, such as bleeding varices, or leukopenia or thrombocytopenia from hypersplenism. If the patient drinks alcoholic beverages, he or she may be incorrectly labeled as having alcoholic cirrhosis. Finally, the patient may present with liver failure which, depending on its severity, may include jaundice, hypoalbuminemia, ascites, peripheral edema, low levels of clotting factors, bleeding, and encephalopathy.

The second type of clinical presentation includes perhaps 25% of patients and involves behavioral and mental abnormalities. This type of presentation typically occurs in the late teenage years and early 20s, but again the overall age of presentation is quite broad, from 15 to 60 years. The list of abnormalities includes easy loss of emotional control, crying episodes, temper tantrums, difficulty focusing on tasks, and memory loss (as with patient 1), insomnia, and sometimes more bizarre behaviors such as loss of sexual inhibitions. True psychoses are rare, but patients occasionally have hallucinations or delusions. Occasionally, patients will have seizures or migraine headaches. Often these patients, typically teenagers or young adults, are wrongfully accused of substance abuse. The change in behavior in a previously psychiatrically normal youngster suggests this misdiagnosis. Usually, these patients are not diagnosed at this stage, and progress to develop a neurological movement disorder. When the physician is presented with a patient with early symptoms of a movement disorder, behavioral abnormalities may be helpful diagnostically in suggesting the possibility of Wilson's disease, as they might have been with patient 1. However, to be considered relevant, the behavioral or mental abnormalities should have begun within the 3 or 4 years prior to the onset of neurological symptoms.

The third mode of presentation is neurological, and involves about 50% of patients, including the 25% who first present with significant behavioral abnormalities. The neurological presentations typically occur when the patient is in his or her early 20s, although again the age of presentation is quite broad, from 15 to 60 years. Copper toxicity causes damage to the areas of the brain that coordinate movement, such as the lenticular nuclei; hence its classification as a movement disorder. The

Table 1
Neurological Signs in Patients With Wilson's Disease Presenting With Neurological Disease

[a]Signs	Comment
Dysarthria	Present in almost all patients. The various abnormalities are not specific for Wilson's.
Dystonia	Present somewhere in the body in about two-thirds of patients.
Incoordination	Present in over one-half of patients.
Dysdiadochokinesia	
Rigidity	Present in about one-half of patients.
Facial expression abnormality	
Tremor	Present in about one-third of patients. Several different tremor types can occur, none specific for Wilson's disease.
Abnormal eye movement	Present in about one-third of patients.
Drooling	
Dysphagia	
Bradykinesia	
Motor impersistence	Present in about one-fifth of patients.
Athetosis	Present in about one-tenth of patients.

[a]Signs are listed roughly in order of frequency in the author's experience.

list of the more frequent signs is given in Table 1. The three basic problems are dystonia, incoordination, and tremor, which, working separately or together, account for most of the signs in Table 1. Almost all patients presenting neurologically have some dysarthria, which results from dystonia and incoordination of speech-related muscles. Speech abnormalities can be a variety of types, and no type is specific for Wilson's disease. Some patients have drooling as a result of facial dystonia. The facies, and other aspects of the disease including difficulty initiating walking, can closely resemble Parkinson's disease. Dysphagia may be present. Tremor occurs in perhaps one-third of Wilson's disease patients presenting neurologically, and can be of a variety of types, none specific for Wilson's disease. Incoordination may begin with difficulty in fine movements, such as handwriting and buttoning buttons. Micrographia may occur, but it is more common for handwriting to simply look sloppy. As the disease progresses, incoordination may involve larger muscle groups and make it difficult to feed oneself and carry out other tasks. The patient may become prone to stumbling and falling. Dystonia can involve any muscle group, including the face, as previously described, the upper and lower extremities, the neck, and the muscles of the trunk that control posture. The dystonia may cause the extremities or other parts of the body to be pulled into abnormal and grotesque positions that interfere with function (as with patient 2).

Patients may also have the types of behavioral problems discussed earlier, and may complain of memory loss, difficulty focusing on tasks, migraine headaches, and occasionally have a history of seizures. Sensory disturbances, muscle weakness, and grossly impaired cognition are not part of the disease. Autonomic disturbances, such as orthostatic hypotension, sweating abnormalities, or bowel, bladder, or sexual dysfunction may be present. Patients often have detectable abnormalities relating to the liver, such as elevation of serum transaminase enzymes, or thrombocytopenia or leukopenia resulting from hypersplenism owing to occult cirrhosis.

A single major symptom, such as tremor (patient 1) or dysarthria, may be the sole manifestation for a long period of time, perhaps 1 or 2 years. Note that patient 1, who was misdiagnosed as essential tremor, had only tremor for a long period of time.

Most female patients prior to presenting with any of the above classical presentations will have exhibited amenorrhea for at least 1 year or longer (patient 2), and may have had one or more spontaneous abortions. Some patients will note a type of osteoarthritis, particularly of the knees. Cholelithiasis and nephrolitheasis are more common than in the general population. Cardiac abnormalities have been reported, but are uncommon in our experience. Patients may have microscopic hematuria and exhibit excess loss of amino acids, phosphate, urate, or sugar in the urine, but a full-blown Fanconi syndrome is rare. Sunflower cataracts and corneal copper deposits (Kayser-Fleischer rings) occur frequently, particularly in the neurological and behavioral presentations of the disease.

Finally, some patients will be diagnosed in what we call the "presymptomatic" state. This will usually occur when siblings of a newly diagnosed case are screened. Each sibling is at 25% risk for having the disease genotype, but has not yet become clinically ill. The disease is believed to be almost 100% penetrant, so it is important that these patients be diagnosed and treated prophylactically. At the time of diagnosis, these patients have usually suffered some liver damage, and may have mildly elevated serum transaminase enzymes and/or exhibit evidence of hypersplenism, such as leukopenia or thrombocytopenia. They may also have Kayser-Fleischer rings. Occasionally, presymptomatic patients will come to attention because of a chance observation, such as the presence of Kayser-Fleischer rings.

RECOGNITION, SCREENING, AND DEFINITIVE DIAGNOSIS

The failure to recognize that a given patient presenting to a clinician might have Wilson's disease is a major obstacle. In most cases, the diagnosis is probably missed for two major reasons. One is the relative rarity of the disease, and the second is the great variety of forms in which the disease can present itself. Yet recognition of the possibility of Wilson's, followed by an appropriate work-up and speedy diagnosis, are critically important because the disease can be so effectively treated, and the longer the disease progresses before treatment, the greater the amount of irreversible damage to brain and liver.

Here, we comment only briefly on the recognition of hepatic and psychiatric presentations, and focus on recognizing the neurological presentation, because of

Table 2
Tests for Screening and Definitive Diagnosis in the Neurological and Psychiatric Presentation of Wilson's Disease

Procedure	Interpretation	Comment
Ophthalmologist slit lamp examination for Kayser-Fleischer rings	99+% of these patients are positive.	False-positives and false-negatives are extremely rare. See text regarding obstructive liver disease.
24-hour urine copper	Symptomatic patients always have values over 100 μg (normal 20–50).	Presymptomatic patients over 100 μg only about one-half of time. Heterozygous carriers may have values up to about 65.

the subject of this book. In unexplained hepatitis, particularly recurring hepatitis, and particularly in viral negative hepatitis, screening for Wilson's disease is important. In unexplained cirrhosis in patients aged 50 years or younger, or where a diagnosis of alcoholic cirrhosis is being considered, particularly if the patient denies excessive drinking, screening for Wilson's disease should occur. In unexplained (or poorly explained) hepatic decompensation in patients under age 50, in previously psychiatrically normal patients under age 50 who develop behavioral disturbances over a period of 1 or 2 years, and in patients who are labeled as substance abusers without clear evidence or who deny abusing substances, screening for Wilson's disease should occur.

With regard to neurological presentations, any patient under the age of 50 years who develops one or more signs or symptoms of a movement disorder (*see* Table 1) should be screened for Wilson's disease unless there is *positive* information providing for an alternate diagnosis. In particular, *any* patient under age 50 who is considered for a diagnosis of essential tremor or Parkinson's disease should be screened for Wilson's disease (patient 1). There may already be clues in the patient's laboratory tests to bolster the neurologist's decision, such as mildly elevated transaminase enzymes (in about 50% of neurological patients) or leukopenia or thrombocytopenia (in about 35% of neurological patients); however, this should not be the determining factor in ordering screening tests. Because a slit lamp examination is required for a diagnosis to be definitive, it doesn't hurt to take a peek at the patient's eyes (although again, this should not be a determining factor). If the eyes are the right color (such as blue), Kayser-Fleischer rings may be readily visible.

Screening for Wilson's disease in the neurological (and psychiatric) presentation is easier than in the hepatic presentation and in presymptomatic patients (Table 2). This is because first, over 99% of such patients have Kayser-Fleischer rings on slit lamp examination by an ophthalmologist (178 out of 179 patients, in our series); and second, 100% of such patients (90 out of 90, in our series) have diagnostic elevations (> 100 μg/24 hours, with normal less than 50) of urine copper (Table 2). This combination of tests is not only adequate for screening but for definitive

diagnosis in this type of patient, obviating the need for a liver biopsy. I recommend using both tests, because a rare neurological Wilson's patient may not have the rings, and because laboratories can make mistakes in measuring urine copper. If the two tests are concordant (either both diagnostic or both normal), further work-up is not needed. If discordant, both should be repeated, with different operatives. False-positives and -negatives for Kayser-Fleischer rings are quite rare. However, if the patient has obstructive liver disease of a year's duration or longer, Kayser-Fleischer rings, elevated urine copper, and elevated liver copper can occur in the absence of Wilson's. The serum ceruloplasmin can be helpful in affecting index of suspicion, but should not be used as a definitive test. It is low in 80% of patients with Wilson's disease, including those with neurological disease, but is normal in 20%. Furthermore, carriers of one copy of the Wilson's disease gene have low ceruloplasmin values 20% of the time. If a liver biopsy is done, it should include measure of copper quantitatively, and will always show values of 200 μg/g dry weight of liver, or higher (normal 20–50).

The same screening guidelines apply to psychiatrically presenting patients as apply to neurologically presenting patients (Table 2). However, patients with Wilson's disease presenting with liver disease have Kayser-Fleischer rings only about one-half of the time. Their 24-hour urine copper will always be elevated, but the presence of active hepatitis or chronic obstructive liver disease can elevate urine copper in the absence of Wilson's disease. A liver biopsy with measurement of copper is usually required with the liver disease presentation.

Presymptomatic affected patients have Kayser-Fleischer rings about one-third of the time, and diagnostically elevated urine copper about half the time. If the urine copper is clearly normal (below 55 μg/24 hours), and the measurement is valid, Wilson's disease is excluded. If the urine copper is in the gray zone (between 55 and 100 μg), the person may be just a heterozygous carrier, who can have mild elevations of urine copper but not require treatment, or a presymptomatic patient, who does require treatment. In this case, a liver biopsy should be done with quantitative assay of copper. Patients are always over 200 μg/g dry weight, whereas carriers are 125 μg or less.

The penicillamine provocative test (in which a dose of penicillamine is given and urine copper measured) and the radiocopper test are not useful, in our experience, for the diagnosis of Wilson's disease. There is serious overlap in values between carriers and affected patients. Mutation screening is also not useful because of the large number of mutations and the lack of prevalence of one or a few mutations in accounting for the disease. However, once a diagnosis is made in a sibling, all siblings can be screened and genotyped very effectively by haplotype analysis.

ANTICOPPER DRUGS

The anticopper drugs available are shown in Table 3, and include TM, which is likely to become available soon. The earliest drug available was penicillamine, which is a chelator that acts by increasing urinary excretion of copper *(12)*. It is

Table 3
Anticopper Drugs

Drug	Trade name	Usual daily dose	Comment
Penicillamine	Cuprimine® (Merck)	1 g in divided doses	Chelator; very long list of side effects (see Physician's Desk Reference) and makes 50% of neurologic patients worse, and 50% of these never recover.
Trientine	Syprine® (Merck)	1 g in divided doses	Chelator; much safer than penicillamine but has some side effects. Probably makes about 20% of neurological patients worse initially.
Zinc	Galzin® (Gate)	150 mg in divided doses	Acts by blocking intestinal copper absorption. Very nontoxic.
Tetrathiomolybdate	None	120 mg in divided doses	Acts by complexing copper, preventing intestinal absorption, and binding free copper in the blood. Relatively nontoxic.

effective at producing a negative copper balance, but has numerous side effects *(27,30)* which are rapidly decreasing its use, given the advent of newer, effective, and safer drugs. Penicillamine also has the severe disadvantage in newly diagnosed neurologically presenting patients of making about 50% of them neurologically worse, and only one-half of that number recover to their pre-penicillamine baseline *(32)*. Thus, penicillamine makes 25% of neurologically presenting patients permanently worse (as with patient 2). The second oldest drug is trientine, which is also a chelator that increases the urinary excretion of copper *(13)*. Trientine is also uniformly effective, and has a much better safety profile than penicillamine, although it too has some side effects.

The third drug is zinc. Zinc acts by inducing intestinal metallothionein, which blocks intestinal absorption of copper *(33)*. Zinc is uniformly effective and has only one side effect—that of causing mild epigastric burning or pain in about 10% of patients *(16)*. The fourth drug is TM *(17,18)*, which acts by forming a tripartite complex with copper and protein. Given with food, it prevents copper absorption. Given between meals, TM is well absorbed and causes the available copper in the blood to combine with serum albumin in a very stable complex. In this way, the potentially toxic copper of the body can be quickly titrated and safely complexed. Side effects that we have observed with TM are discussed later.

Here, we focus on the initial treatment of the neurological presentation followed by maintenance therapy. References for treating hepatic and presymptomatic patients are readily available *(29–31,34)*. The initial treatment of the neurologically presenting patient is problematic because the drug used most often by physicians,

penicillamine, is contraindicated in these patients (patient 2). Penicillamine has an approx 25% chance of making the patient permanently, and often disastrously, worse neurologically, as it did with patient 2 *(32)*. The problem of initial treatment of these patients is compounded by the fact that the excellent maintenance drug, zinc, acts too slowly, in our opinion, for this type of acutely ill patient. Prior to our work (discussed later), trientine had been untried in this setting, but because it shares penicillamine's mechanism of action, it was suspected of also causing initial neurological worsening.

Because of the therapeutic need of these patients, TM was developed *(17,18,35,36)*. TM is very fast-acting and, based on animal studies, appears to be a very safe drug. Over a period of years we have treated 55 neurologically presenting patients with an 8-week course of TM *(18)*. To evaluate possible neurological worsening, we developed a semi-quantitative neurological examination (scored 0–38, with 0 normal) and a semi-quantitative speech examination (scored 0–7, with 0 normal). Criteria for worsening included a consistent deterioration of five or more points in the neurological test and three or more points in the speech score. Only 2 of the 55 patients (3.6%) reached our criteria for neurological worsening in the open-label study *(18)*, compared with an estimated 50% who are initiated on penicillamine *(32)*.

Subsequently we (together with Dr. Michael Schilsky and his group at New York's Mount Sinai) have initiated a double-blind study comparing TM and trientine for initial therapy. The study is not completed, but the results so far suggest that trientine will fall somewhere in between penicillamine and TM in terms of risk of initial neurological worsening (about 20%).

The dose of TM we have used in most of these patients is 20 mg three times daily with meals, and 60 mg without food, for 8 weeks. This dose produces a 10–15% incidence of overtreatment bone-marrow suppression within 3–6 weeks, which quickly responds to a halving of the dose. It also produces a 10–15% incidence within 3–6 weeks of an increase in serum transaminase enzymes, the mechanism for which is unknown, but which also responds quickly to a halving of the dose. Because of these observations, we are now doing a double-blind comparison of the original TM regimen given for 8 weeks with a new TM regimen in which patients get the regular 120 mg dose for 2 weeks, then drop down to half the regular dose (60 mg) for an additional 14 weeks.

ANTICOPPER DRUG TREATMENT RECOMMENDATIONS

Given the above background, our recommended first drug for initial therapy is TM (Table 4). TM is not currently commercially available, but is expected to become so sometime in 2005. In the meantime, consideration can be given to referring patients to the University of Michigan for participation in the above described clinical trial. If that is not practical, our second choice would be zinc therapy, and our third would be trientine. Monitoring recommendations for the three drugs are given in Table 5. Our recommendation given the current state of knowledge is to

Table 4
Recommendations for Anticopper Drug Therapy in Neurologically Presenting Patients With Wilson's Disease

Disease stage	First choice	Second choice	Third choice
Initial therapy	Tetrathiomolybdate	Zinc	Trientine
Maintenance therapy	Zinc	Trientine	Penicillamine

Table 5
Monitoring Recommendations for the Anticopper Drugs

Drug	Monitoring for efficacy/compliance	Monitoring for toxicity
Tetrathiomolybdate	Not usually necessary because of short-term use.	See patient once weekly for evaluation, CBC, and LFTs.
Zinc	24-hour urine copper and zinc every 3 months for 6 months, every 6 months for 2 years, then annually (with good compliance).	See and examine at the same schedule as for efficacy. CBC and LFTs at least annually.
Trientine	24-hour urine copper and non-Cp serum copper at 1, 3, 6, and 12 months, then annually.	CBC, LFTs, creatinine, and urinalysis weekly for 4 weeks, biweekly for 2 months, monthly for 6 months, every 6 months for 2 years, then annually.
Penicillamine	Same as trientine.	Same as for trientine except the studies should be twice weekly for the first 4 weeks.

Abbreviations: CBC, complete blood counts; LFTs, liver function tests; Cp, ceruloplasmin.

give TM or trientine for initial therapy for 2 to 4 months, then transition to maintenance therapy.

Our first choice for maintenance therapy is zinc. Zinc is fully effective and has many fewer side effects than penicillamine or trientine *(16)*. Monitoring zinc therapy (Table 5) is also easier than with the other drugs *(16,29–31)*. Because zinc does not directly affect urine copper, the 24-hour urine copper becomes a good reflector of the body status of copper. In untreated Wilson's disease, the urine copper may be quite elevated, up to several hundred micrograms per 24 hours (normal 20–50 μg). With zinc therapy, this will gradually come down so that by the end of the first year it is usually less than 125 μg. We view anything below 125 μg as indicating adequate control. Minor fluctuations over time are to be expected, but major increases (30% or more) suggest noncompliance. Another way to monitor patients is to measure 24-hour urine zinc, using the same sample. In an adequately treated patient, the urine zinc should be 2 mg or higher per day. If levels fall below that number, it gives an early warning signal of noncompliance. Twenty-four-hour

urine zinc levels will decrease within 2 to 3 weeks of significant noncompliance, whereas it takes 2 to 3 months for urine copper to increase. Urine copper and zinc should be monitored every 3 months early during maintenance therapy, and as the patient exhibits good compliance, the frequency decreased to every 6 months and then to annually. Every patient should be monitored at least annually. If the urine copper gets down into the normal range, overtreatment and copper deficiency may follow. At this point, it is a good idea to begin backing off on the zinc dose. At the time of urine evaluation, blood counts and liver function tests should also be carried out.

The second choice for maintenance therapy is trientine. Trientine can cause side effects such as proteinuria, bone marrow depression, and autoimmune disease. Patients should be monitored by blood and urine studies, as well as asked about side effects, every week for 4 weeks, biweekly for 2 months, monthly for 6 months, every 6 months for 2 years, and then annually (Table 5). Copper status can be evaluated at 1, 3, 6, and 12 months for the first year, and then at least annually in compliant patients. Urine copper, blood copper, and blood ceruloplasmin should be used. The 24-hour urine copper will start out at about 1 mg, and go down to 200–300 μg by 1 year of adequate treatment. The problem with interpreting this value in terms of compliance is that it represents both the action of the drug and body-loading of copper. The best that usually can be done is to take note of any sudden significant increase and ask the patient about compliance. With trientine, it is more important to concomitantly measure blood copper and ceruloplasmin then it is with zinc. The copper in ceruloplasmin can be subtracted from the blood copper to determine the nonceruloplasmin plasma copper, often called the free copper (this is done by subtracting 3.0 μg of copper for every milligram per deciliter of ceruloplasmin, and subtracting that number from the serum copper in microgram per deciliter). This number is normally 10–15 μg/dL of serum, and may be very high (50 μg or so) in untreated patients. It should come down to 25 μg or less during the first year of therapy and remain there. If it bounces up, it suggests noncompliance.

Penicillamine is the third choice for maintenance therapy and is not highly recommended because of its long list of side effects. These include an initial hypersensitivity reaction in about 25% of patients, proteinuria, bone-marrow suppression, autoimmune disturbances, skin wrinkling and other skin side effects, and possible vascular wall deterioration. It is monitored much in the same manner as trientine (Table 5).

Assuming that the patient does not suffer initial neurological deterioration, the prognosis is quite good for substantial neurological recovery *(18,27–31)*. This usually begins about 5 to 6 months after initiation of therapy, and is relatively complete by about the 2-year mark. Generally, symptoms and disabilities remaining at that time will be permanent. During the initial 2-year period, it is important for the patient to try to maintain whatever compromised functions he or she has. The patient should participate in speech therapy, or at least continually work at speaking if he or she has dysarthria, and the patient should remain physically active, trying to maintain as much function as possible in the face of dystonia and incoordination.

Physical therapy should be used for this purpose if available. Botulinum toxin injections may be useful to relieve dystonia in key areas. All the medications normally employed for relieving tremor or dystonia can be used *(37)*, with the one caveat that drugs that have major hepatic toxicity should be avoided. If the patient has dysphagia that is causing aspiration, he or she should have a gastrostomy placed and receive tube feedings. The tube can be pulled when swallowing normalizes.

Generally, it is a good idea to wait for the end of the 2-year period of improvement before contemplating surgical correction of abnormalities resulting from dystonia.

Improvement in behavioral symptoms is also usually good, and follows the same course as improvement in neurological symptoms. Various drugs used in psychiatry to treat symptoms such as depression or anxiety can also be used in these patients with the same caveat as above, avoiding drugs with major hepatic toxicity.

CONCLUSION

Wilson's disease is a rare disorder with protean clinical manifestations. Patients who present for evaluation of symptomatic Wilson's disease satisfy criteria for a movement disorder emergency, because of the serious consequences of a missed diagnosis, and also because they risk permanent neurological deterioration if they are mismanaged. With adequate clinical suspicion and careful application of anticopper strategies, most patients with Wilson's disease can expect to lead a normal life.

REFERENCES

1. Wilson SAK. Progressive lenticular degeneration: a familial nervous disease associated with cirrhosis of the liver. Brain 1912;34:295–509.
2. Kayser B. Ueber einen Fall von angeborener grünlicher Verfärbung der kornea. Klin Mbl Augenheilk 1902;40:22–25.
3. Fleischer B. Zwei weitere Fälle von grünliche Verfärbung der Kornea. Klin Mbl Augenheilk 1903;41:489–491.
4. Glazebrook AJ. Wilson's disease. Edinburgh Med J 1945;52:83–87.
5. Cumings JN. The copper and iron content of brain and liver in the normal and in hepato-lenticular degeneration. Brain 1948;71:410–415.
6. Mandelbrote BM, Stanier MW, Thompson RHS, Thruston MN. Studies on copper metabolism in demyelinating disease of the central nervous system. Brain 1948;71:212–228.
7. Ravestyn AH. Metabolism of copper in man. Acta Med Scand 1944;118:163–196.
8. Frommer DJ. Defective biliary excretion of copper in Wilson's disease. Gut 1974;15:125–129.
9. Bearn AG, Kunkel HG. Biochemical abnormalities in Wilson's disease. J Clin Invest 1952;31:616.
10. Scheinberg IH, Gitlin D. Deficiency of ceruloplasmin in patients with hepatolenticular degeneration (Wilson's disease). Science 1952;116:484–485.
11. Cumings JN. The effects of BAL in hepatolenticular degeneration. Brain 1951;74:10–22.
12. Walshe JM. Penicillamine. A new oral therapy for Wilson's disease. Am J Med 1956;21:487–495.
13. Walshe JM. Treatment of Wilson's disease with trientine (triethylene tetramine) dihydrochloride. Lancet 1982;1:643–647.
14. Schouwink G. De hepatocerebrale degeneratie, me een onderzoek naar de zinktofwisseling. University of Amsterdam: MD Thesis 1961.

15. Brewer GJ, Hill GM, Prasad AS, Cossack ZT, Rabbani P. Oral zinc therapy for Wilson's disease. Ann Intern Med 1983;99:314–320.
16. Brewer GJ, Dick RD, Johnson VD, Brunberg JA, Kluin KJ, Fink JK. The Treatment of Wilson's Disease with Zinc XV. Long-Term Follow-up Studies. J Lab Clin Med 1998;132:264–278.
17. Brewer GJ, Dick RD, Yuzbasiyan-Gurkan V, Tanakow R, Young AB, Kluin KJ. Initial therapy of patients with Wilson's disease with tetrathiomolybdate. Arch Neurol 1991;48:42–47.
18. Brewer GJ, Hedera P, Kluin KJ, et al. Treatment of Wilson's disease with tetrathiomolybdate III. Initial therapy in a total of 55 neurologically affected patients and follow-up with zinc therapy. Arch Neurol 2003;60:378–375.
19. Bearn AG. A genetical analysis of thirty families with Wilson's disease (hepatolenticular degeneration). Ann Hum Genet 1960;24:33–43.
20. Bull PC, Thomas GR, Rommens JM, Forbes JR, Cox DW. The Wilson disease gene is a putative copper transporting P-type ATPase similar to the Menkes gene. Nat Genet 1993;5:327–337.
21. Tanzi RE, Petrukhin K, Chernov I, et al. The Wilson disease gene is a copper transporting ATPase with homology to the Menkes disease gene. Nat Genet 1993;5:44–50.
22. Yamaguchi Y, Heiny ME, Gitlin JD. Isolation and characterization of a human liver cDNA as a candidate gene for Wilson disease. Biochem Biophy Res Commun 1993;197:271–277.
23. Vulpe C, Levinson B, Whiney S, Packman S, Gitschier J. Isolation of a candidate gene for Menkes disease and evidence that it encodes a copper-transporting ATP-ase. Nat Genet 1993;3:7–13.
24. Chelly J, Tumer Z, Tonnesen T, et al. Isolation of a candidate gene for Menkes disease that encodes a potential heavy metal binding protein. Nat Genet 1993;3:14–19.
25. Mercer JF, Livingston J, Hall B, et al. Isolation of a partial candidate gene for Menkes disease by positional cloning. Nat Genet 1993;3:20–25.
26. Cox DW, Roberts EA. Wilson disease. GeneClinics, University of Washington, Seattle. Online. Available: http://www.geneclinics.org/profiles/wilson/details.html.
27. Brewer GJ, Yuzbasiyan-Gurkan V. Wilson Disease. Medicine 1992;71:139–164.
28. Scheinberg IH, Sternlieb I. Wilson's Disease. In: Smith LH Jr, ed. Major Problems in Internal Medicine, vol. 23. W.B. Saunders Company, Philadelphia: 1984.
29. Brewer GJ. Recognition, diagnosis and management of Wilson's disease. PSEBM 2000;223(1):39–49.
30. Brewer, GJ. Wilson's Disease: A Clinician's Guide to Recognition, Diagnosis, and Management. Kluwer Academic, Boston: 2001.
31. Brewer GJ. Wilson's Disease In: Kasper DL, Braunward E, Fauci AS, et al. eds. Harrison's Principles of Internal Medicine. McGraw-Hill Companies, New York, 2004.
32. Brewer GJ, Terry CA, Aisen AM, Hill GM. Worsening of neurologic syndrome in patients with Wilson's disease with initial penicillamine therapy. Arch Neurol 1987;44:490–493.
33. Yuzbasiyan-Gurkan V, Grider A, Nostrant T, Cousins RJ, Brewer GJ. The treatment of Wilson's disease with zinc: X. Intestinal metallothionein induction. J Lab Clin Med 1992;120:380–386.
34. Askari FK, Greenson J, Dick RD, Johnson VD, Brewer GJ. Treatment of Wilson's disease with Zinc XVIII. Initial treatment of the hepatic decompensation presentation with trientine and zinc. J Lab Clin Med 2003;142(6):385–390.
35. Brewer GJ, Dick RD, Johnson V, et al. Treatment of Wilson's disease with tetrathiomolybdate I. Initial therapy in 17 neurologically affected patients. Arch Neurol 1994;51:545– 554.
36. Brewer GJ, Johnson V, Dick RD, Kluin KJ, Fink JK, Brunberg JA. Treatment of Wilson's disease with ammonium tetrathiomolybdate: II. Initial therapy in 33 neurologically affected patients and follow-up on zinc therapy. Arch Neurol 1996;53:1017–1025.
37. Fink JK, Hedera P, Brewer GJ. Hepatolenticular degeneration (Wilson's disease). Neurologist 1999;5:171–185.

19

Dopa-Responsive Dystonia

Yoshiaki Furukawa, Mark Guttman, and Stephen J. Kish

PATIENT VIGNETTES

Patient 1: A 6-year-old girl with gait disturbance was introduced by an orthopedist in 1990, before the discovery of causative genes in dopa-responsive dystonia (DRD). Although early motor development was normal, she had Trendelenburg's symptoms resulting from a congenital dislocation of the left hip (acetabular dysplasia). In addition, she developed flexion-inversion of the left foot at the age of 3 years, which became aggravated toward the evening and was alleviated in the morning after sleep. Her postural dystonia spread to other limbs within 3 years but was more pronounced in the legs. Neurological examination also revealed symmetric hyperreflexia without extensor plantar responses, and rigid hypertonicity in the legs. Investigations, including copper metabolism and brain magnetic resonance imaging, were normal. Therapeutic trials with levodopa and tetrahydrobiopterin (BH4; the cofactor for tyrosine hydroxylase) were considered, and a lumbar puncture was performed to measure cerebrospinal fluid (CSF) pterins. She remarkably responded to low doses of levodopa but not to acute BH4 administration. After increasing the dosage of levodopa (20 mg/kg/day, without a decarboxylase inhibitor [DCI]) and undergoing an operation (acetabuloplasty) for the complicated condition, she became completely normal and was diagnosed as DRD. The diagnosis was supported by CSF data (decreased total biopterin and neopterin) and was confirmed later by genetic analysis *(1,2)*.

Patient 2: A 45-year-old woman states that her long-standing foot dystonia has deteriorated over the past year. She also describes that she has developed a tremor involving her right arm in the last few months. She manifested her dystonic posturing (inturning) at the age of 7 years, and the initial treatment strategy has been beneficial, until recently with trihexyphenidyl. She noticed that her foot dystonia was worse in the late afternoon and evening. She discloses a family history of overt dystonia in her brother, father, and paternal grandfather. Her two daughters (identical twins) have occasionally manifested mild dystonic posture of the foot after extreme exercise. On examination, she showed dystonia of the feet, with the right being worse. She had increased tone in her right leg and arm. Rapid alternating movements were slow in

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

the right foot and hand and in the left foot to a lesser extent. She had a mild postural tremor of her right hand. Her walking revealed dystonic posturing of the right foot. Investigations included normal brain computed tomography and copper metabolism studies. She was successfully switched from trihexyphenidyl to levodopa with a DCI and has had no dystonia and parkinsonism on examination. The diagnosis of DRD was confirmed by genetic analysis *(3)*.

INTRODUCTION

Dopa-responsive dystonia (DRD) is a clinical syndrome characterized by childhood-onset dystonia and a dramatic and sustained response to low doses of levodopa *(4–7)*. This clinical syndrome typically presents with gait disturbance owing to foot dystonia, later development of some parkinsonian features, and diurnal fluctuation of symptoms (worsening of symptoms toward evening and their alleviation in the morning after sleep) (Table 1). The sustained levodopa responsiveness without motor adverse effects of chronic levodopa therapy such as dopa-induced dyskinesias distinguish DRD from early-onset parkinsonism with dystonia *(2,8)*. Because DRD responds so well to treatment with levodopa, and because failure to recognize this disorder causes unacceptable morbidity, we choose to classify DRD as a movement disorder emergency.

DRD is differentiated from primary dystonias and is classified under the dystonia-plus category *(9)*. There are three known causative loci for DRD (locus heterogeneity): (1) the *GCH1* gene on chromosome 14q22.1-q22.2, which encodes guanosine triphosphate (GTP) cyclohydrolase I (GTPCH), the first enzyme in the biosynthetic pathway for tetrahydrobiopterin (BH4) (Fig. 1); (2) the *TH* gene on 11p15.5, coding for the enzyme tyrosine hydroxylase (TH) that catalyzes the rate-limiting step in catecholamine biosynthesis (Fig. 1); and (3) an as-yet undefined gene on 14q13 (*DYT14*) *(10–15)*. Many patients with DRD have shown dominantly inherited *GCH1* mutations (GTPCH-deficient DRD; the major form of DRD) *(3,16)*, whereas only four DRD families associated with recessively inherited *TH* mutations (TH-deficient DRD; the mild form of TH deficiency) and one pedigree with autosomal-dominant DRD linked to the *DYT14* locus have been reported *(13,14,17–19)*. However, because no mutations in either the coding region or the splice sites of *GCH1* were identified in approx 40% of DRD families using conventional genomic DNA sequencing of *GCH1*, this DNA test alone is not sufficient for routine clinical practice *(3,16)*. Thus, notwithstanding the discovery of *GCH1* and *TH* mutations in DRD, a therapeutic trial with low-dose levodopa is still the most practical approach to the diagnosis of this treatable disorder. Because clinical suspicion is a key to the diagnosis, physicians should know not only the classic phenotype of GTPCH-deficient and TH-deficient DRD, but also the broad phenotypic spectrum (allelic heterogeneity) in GTPCH and TH deficiencies.

This chapter summarizes clinical features in DRD and in genetically related disorders, and recent advances in the genetics and biochemistry of DRD.

Table 1
Clinical Characteristics of Classic Dopa-Responsive Dystonia

1. Onset usually from 1 to 12 years of age (mean, 6 years); early motor development is normal.
2. Onset of dystonia in a limb, typically foot dystonia (pes equinovarus) resulting in gait disturbance.
3. Later development of some parkinsonian features; tremor is mainly postural.
4. Presence of brisk reflexes in the legs, ankle clonus, and/or the striatal toe[a] in many patients.
5. Diurnal fluctuation of symptoms in approx 80% of patients; the degree of fluctuation is variable.
6. Gradual progression to generalized dystonia, typically more pronounced dystonia in the legs throughout the disease course.
7. Frequent attenuation in the magnitude of diurnal fluctuation with age and disease progression.
8. A dramatic and sustained response (complete or near-complete responsiveness of symptoms) to low doses of levodopa.
9. Maximum benefit is usually achieved by less than 300 (or 400)[b] mg/day of levodopa with a decarboxylase inhibitor.
10. Absence of motor adverse effects of chronic levodopa therapy under optimal doses of levodopa.
11. Female predominance of clinically affected individuals in autosomal-dominant dopa-responsive dystonia (gender-related incomplete penetrance).

[a]Dystonic extension of the big toe; this may be misinterpreted as a Babinski response (*see* "Clinical Observations" section in the text).
[b]See "Treatment" section in the text.

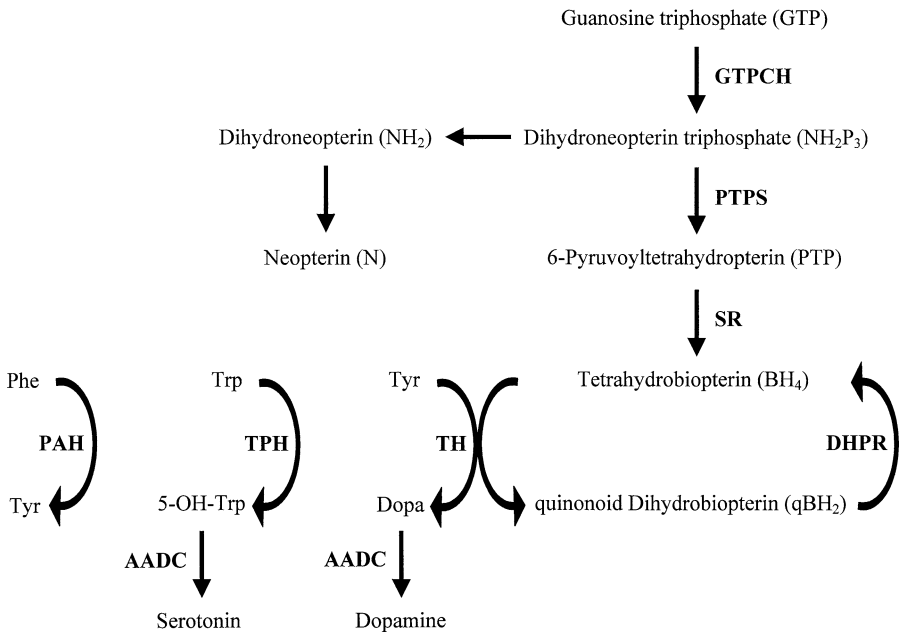


Fig. 1. Simplified tetrahydrobiopterin (BH4) biosynthetic pathway and BH4-dependent hydroxylation of aromatic amino acids. GTPCH, GTP cyclohydrolase I; PTPS, 6-pyruvoyltetrahydropterin synthase; SR, sepiapterin reductase; PAH, phenylalanine hydroxylase; TPH, tryptophan hydroxylase; TH, tyrosine hydroxylase; DHPR, dihydropteridine reductase; and AADC, aromatic L-amino acid decarboxylase.

CLINICAL OBSERVATIONS

Classic DRD

In 1971, Segawa *(20)* and Castaigne *(21)* each reported clinical characteristics of one family with DRD, which they called at that time "hereditary progressive basal ganglia disease with marked fluctuation" and "progressive extrapyramidal disorder," respectively. Advances in the genetics and biochemistry of DRD have demonstrated that the former had autosomal-dominant GTPCH deficiency and the latter had autosomal-recessive TH deficiency *(11,12,18,22)*. In both families, a dramatic and sustained response to low doses of levodopa without motor side effects during chronic levodopa treatment (for more than 30 years) have been confirmed *(5,18,23–26)*. In patients with DRD, there is no abnormality in the perinatal and postnatal period. Early motor development (e.g., sitting and crawling) is normal (Table 1). The average age of onset of typical DRD is approx 6 years (range, 1–12 years) *(5,6)*.

Initial symptoms in most patients with childhood-onset DRD are gait difficulty as a result of dystonia in the leg, typically flexion-inversion of the foot (pes

equinovarus). Because of this dystonic posturing, patients often wear the outer side of their shoes down easily. A relatively small number of patients have onset with arm or neck dystonia, tremor (mainly postural), or slowness of movements. In childhood-onset patients, gradual progression to generalized dystonia occurs, but dystonia is typically more pronounced in the lower limbs throughout the disease course. There is a tendency to fall, and standing position with equinovarus posturing of the feet can induce increased lumbar lordosis, flexion of the hip joints, and hyperextension of the knee joints. A variable degree of rigidity and slowness of movements are recognized in the affected limbs. Rapid fatiguing of effort with repetitive motor tasks (e.g., foot tapping) is often observed. On neurological examination, in addition to dystonic and parkinsonian elements, some clinical findings suggestive of pyramidal signs in the lower extremities (brisk reflexes, ankle clonus, spasticity, and/or [intermittent] extensor plantar responses) are detected in many patients. Normal efferent cortical spinal activity with magnetoelectrical stimulation of motor cortex has suggested a nonpyramidal basis for these findings *(27)*. Dystonic extension of the big toe in DRD (the striatal toe *[28,29]*), which occurs spontaneously or is induced by plantar stimulation, may be misinterpreted as an extensor plantar response. Diurnal fluctuation of symptoms occurs in approx 80% of patients. The degree of fluctuation is variable, with some patients being normal in the morning, whereas others are only less severely affected in the morning when compared with later in the day. Some patients only show exercise-induced exacerbation or manifestation of dystonia, or complain of prominent stiffness and fatigue after exercise. The magnitude of diurnal fluctuation often attenuates with age and disease progression. There are no intellectual, cerebellar, sensory, or autonomic disturbances in DRD patients.

A predominance of clinically affected females is observed in autosomal-dominant DRD. The female-to-male ratio has been reported to be 2:1 to 6:1 in childhood-onset patients *(5,6)*. No increased prevalence of DRD is evident in any ethnic group. Estimates suggest that the prevalence in both England and Japan is 0.5 per million and that 5 to 10% of dystonia patients in childhood or adolescence have DRD *(4,29)*. In general, the severity of gait disturbance and dystonia in adolescent-onset patients is milder than that in childhood-onset patients. Patients with adolescent-onset DRD seldom develop severe generalized dystonia. However, dystonia in female patients can be markedly exacerbated after taking oral contraceptives *(30)*. Teenage-onset patients with slow progression may become more symptomatic in mid-adulthood owing to the development of overt parkinsonian features *(31,32)*.

Phenotypic Heterogeneity

A wide range of symptoms and signs has been reported in genetically confirmed patients with DRD, especially with DRD resulting from *GCH1* mutations. An earlier linkage study demonstrated "benign" adult-onset parkinsonism (showing slow progression and no motor adverse effects of levodopa) as a phenotypic expression of autosomal-dominant DRD *(10)*. Patients with this phenotype manifest no dystonic symptoms prior to the onset of their parkinsonism, including a resting tremor,

in mid- or late-adulthood *(10,33,34)*. In contrast with patients with Parkinson's disease (PD), patients with adult-onset parkinsonism in DRD pedigrees markedly respond to low doses of levodopa and remain functionally normal for a long period of time without developing motor response fluctuations, freezing episodes, and dopa-induced dyskinesias under optimal doses of levodopa. In some of these DRD pedigrees, heterozygous *GCH1* mutations have been identified *(35–40)*. An age-related decline of striatal biopterin during adulthood could contribute to this parkinsonian phenotype *(16,41)*.

There have been some patients with DRD who were initially misdiagnosed as having cerebral palsy (the spastic diplegic form) or spastic paraplegia (the familial or apparently sporadic form) because of hyperreflexia, clonus, spasticity, and/or extensor plantar responses in the legs *(19,36,40,42–45)*. As mentioned, a nonpyramidal basis for these findings in DRD has been suggested *(27)*. An extensor plantar response observed in DRD often disappears after levodopa administration is started, suggesting that the previous finding may be a dystonic phenomenon (the striatal toe) rather than a Babinski response. Mutations in *GCH1* and *TH* have been identified in patients with DRD simulating cerebral palsy (including other forms) or spastic paraplegia *(19,36,40,46)*. Thus, although the differential diagnosis of cerebral palsy and of spastic paraplegia should include DRD, this appears to be still underappreciated.

The clinical phenotype of DRD associated with heterozygous mutations in *GCH1* has been extended to include various types of focal dystonia (e.g., adult-onset guitarist's cramp) and spontaneous remission of dystonia and/or parkinsonism (sometimes with a relapse in the later course of illness) *(35,36,47–50)*. In our experience, however, pure writer's cramp and isolated scoliosis were not always associated with *GCH1* mutations found in the probands with the classic phenotype *(16,40,53)*. Recently, autosomal-dominant GTPCH deficiency presenting as myoclonus-dystonia responsive to levodopa and a family with dominantly inherited GTPCH deficiency, in which members had dystonia, parkinsonism, depression, anxiety, and/or clinical deafness, have been reported *(51,52)*.

MOLECULAR GENETICS

GTPCH-Deficient DRD

The enzyme GTPCH is encoded by a single copy gene, *GCH1*, which is composed of six exons spanning approx 30 kilobases (kb) *(54)*. This enzyme catalyzes the rate-limiting step in the biosynthesis of BH4 (Fig. 1). BH4 is the natural cofactor not only for TH but also for phenylalanine hydroxylase and tryptophan hydroxylase, and most patients with autosomal-recessive GTPCH deficiency (usually homozygotes) have BH4-dependent hyperphenylalaninemia (HPA) and severe neurological dysfunction *(54–57)*. In contrast with these patients, GTPCH-deficient DRD patients (usually heterozygotes) never develop HPA. There is another phenotype of GTPCH deficiency, dystonia with motor delay, associated with compound heterozygosity for *GCH1* mutations *(30,39)*.

In patients with these GTPCH deficiencies, more than 100 independent *GCH1* mutations have been identified. The reason why many different mutations occur throughout all of the exons of *GCH1* is unknown, and no clear correlations between specific clinical features and types of mutations are established. Usual genomic DNA sequencing of *GCH1* fails to reveal any mutations in the coding region (including the splice sites) of this gene in approx 40% of pedigrees with DRD *(16)*. This makes the genetic diagnosis of GTPCH-deficient DRD difficult. Because "coding region mutation-negative" DRD pedigrees include families having an apparently sporadic patient or only a few affected siblings, some of these families may have autosomal-recessive TH-deficient DRD. For coding region mutation-negative pedigrees, in which positive results of linkage analysis of the *GCH1* locus or biochemical data indicating GTPCH dysfunction are obtained, possible explanations are: (1) a large deletion of one or more exons of *GCH1*; (2) a mutation in noncoding regulatory regions of *GCH1*; (3) an intragenic duplication or inversion of *GCH1*; and (4) a mutation in as-yet undetermined regulatory genes having an influence on *GCH1* expression or other genes, the products of which interact with GTPCH and can modify the enzyme function. In fact, large heterozygous deletions in *GCH1*, which are undetectable by the conventional genomic DNA sequence analysis of this gene, have been found in three coding region mutation-negative DRD families, including the four-generation family shown in the case of patient 2 *(3,50)*. Such a large genomic deletion in *GCH1* is an important subtype and should be analyzed in coding region mutation-negative DRD patients. Southern blotting, cDNA analysis, and quantitative duplex polymerase chain reaction are useful for the detection of exon deletions in *GCH1*. Approximately 30 to 50% of patients with DRD have been reported to have no family history of dystonia *(5,6)*. Some of these apparently sporadic cases can be explained by gender-related incomplete penetrance of *GCH1* mutations (87 and 38% in female and male mutation carriers, respectively *[58]*), different *de novo* mutations in *GCH1* (suggesting a relatively high spontaneous mutation rate in this gene *[58]*), and recessively inherited *TH* mutations *(19)*.

TH-Deficient DRD

Human *TH* consists of 14 exons spanning approx 8.5 kb *(59)*. The enzyme TH, a BH4-dependent monooxygenase, catalyzes the rate-limiting step in the biosynthesis of catecholamines (Fig. 1). In patients with the mild form (TH-deficient DRD) or the severe form (infantile parkinsonism with motor delay) of autosomal-recessive TH deficiency *(60)*, 13 independent *TH* mutations (10 missense mutations, two small deletions, and one branch site mutation) have been reported *(13,17–19,61–72)*. Six patients with the mild form of TH deficiency from four unrelated families had normal early development *(13,17–19,21,24,25,61)*.

Although Bartholomé and Lüdecke *(17)* have reported that DRD resulting from *TH* mutations is characterized by leg dystonia (onset at approx 4 years of age), diurnal fluctuation of symptoms, and a good response to levodopa therapy, further accumulation of genetically proven patients are necessary to establish the clinical features of TH deficiency, including those of TH-deficient DRD. This group found

a homozygous *TH* mutation in two brothers with DRD *(13)*. The mutated recombinant enzyme showed approx 15% of specific activity compared with the wild-type in a coupled in vitro transcription–translation assay system *(61)*. A sustained response to levodopa treatment without any motor side effects for more than 30 years has been confirmed in two brothers (onset at age 2 and 5 years, respectively) originally reported by Castaigne *(21)* and in another male patient (onset at age 20 months) *(18)*. These three patients were compound heterozygous for *TH* mutations *(18)*. One other compound heterozygote, a 10-year-old boy, developed DRD simulating spastic paraplegia at 13 months of age *(19)*. Because all of the six patients with TH-deficient DRD reported to date are males, female predominance, which has been confirmed in GTPCH-deficient DRD *(35,58)*, may not be a clinical characteristic in the mild form of TH deficiency *(60)*.

DRD Linked to the DYT14 Locus

Only one family with DRD linked to the *DYT14* locus has been reported *(14)*. A genome-wide linkage analysis performed in the family mapped a novel causative gene for autosomal-dominant DRD to chromosome 14q13 (outside the *GCH1* gene on 14q22.1-q22.2 *[11]*). A 77-year-old woman in this family developed dystonia of the lower extremities by age 3 years *(14)*. There was diurnal fluctuation of her symptoms. Her dystonia progressed to the upper extremities and she was wheelchair-bound by age 12 years. She had no appropriate medical assessment for her condition until age 73 years, when neurological examination revealed parkinsonism, including a resting tremor of her left leg, and dystonic posture of all the limbs. Levodopa therapy (300 mg/day, with a DCI) markedly alleviated these symptoms and signs. Neuropathological findings in this 77-year-old patient were similar to those in two DRD patients with GTPCH dysfunction reported previously *(14,32,73)*.

Genetically Related Disorders

Severe GTPCH Deficiency

Patients with autosomal-recessive GTPCH deficiency usually develop BH4-dependent HPA in the first 6 months of life *(54–57)*. There was no detectable GTPCH activity in liver biopsy specimens in patients with GTPCH-deficient HPA, and two genetically confirmed patients (homozygotes for *GCH1* mutations *[54,56]*) demonstrated very high plasma phenylalanine levels. This disorder presents with severe neurological dysfunction, including convulsions, mental retardation, swallowing difficulties, developmental motor delay, truncal hypotonia, limb hypertonia, and involuntary movements. In the first report of recessively inherited GTPCH deficiency by Niederwieser *(55)*, hyperreflexia with extensor plantar responses were also described. In contrast with GTPCH-deficient DRD patients, BH4 administration and neurotransmitter replacement therapy (levodopa and 5-hydroxytryptophan) are necessary for GTPCH-deficient HPA patients *(55,57)*.

Moderate GTPCH Deficiency

A novel phenotype of GTPCH deficiency (dystonia with motor delay), which is clinically and biochemically intermediate between GTPCH-deficient DRD (mild) and GTPCH-deficient HPA (severe), has been found in three compound heterozygotes for *GCH1* mutations *(30,39)*. This phenotype is characterized by developmental motor delay, limb dystonia (with truncal hypotonia) that progresses to generalized dystonia, and no overt HPA in infancy. Such compound heterozygotes could be misdiagnosed initially as having cerebral palsy *(39)*. There may be some patients with dystonia and motor delay caused by compound heterozygous *GCH1* mutations; one is detectable by the conventional genomic DNA sequence analysis of this gene but the other is not (e.g., a large heterozygous deletion *[3,50]*) *(60)*. In two of the three compound heterozygotes *(30,39)*, their mothers and maternal grandmothers (all heterozygotes) developed DRD symptoms, suggesting that these two patients have at least one dominant allele, whereas compound heterozygous genotypes generally involve different recessive alleles at a locus. The finding of compound heterozygotes in these DRD pedigrees also suggests that intrafamilial phenotypic heterogeneity in some GTPCH-deficient DRD families may be explained by an additional *GCH1* mutation *(7,60)*. It is worth noting that one compound heterozygote for *GCH1* mutations responded remarkably to low doses of levodopa and made further improvement in motor function when BH4 was chronically added to maintenance levodopa treatment *(30)*. This observation suggests that early combination therapy of levodopa and BH4 may be suitable for some compound heterozygotes manifesting the dystonia with motor delay phenotype.

Severe TH Deficiency

In contrast with patients with the mild form of TH deficiency (TH-deficient DRD), all of the nine reported patients with the severe form of TH deficiency from nine unrelated families had onset of symptoms at less than 6 months of age, with developmental motor delay, truncal hypotonia, rigidity of extremities, and hypokinesia *(62–72)*. Ptosis and/or oculogyric crises were often observed. Diurnal fluctuation was not recognized in most of these patients showing the infantile parkinsonism with motor delay phenotype *(60)*. Very severely affected cases also developed mental retardation and hyperprolactinemia; although dopamine is a prolactin-inhibiting factor at the hypothalamus level, serum prolactin concentrations are usually normal in patients with GTPCH-deficient DRD *(39)*. In one patient, in whom a homozygous *TH* missense mutation was found, the mutant TH revealed only 0.3–16% of wild-type enzyme activity in three complementary expression systems *(62,64)*. A clinical comparison between two compound heterozygotes for *TH* mutations, one with the severe form of TH deficiency *(63,67,69)* and the other with the mild form *(19)*, have suggested that an effect on TH activity in vivo of a missense mutation in the catalytic domain may be more severe than that in the tetramerization domain of this enzyme *(16)*. It is often difficult to increase levodopa doses smoothly in patients with the severe form of TH deficiency, especially at the

initiation of treatment, because of the development of intolerable dyskinesias. For these patients, combined administration of levodopa and selegiline (a monoamine oxidase-B inhibitor) has been recommended *(70,74)*.

LABORATORY INVESTIGATIONS

Routine blood counts and chemistries, plasma and urine amino acids, serum copper and ceruloplasmin, and brain computed tomography and magnetic resonance imaging are normal in patients with DRD.

Cerebrospinal Fluid Pterin Analysis

Before the discovery of *GCH1* mutations, a functional abnormality of brain GTPCH was suggested by decreased levels of cerebrospinal fluid (CSF) total biopterin (BP) and total neopterin (NP) in autosomal-dominant DRD *(1,8,75–79)*. BP includes BH4, quinonoid dihydrobiopterin, and 7,8-dihydrobiopterin, and NP consists of degradation products (dihydroneopterin and neopterin) of dihydroneopterin triphosphate, which is synthesized from GTP by GTPCH (*80*; Fig. 1). Most of brain BP exists as BH4, and more than 70% of CSF NP exists as the dihydro form *(80)*. Generally, NP is considered to reflect GTPCH activity, and low levels of both BP and NP in CSF have been demonstrated in genetically proven patients with GTPCH-deficient DRD (including the apparently sporadic patient 1), dystonia with motor delay, and GTPCH-deficient HPA *(1,2,30,52,56,81)*. Reduced brain BP and NP concentrations were confirmed in the two autopsied patients with DRD *(16,32)*.

GTPCH Activity Assay

Ichinose *(11)* reported that GTPCH activity levels in phytohemagglutinin (PHA)-stimulated mononuclear blood cells were decreased in patients with DRD having *GCH1* mutations compared with normal controls. Using cultured lymphoblasts, however, Bezin *(83)* has suggested that the PHA induction alone misrepresents the actual status of GTPCH activity. Activity of GTPCH in PHA-stimulated mononuclear blood cells was lower in normal females than in normal males in the previous report *(11)*. Nevertheless, there was no difference of this activity between females and males in a recent report from the same group *(82)*. Unfortunately, nonstimulated GTPCH activity in mononuclear blood cells is too low to be measured. Although measurement of GTPCH activity in cytokine-stimulated fibroblasts was recently reported to be useful for the diagnosis of DRD, the reason why the activity was lower in GTPCH-deficient DRD than in GTPCH-deficient HPA remains to be explained *(84)*. In co-expression studies, it has been demonstrated that GTPCH with dominantly inherited *GCH1* mutations, but not recessively inherited ones, inactivated the wild-type enzyme, suggesting a critical role of this dominant negative effect in autosomal-dominant GTPCH-deficient DRD *(85–87)*. However, Suzuki *(88)* has suggested that such a dominant negative effect is unlikely to explain low enzyme activity in PHA-stimulated mononuclear blood cells from GTPCH-deficient DRD patients (<20% of controls *[11]*) and that a reduction of the

amount of GTPCH protein found in these cells may contribute to the mechanism of dominant inheritance.

Phenylalanine-Loading Test

Patients with DRD never develop HPA. However, a subclinical defect in phenylalanine metabolism (resulting from partial BH4 deficiency in the liver) can often be detected in GTPCH-deficient DRD patients by the phenylalanine-loading test, analyzing plasma phenylalanine-to-tyrosine ratios for 6 or 4 hours following an oral phenylalanine load (100 mg/kg) *(89–91)*. Nevertheless, both false-negative and false-positive results of this test have been reported *(90,91)*. The reason for the difference in susceptibility to a BH4-deficient condition between TH and phenylalanine hydroxylase could relate to different Km (Michaelis constant) values of the hydroxylases for BH4 *(60,92)*.

Neuroimaging Studies

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) investigations using presynaptic dopaminergic markers, (1) [^{18}F]-6-fluorodopa whose uptake rate constant is an index of dopa uptake, decarboxylation, and storage mechanisms, and (2) ligands ([^{123}I]β-CIT and -fluoropropyl-CIT) which bind to the dopamine transporter (DAT), have shown normal or near-normal results in the striatum of DRD patients *(34,78,93–98)*. These PET and SPECT findings are consistent with normal striatal levels of aromatic L-amino acid decarboxylase (AADC) protein and the DAT examined by [^{3}H]WIN 35428 binding in the autopsied DRD patients with GTPCH dysfunction *(32)*. Using [^{11}C]-raclopride PET, two groups have reported elevated D2-receptor binding in the striatum of patients with DRD *(97,99)*. This increased receptor binding could be caused by receptor upregulation or diminished competition for the tracer as a consequence of low synaptic dopamine concentration.

Neuropathology and Neurochemistry

Neuropathological studies demonstrated no Lewy bodies, and a normal population of cells with reduced melanin in the substantia nigra of two DRD patients (case 1 [19 years] and case 2 [68 years]) and one asymptomatic case (55 years) with GTPCH dysfunction *(32,38,73)*. These pathological characteristics were similar to those in the patient (77 years) with DRD linked to the *DYT14* locus *(14)*. Case 1 had a *GCH1* nonsense mutation (Glu65Ter) on one allele and a polymorphism in *GCH1* (Pro23Leu *[60,100]*) on the other allele *(32)*. In case 2, no mutation in either the coding region or the splice sites of *GCH1* was found *(32)*. The asymptomatic case in a family with DRD (linked to the *GCH1* locus *[10]*) had a heterozygous missense mutation (Gly108Asp) in *GCH1 (38)*. This missense mutation was not identified on 150 normal control chromosomes. There have been no reports of autopsied patients with TH-deficient DRD, and neurochemical analysis was not conducted in the patient with *DYT14* dystonia.

In the putamen of cases 1 and 2, BP and NP concentrations were substantially reduced (mean, –84% and –62%) compared with age-matched normal controls *(32)*. Striatal subregional dopamine data pointed to an involvement of the caudal portion of the putamen as the striatal subregion that was most affected by dopamine loss (–88%) in both patients *(32,73)*. Dopamine concentration in this striatal subdivision was reported to be normal in an autopsied patient with *DYT1* dystonia *(101)*. It is known that the caudal putamen is most affected by loss of dopamine in patients with PD *(102,103)*. In the asymptomatic case, decreases in BP and NP levels in the putamen (–82% and –57%) paralleled those in cases 1 and 2 *(38)*. Dopamine concentration in the caudal subdivision of the putamen was not as severely reduced (–44%) as in the symptomatic cases. Consistent with other postmortem data suggesting that greater than 60 to 80% of striatal dopamine loss is necessary for overt motor symptoms to occur *(103)*, the maximal 44% dopamine reduction in the striatum of the *GCH1* mutation carrier was not sufficient to produce any DRD symptoms.

In contrast with patients with PD *(104,105)*, striatal levels of AADC protein, the DAT, and the vesicular monoamine transporter (measured by [^{3}H]dihydrotetrabenazine binding) were normal in cases 1 and 2, indicating that striatal dopamine nerve terminals are preserved in GTPCH-deficient DRD patients *(32)*. However, TH protein levels were markedly decreased in the putamen (>–97%) of both symptomatic cases. These biochemical findings have suggested that striatal dopamine reduction in GTPCH-deficient DRD is caused not only by decreased TH activity as a result of low cofactor concentration, but also by actual loss of TH protein. The human brain data are compatible with TH protein loss, associated with normal AADC activity in brains of BH4-deficient mice *(106,107)*. In contrast with the symptomatic cases, concentration of TH protein in the putamen was only moderately reduced (–52%) in the asymptomatic case *(38)*. Striatal TH protein reduction in GTPCH-deficient DRD may be caused by a diminished regulatory effect of BH4 on the steady-state level (stability/expression) of TH molecules *(32)*. Because TH protein concentrations in the substantia nigra, where striatal TH molecules are synthesized, were normal in cases 1 and 2, BH4 could control stability rather than expression of this enzyme *(16,32)*. This is supported by a recent report showing loss of TH protein, but not of *TH* mRNA, in brains of BH4-deficient mice *(107)*. Alternatively, there might be an abnormality of TH protein transport from the substantia nigra to the striatum resulting from congenital partial GTPCH deficiency *(16,32)*. The neurochemical findings in the asymptomatic *GCH1* mutation carrier suggest that the extent of striatal TH protein loss may be critical in determining the symptomatic state of GTPCH-deficient DRD *(38)*.

DIAGNOSIS

Which laboratory investigations are practical for the diagnosis of DRD? Because not all patients with DRD have mutations in the coding region (including the splicing junctions) of *GCH1* or *TH*, which can be detected by usual genomic DNA sequencing of these genes, the present genetic testing for DRD is not suitable for

routine clinical practice. Measurement of GTPCH activity in PHA-stimulated mononuclear blood cells *(11,82)* as well as cytokine-stimulated fibroblasts *(84)* is technically demanding, and is conducted in only a few research laboratories. Moreover, the activity test using mononuclear blood cells should be performed within 20 hours after blood sampling *(82,84)*. The enzyme TH is mainly expressed in the brain and the adrenal medulla, and direct measurement of its activity is not a diagnostic option. In the phenylalanine-loading test *(89)*, a small number of DRD patients confirmed to have *GCH1* mutations showed no abnormality of phenylalanine metabolism *(90)*. In contrast, there have been no negative reports on the results of CSF NP measurement (low NP concentrations) in genetically proven patients with GTPCH-deficient DRD, dystonia with motor delay, and GTPCH-deficient HPA *(1,2,30,46,52,56,81,96,108)*, except for one report showing a borderline value in an atypical case with dominantly inherited GTPCH deficiency *(51)*. Decreased NP levels in CSF are not observed in other types of BH4 deficiency *(57,109)*. Because of the known influence of age and immune status on NP, it is necessary to have age-matched control data and to exclude samples with infections when a patient is diagnosed as having GTPCH deficiency by reduced concentrations of both NP and BP in CSF *(1,80)*. Precise determination of CSF levels of neurotransmitter metabolites (before starting levodopa therapy) has been reported to be useful for the diagnosis of TH deficiency (low homovanillic acid [HVA] and 3-methoxy-4-hydroxyphenylethyleneglycol associated with normal 5-hydroxyindolacetic acid) *(62,63,65–72)*. Thus, although a lumbar puncture is invasive, CSF analyses of pterins and neurotransmitter metabolites are informative for the diagnoses of both GTPCH and TH deficiencies *(8,57,67,80,110)*. Unfortunately, however, these analyses are available in relatively limited laboratories. Taken together, a therapeutic trial with low doses of levodopa based on clinical suspicion is still the most practical approach to the diagnosis of DRD.

The major differential diagnoses of DRD include early-onset parkinsonism (EOP), *DYT1* dystonia, cerebral palsy, and spastic paraplegia. Patients with EOP responding markedly to levodopa, especially those with onset below age 20 years, often develop gait disturbance owing to foot dystonia as the initial symptom *(2,8)*. Furthermore, these patients with EOP can demonstrate mild to moderate diurnal fluctuation (sleep benefit) prior to levodopa administration. Accordingly, the clinical differentiation between patients with EOP with dystonia and patients with DRD in the early course of the disorder is sometimes difficult. The most reliable clinical distinction between EOP and DRD is the occurrence of motor adverse effects of chronic levodopa therapy (wearing-off and on–off phenomena and dopa-induced dyskinesias) in EOP. Under optimal doses, patients with DRD, even on long-term levodopa treatment, do not develop these complications. However, this is a retrospective difference. An investigation of the nigrostriatal dopaminergic terminals by PET or SPECT can differentiate DRD (normal or near-normal) from EOP (markedly reduced) *(93,94,96,98)*, whereas this investigation probably will not distinguish between GTPCH-deficient DRD and TH-deficient DRD. Measurements of both BP and NP in CSF can be useful for the differential diagnoses of the following

disorders responsive to levodopa *(2,7,8,32,63,70)*: GTPCH-deficient DRD (low BP and NP), TH-deficient DRD (normal BP and NP), and PD or EOP (low BP associated with normal NP), including the autosomal-recessive form caused by *parkin* mutations *(111)*. A "dramatic" (and retrospectively sustained) response to low doses of levodopa in DRD distinguishes this disorder from all other forms of dystonia, including *DYT1* dystonia (typically early-onset limb dystonia spreading to at least one other limb but not to cranial muscles) resulting from a 3-bp deletion in the *TOR1A* gene *(112)*, and from cerebral palsy as well as spastic paraplegia.

TREATMENT

There is general agreement that patients with childhood-onset dystonic symptoms of unknown etiology should be treated initially with levodopa *(7,113)*. Initial use of a dose of levodopa with a DCI, 6.25/25 mg of carbidopa/levodopa (C/L; Sinemet) two to three times a day, and gradual increase to higher doses have been recommended *(113)*. Although patients with DRD may develop dyskinesias (mainly choreic movements) at the initiation of levodopa treatment, such dyskinesias subside following dose reduction and do not reappear with later slow dose increment *(5,6)*: note that these transient dyskinesias are different from those with motor response fluctuations observed in patients with PD and EOP during chronic levodopa treatment. Because some children with DRD showed remarkable responsiveness to smaller doses and a child with the dystonia with motor delay phenotype developed very severe dyskinesia (which lasted 4 days) after receiving a single 50 mg dose of levodopa with a DCI *(30,114)*, we suggest starting a therapeutic trial using a dose of 6.25/25 mg of C/L, once a day, for dystonia children without developmental motor delay and a dose of 3.1/12.5 mg, once a day, or even less for those with overt motor delay in infancy. In fact, the child manifesting the dystonia with motor delay phenotype was successfully treated with an initial dosage of 8 mg/day of levodopa with a DCI *(30)*. For adult patients, we suggest an initial dose of 12.5/50 mg of C/L once or twice a day. In patients with DRD, motor benefit can be recognized immediately or within a few days and full benefit occurs within several days to a few months after beginning levodopa administration. Maximum benefit (complete or near-complete responsiveness of symptoms) is usually achieved by less than 300 mg/day of levodopa with a DCI (25/100 mg of C/L, three times a day) (Table 1) or by less than 20–30 mg/kg/day of levodopa without a DCI *(5,6,113)*. Some genetically confirmed adult patients with GTPCH-deficient DRD needed 400 mg/day of levodopa with a DCI *(40,114)*. According to Nygaard and Duvoisin *(115)*, no dose of levodopa (with carbidopa) greater than 400 mg/day has been necessary for DRD patients. A continued stable response to levodopa therapy and no complications for more than 30 years have been confirmed in patients with GTPCH-deficient DRD and TH-deficient DRD *(5,18,23–26)*. Even DRD patients untreated for more than 40 years (including the 77-year-old patient with *DYT14* dystonia) showed a remarkable response at initiation of levodopa treatment *(5,6,14)*. Although patients with DRD can respond to trihexyphenidyl and bromocriptine, the efficacy of levodopa is generally superior to that of these other drugs *(5,113)*.

The limited clinical literature demonstrates that acute BH4 treatment may be much less effective than levodopa therapy for patients with GTPCH-deficient DRD, including the apparently sporadic patient 1 *(2,75,116)*: BH4 is available from Schircks Laboratories, Jona, Switzerland. In this genetically proven patient, BH4 (40 mg/kg/day) was orally administered for 5 consecutive days *(2)*. Although the dosage of BH4 should be sufficient to enter the brain *(117–119)*, no functional benefit was found from this acute oral BH4 administration. Even after intravenous infusion of BH4 in GTPCH-deficient DRD patients, CSF HVA concentrations were unchanged despite marked elevation of BP levels in CSF *(116)*. The low efficacy of such acute administration of BH4 (adequate to cross the blood–brain barrier) may be explained by striatal TH protein loss (observed in the two autopsied patients with DRD), which would be expected to limit any acute stimulatory effect of the cofactor BH4 on dopamine biosynthesis *(32)*. In contrast, the remarkable efficacy of levodopa (which bypasses TH in the biosynthetic pathway of dopamine) can be explained by the normal protein levels of AADC, for which levodopa is a substrate. Assuming that BH4 does, in fact, influence the steady-state level of TH protein in the human brain, it could be expected that repeated administration of BH4, if sufficiently prolonged, might upregulate TH protein concentration in the nigrostriatal dopaminergic terminals in GTPCH-deficient DRD.

CONCLUSION

Since the discovery of *GCH1* and *TH* mutations responsible for DRD, our understanding of this disorder has greatly increased. However, a traditional therapeutic trial with relatively low doses of levodopa is still the most practical approach to the diagnosis of DRD, as not all DRD patients have *GCH1* or *TH* mutations detectable by conventional genomic DNA sequencing of these genes. Because patients with DRD demonstrate complete or near-complete and sustained responsiveness of symptoms to levodopa therapy, the trial should be considered in all children with dystonic and/or parkinsonian symptoms or with unexplained gait disorders. The diagnostic alternatives (e.g., *DYT1* dystonia, cerebral palsy, and spastic paraplegia), except for EOP responding to levodopa, can be distinguished from DRD by this dramatic response at initiation of levodopa treatment. For the differentiation between DRD (metabolic disorder) and EOP (degenerative disorder) in the early course, a PET or SPECT study of the nigrostriatal dopaminergic terminals can be useful. Analyses of pterins and neurotransmitter metabolites in CSF appear to be useful for the diagnosis of GTPCH-deficient DRD (the major form of DRD) and of TH-deficient DRD (the mild form of TH deficiency). Findings of the new causative gene on the *DYT14* locus and the precise mechanism of striatal TH protein loss in GTPCH-deficient DRD will better define the pathogenesis of DRD.

NOTE ADDED IN PROOF

Since submission of this manuscript, an additional patient with the severe form of TH deficiency (a homozygote for a missense mutation [Leu236Pro]) has been reported *(120)*; although this report emphasizes that TH deficiency can cause pro-

gressive encephalopathy and "dopa-nonresponsive dystonia," the DRD phenotype (*see* "TH-Deficient DRD" in this chapter) should not be missed out of the spectrum of TH deficiency *(121)*.

It has also been reported recently that amantadine suppressed severe dopa-induced choreic dyskinesia, which developed at initiation of levodopa treatment, in two compound heterozygotes for *GCH1* mutations manifesting the dystonia with motor delay phenotype (*see* "Moderate GTPCH Deficiency") *(122)*.

LEGENDS TO CD-ROM

Segment 1: The 45-yr-old woman (patient 2), the proband in the four-generation dystonia family shown in the patient vignettes section, has dystonic posturing of the feet on walking with the right being much worse. Her slow walking also reveals dystonic posture of the right arm, diminished right-arm swing, and mild postural instability and turning.

Segment 2: After receiving a single 100 mg dose of levodopa with decarboxylase inhibitor (benserazide/levodopa 25/100 mg), the patient has no dystonic posturing of the feet and demonstrates fast and stable walking, whereas her right arm remains slightly impaired.

REFERENCES

1. Furukawa Y, Nishi K, Kondo T, Mizuno Y, Narabayashi H. CSF biopterin levels and clinical features of patients with juvenile parkinsonism. Adv Neurol 1993;60:562–567.
2. Furukawa Y, Shimadzu M, Rajput AH, et al. GTP-cyclohydrolase I gene mutations in hereditary progressive and dopa-responsive dystonia. Ann Neurol 1996;39:609–617.
3. Furukawa Y, Guttman M, Sparagana SP, et al. Dopa-responsive dystonia due to a large deletion in the GTP cyclohydrolase I gene. Ann Neurol 2000:47;517–520.
4. Nygaard TG. Dopa-responsive dystonia: delineation of the clinical syndrome and clues to pathogenesis. Adv Neurol 1993;60:577–585.
5. Segawa M, Nomura Y. Hereditary progressive dystonia with marked diurnal fluctuation. In: Segawa M, ed. Hereditary progressive dystonia with marked diurnal fluctuation. Parthenon, New York, NY: 1993;3–19.
6. Nygaard TG, Snow BJ, Fahn S, Calne DB. Dopa-responsive dystonia: clinical characteristics and definition. In: Segawa M, ed. Hereditary progressive dystonia with marked diurnal fluctuation. Parthenon, New York, NY: 1993;21–35.
7. Furukawa Y, Kish SJ. Dopa-responsive dystonia: recent advances and remaining issues to be addressed. Mov Disord 1999:14;709–715.
8. Furukawa Y, Mizuno Y, Narabayashi H. Early-onset parkinsonism with dystonia: clinical and biochemical differences from hereditary progressive dystonia or DOPA-responsive dystonia. Adv Neurol 1996;69:327–337.
9. Fahn S, Bressman SB, Marsden CD. Classification of dystonia. Adv Neurol 1998;78:1–10.
10. Nygaard TG, Wilhelmsen KC, Risch NJ, et al. Linkage mapping of dopa-responsive dystonia (DRD) to chromosome 14q. Nat Genet 1993;5:386–391.
11. Ichinose H, Ohye T, Takahashi E, et al. Hereditary progressive dystonia with marked diurnal fluctuation caused by mutations in the GTP cyclohydrolase I gene. Nat Genet 1994;8:236–242.
12. Tanaka H, Endo K, Tsuji S, et al. The gene for hereditary progressive dystonia with marked diurnal fluctuation maps to chromosome 14q. Ann Neurol 1995;37:405–408.
13. Lüdecke B, Dworniczak B, Bartholomé K. A point mutation in the tyrosine hydroxylase gene associated with Segawa's syndrome. Hum Genet 1995;95:123–125.

14. Grötzsch H, Pizzolato G-P, Ghika J, et al. Neuropathology of a case of dopa-responsive dystonia associated with a new genetic locus, *DYT 14*. Neurology 2002;58:1839–1842.
15. Furukawa Y, Rajput AH. Inherited myoclonus-dystonia: how many causative genes and clinical phenotypes? Neurology 2002;59:1130–1131.
16. Furukawa Y. Genetics and Biochemistry of dopa-responsive dystonia: significance of striatal tyrosine hydroxylase protein loss. Adv Neurol 2003;91:401–410.
17. Bartholomé K, Lüdecke B. Mutations in the tyrosine hydroxylase gene cause various forms of L-dopa-responsive dystonia. Adv Pharmacol 1998;42:48–49.
18. Swaans RJM, Rondot P, Renier WO, van den Heuvel LPWJ, Steenbergen-Spanjers GCH, Wevers RA. Four novel mutations in the tyrosine hydroxylase gene in patients with infantile parkinsonism. Ann Hum Genet 2000;64:25–31.
19. Furukawa Y, Graf WD, Wong H, Shimadzu M, Kish SJ. Dopa-responsive dystonia simulating spastic paraplegia due to tyrosine hydroxylase (TH) gene mutations. Neurology 2001:56;260–263.
20. Segawa M, Ohmi K, Itoh S, Aoyama M, Hayakawa H. Childhood basal ganglia disease with remarkable response to L-DOPA: hereditary progressive basal ganglia disease with marked fluctuation. Shinryo 1971;24:667–672.
21. Castaigne P, Rondot P, Ribadeau-Dumas JL, Saïd G. Affection extrapyramidale évoluant chez deux jeunes frères: effets remarquables du traitement par la L-Dopa. Rev Neurol 1971;124:162–166.
22. Inagaki H, Ohye T, Suzuki T, et al. Decrease in GTP cyclohydrolase I gene expression caused by inactivation of one allele in hereditary progressive dystonia with marked diurnal fluctuation. Biochem Biophys Res Commun 1999;260:747–751.
23. Segawa M, Hosaka A, Miyagawa F, Nomura Y, Imai H. Hereditary progressive dystonia with marked diurnal fluctuation. Adv Neurol 1976;14:215–233.
24. Rondot P, Ziegler M. Dystonia-L-dopa responsive or juvenile parkinsonism? J Neurol Transm 1983;Suppl 19:273–281.
25. Rondot P, Aicardi J, Goutières F, Ziegler M. Dystonies dopa-sensibles. Rev Neurol 1992;148:680–686.
26. Segawa M. Hereditary progressive dystonia with marked diurnal fluctuation. Brain Dev 2000;22(Suppl 1):S65–S80.
27. Müller K, Hömberg V, Lenard HG. Motor control in childhood onset dopa-responsive dystonia (Segawa syndrome). Neuropediatrics 1989;20:185–191.
28. Duvoisin RC, Yahr MD, Lieberman J, Antunes J, Rhee S. The striatal foot. Trans Am Neurol Assoc 1972;97:267.
29. Nygaard TG, Marsden CD, Duvoisin RC. Dopa-responsive dystonia. Adv Neurol 1988;50:377–384.
30. Furukawa Y, Kish SJ, Bebin EM, et al. Dystonia with motor delay in compound heterozygotes for GTP-cyclohydrolase I gene mutations. Ann Neurol 1998;44:10–16.
31. Nygaard TG, Duvoisin RC. Hereditary dystonia-parkinsonism syndrome of juvenile onset. Neurology 1986;36:1424–1428.
32. Furukawa Y, Nygaard TG, Gütlich M, et al. Striatal biopterin and tyrosine hydroxylase protein reduction in dopa-responsive dystonia. Neurology 1999;53:1032–1041.
33. Nygaard TG, Trugman JM, de Yebenes JG, Fahn S. Dopa-responsive dystonia: the spectrum of clinical manifestations in a large North American family. Neurology 1990;40:66–69.
34. Nygaard TG, Takahashi H, Heiman GA, Snow BJ, Fahn S, Calne DB. Long-term treatment response and fluorodopa positron emission tomographic scanning of parkinsonism in a family with dopa-responsive dystonia. Ann Neurol 1992;32:603–608.
35. Steinberger D, Weber Y, Korinthenberg R, et al. High penetrance and pronounced variation in expressivity of *GCH1* mutations in five families with dopa-responsive dystonia. Ann Neurol 1998;43:634–639.
36. Tassin J, Dürr A, Bonnet A-M, et al. Levodopa-responsive dystonia: GTP cyclohydrolase I or parkin mutations? Brain 2000;123:1112–1121.
37. Hoenicka J, Vidal L, Godoy M, Ochoa JJ, de Yébenes JG. New nonsense mutation in the GTP-cyclohydrolase I gene in L-DOPA responsive dystonia-parkinsonism. Mov Disord 2001;16:364–366.

38. Furukawa Y, Kapatos G, Haycock JW, et al. Brain biopterin and tyrosine hydroxylase in asymptomatic dopa-responsive dystonia. Ann Neurol 2002;51:637–641.
39. Furukawa Y, Guttman M, Wong H, Farrell SA, Furtado S, Kish SJ. Serum prolactin in symptomatic and asymptomatic dopa-responsive dystonia due to a *GCH1* mutation. Neurology 2003;61:269–270.
40. Grimes DA, Barclay CL, Duff J, Furukawa Y, Lang AE. Phenocopies in a large GCH1 mutation positive family with dopa responsive dystonia: confusing the picture? J Neurol Neurosurg Psychiatry 2002;72:801–804.
41. Furukawa Y, Kish SJ. Influence of development and aging on brain biopterin: implications for dopa-responsive dystonia onset. Neurology 1998;51:632–634.
42. Fink JK, Filling-Katz MR, Barton NW, Macrae PR, Hallett M, Cohen WE. Treatable dystonia presenting as spastic cerebral palsy. Pediatrics 1988;82:137–138.
43. Boyd K, Patterson V. Dopa responsive dystonia: a treatable condition misdiagnosed as cerebral palsy. Br Med J 1989;298:1019–1020.
44. Nygaard TG, Waran SP, Levine RA, Naini AB, Chutorian AM. Dopa-responsive dystonia simulating cerebral palsy. Pediatr Neurol 1994;11:236–240.
45. Patel K, Roskrow T, Davis JS, Heckmatt JZ. Dopa responsive dystonia. Arch Dis Child 1995;73:256–257.
46. Bandmann O, Nygaard TG, Surtees R, Marsden CD, Wood NW, Harding AE. Dopa-responsive dystonia in British patients: new mutations of the GTP-cyclohydrolase I gene and evidence for genetic heterogeneity. Hum Mol Genet 1996;5:403–406.
47. Bandmann O, Valente EM, Holmans P, et al. Dopa-responsive dystonia: a clinical and molecular genetic study. Ann Neurol 1998;44:649–656.
48. Brique S, Destée A, Lambert J-C, et al. A new GTP-cyclohydrolase I mutation in an unusual dopa-responsive dystonia, familial form. NeuroReport 1999;10:487–491.
49. Steinberger D, Topka H, Fischer D, Müller U. *GCH1* mutation in a patient with adult-onset oromandibular dystonia. Neurology 1999;52:877–879.
50. Klein C, Hedrich K, Kabakçi K, et al. Exon deletions in the *GCHI* gene in two of four Turkish families with dopa-responsive dystonia. Neurology 2002;59:1783–1786.
51. Leuzzi V, Carducci CA, Carducci Cl, Cardona F, Artiola C, Antonozzi I. Autosomal dominant GTP-CH deficiency presenting as a dopa-responsive myoclonus-dystonia syndrome. Neurology 2002;59:1241–1243.
52. Hahn H, Trant MR, Brownstein MJ, Harper RA, Milstien S, Butler IJ. Neurologic and psychiatric manifestations in a family with a mutation in exon 2 of the guanosine triphosphate-cyclohydrolase gene. Arch Neurol 2001;58:749–755.
53. Furukawa Y, Kish SJ, Lang AE. Scoliosis in a dopa-responsive dystonia family with a mutation of the GTP cyclohydrolase I gene. Neurology 2000;54:2187.
54. Ichinose H, Ohye T, Matsuda Y, et al. Characterization of mouse and human GTP cyclohydrolase I genes: mutations in patients with GTP cyclohydrolase I deficiency. J Biol Chem 1995;270:10,062–10,071.
55. Niederwieser A, Blau N, Wang M, Joller P, Atarés M, Cardesa-Garcia J. GTP cyclohydrolase I deficiency, a new enzyme defect causing hyperphenylalaninemia with neopterin, biopterin, dopamine, and serotonin deficiencies and muscular hypotonia. Eur J Pediatr 1984;141:208–214.
56. Blau N, Ichinose H, Nagatsu T, Heizmann CW, Zacchello F, Burlina AB. A missense mutation in a patient with guanosine triphosphate cyclohydrolase I deficiency missed in the newborn screening program. J Pediatr 1995;126:401–405.
57. Blau N, Barnes I, Dhondt JL. International database of tetrahydrobiopterin deficiencies. J Inherit Metab Dis 1996;19:8–14.
58. Furukawa Y, Lang AE, Trugman JM, et al. Gender-related penetrance and de novo GTP-cyclohydrolase I gene mutations in dopa-responsive dystonia. Neurology 1998;50:1015–1020.
59. Nagatsu T, Ichinose H. Comparative studies on the structure of human tyrosine hydroxylase with those of the enzyme of various mammals. Comp Biochem Physiol 1991;98C:203–210.

60. Furukawa Y. Update on dopa-responsive dystonia: locus heterogeneity and biochemical features. Adv Neurol 2004;94:127–138.
61. Knappskog PM, Flatmark T, Mallet J, Lüdecke B, Bartholomé K. Recessively inherited L-DOPA-responsive dystonia caused by a point mutation (Q381K) in the tyrosine hydroxylase gene. Hum Mol Genet 1995;4:1209–1212.
62. Lüdecke B, Knappskog PM, Clayton PT, et al. Recessively inherited L-DOPA-responsive parkinsonism in infancy caused by a point mutation (L205P) in the tyrosine hydroxylase gene. Hum Mol Genet 1996;5:1023–1028.
63. Bräutigam C, Wevers RA, Jansen RJT, et al. Biochemical hallmarks of tyrosine hydroxylase deficiency. Clin Chem 1998;44:1897–1904.
64. Surtees R, Clayton P. Infantile parkinsonism-dystonia: tyrosine hydroxylase deficiency. Mov Disord 1998;13:350.
65. van den Heuvel LPWJ, Luiten B, Smeitink JAM, et al. A common point mutation in the tyrosine hydroxylase gene in autosomal recessive L-DOPA-responsive dystonia in the Dutch population. Hum Genet 1998;102:644–646.
66. Bräutigam C, Steenbergen-Spanjers GCH, Hoffmann GF, et al. Biochemical and molecular genetic characteristics of the severe form of tyrosine hydroxylase deficiency. Clin Chem 1999;45:2073–2078.
67. Wevers RA, de Ruk-van Andel JF, Bräutigam C, et al. A review of biochemical and molecular genetic aspects of tyrosine hydroxylase deficiency including a novel mutation (291delC). J Inher Metab Dis 1999;22:364–373.
68. de Lonlay P, Nassogne MC, van Gennip AH, et al. Tyrosine hydroxylase deficiency unresponsive to L-dopa treatment with unusual clinical and biochemical presentation. J Inherit Metab Dis 2000;23:819–825.
69. de Rijk-van Andel JF, Gabreëls FJM, Geurtz B, et al. L-dopa-responsive infantile hypokinetic rigid parkinsonism due to tyrosine hydroxylase deficiency. Neurology 2000;55:1926–1928.
70. Dionisi-Vici C, Hoffmann GF, Leuzzi V, et al. Tyrosine hydroxylase deficiency with severe clinical course: clinical and biochemical investigations and optimization of therapy. J Pediatr 2000;136:560–562.
71. Janssen RJRJ, Wevers RA, Häussler M, et al. A branch site mutation leading to aberrant splicing of the human tyrosine hydroxylase gene in a child with a severe extrapyramidal movement disorder. Ann Hum Genet 2000;64:375–382.
72. Grattan-Smith PJ, Wevers RA, Steenbergen-Spanjers GC, Fung VSC, Earl J, Wilcken B. Tyrosine hydroxylase deficiency: clinical manifestations of catecholamine insufficiency in infancy. Mov Disord 2002;17:354–359.
73. Rajput AH, Gibb WRG, Zhong XH, et al. Dopa-responsive dystonia: pathological and biochemical observations in a case. Ann Neurol 1994;35:396–402.
74. Häussler M, Hoffmann GF, Wevers RA. L-dopa and selegiline for tyrosine hydroxylase deficiency. J Pediatr 2001;138:451–452.
75. LeWitt PA, Miller LP, Levine RA, et al. Tetrahydrobiopterin in dystonia: identification of abnormal metabolism and therapeutic trials. Neurology 1986;36:760–764.
76. Fink JK, Barton N, Cohen W, Lovenberg W, Burns RS, Hallett M. Dystonia with marked diurnal variation associated with biopterin deficiency. Neurology 1988;38:707–711.
77. Fujita S, Shintaku H. The pathogenesis of hereditary progressive dystonia with marked diurnal fluctuation (HPD) and a metabolic abnormality of pteridines. Kushiro J Med 1990;2:64–67.
78. Takahashi H, Levine RA, Galloway MP, Snow BJ, Calne DB, Nygaard TG. Biochemical and fluorodopa positron emission tomographic findings in an asymptomatic carrier of the gene for dopa-responsive dystonia. Ann Neurol 1994;35:354–356.
79. Furukawa Y, Mizuno Y, Nishi K, Narabayashi H. A clue to the pathogenesis of dopa-responsive dystonia. Ann Neurol 1995;37:139–140.
80. Furukawa Y, Shimadzu M, Hornykiewicz O, Kish SJ. Molecular and biochemical aspects of hereditary progressive and dopa-responsive dystonia. Adv Neurol 1998;78:267–282.

81. Hirano M, Imaiso Y, Ueno S. Differential splicing of the GTP cyclohydrolase I RNA in dopa-responsive dystonia. Biochem Biophys Res Commun 1997;234:316–319.
82. Hibiya M, Ichinose H, Ozaki N, et al. Normal values and age-dependent changes in GTP cyclohydrolase I activity in stimulated mononuclear blood cells measured by high-performance liquid chromatography. J Chromatogr B 2000;740:35–42.
83. Bezin L, Nygaard TG, Neville JD, Shen H, Levine RA. Reduced lymphoblast neopterin detects GTP cyclohydrolase dysfunction in dopa-responsive dystonia. Neurology 1998;50:1021–1027.
84. Bonafé L, Thöny B, Leimbacher W, Kierat L, Blau N. Diagnosis of dopa-responsive dystonia and other tetrahydrobiopterin disorders by the study of biopterin metabolism in fibroblasts. Clin Chem 2001;47:477–485.
85. Hirano M, Yanagihara T, Ueno S. Dominant negative effect of GTP cyclohydrolase I mutations in dopa-responsive hereditary progressive dystonia. Ann Neurol 1998;44:365–371.
86. Hirano M, Ueno S. Mutant GTP cyclohydrolase I in autosomal dominant dystonia and recessive hyperphenylalaninemia. Neurology 1999;52:182–184.
87. Hwu W-L, Chiou Y-W, Lai S-Y, Lee Y-M. Dopa-responsive dystonia is induced by a dominant-negative mechanism. Ann Neurol 2000;48:609–613.
88. Suzuki T, Ohye T, Inagaki H, Nagatsu T, Ichinose H. Characterization of wild-type and mutants of recombinant human GTP cyclohydrolase I: relationship to etiology of dopa-responsive dystonia. J Neurochem 1999;73:2510–2516.
89. Hyland K, Fryburg JS, Wilson WG, et al. Oral phenylalanine loading in dopa-responsive dystonia: a possible diagnostic test. Neurology 1997;48:1290–1297.
90. Saunders-Pullman RJ, Raymond D, Hyland K, et al. Markers of disease in dopa-responsive-dystonia. Mov Disord 1998;13(Suppl 2):285.
91. Bandmann O, Goertz M, Zschocke J, et al. The phenylalanine loading test in the differential diagnosis of dystonia. Neurology 2003;60:700–702.
92. Davis MD, Ribeiro P, Tipper J, Kaufman S. '7-Tetrahydrobiopterin,' a naturally occurring analogue of tetrahydrobiopterin, is a cofactor for and a potential inhibitor of the aromatic amino acid hydroxylases. Proc Natl Acad Sci USA 1992;89:10,109–10,113.
93. Snow BJ, Nygaard TG, Takahashi H, Calne DB. Positron emission tomographic studies of dopa-responsive dystonia and early-onset idiopathic parkinsonism. Ann Neurol 1993;34:733–738.
94. Turjanski N, Bhatia K, Burn DJ, Sawle GV, Marsden CD, Brooks DJ. Comparison of striatal ^{18}F-dopa uptake in adult-onset dystonia-parkinsonism, Parkinson's disease, and dopa-responsive dystonia. Neurology 1993;43:1563–1568.
95. Naumann M, Pirker W, Reiners K, Lange K, Becker G, Brücke T. [^{123}I]β-CIT single-photon emission tomography in DOPA-responsive dystonia. Mov Disord 1997;12:448–451.
96. Jeon BS, Jeong J-M, Park S-S, et al. Dopamine transporter density measured by [^{123}I]β-CIT single-photon emission computed tomography is normal in dopa-responsive dystonia. Ann Neurol 1998;43:792–800.
97. Kishore A, Nygaard TG, de la Fuente-Fernandez R, et al. Striatal D2 receptors in symptomatic and asymptomatic carriers of dopa-responsive dystonia measured with [^{11}C]-raclopride and positron-emission tomography. Neurology 1998;50:1028–1032.
98. O'Sullivan JD, Costa DC, Gacinovic S, Lees AJ. SPECT imaging of the dopamine transporter in juvenile-onset dystonia. Neurology 2001;56:266–267.
99. Künig G, Leenders KL, Antonini A, Vontobel P, Weindl A, Meinck HM. D2 receptor binding in dopa-responsive dystonia. Ann Neurol 1998;44:758–762.
100. Hauf M, Cousin P, Solida A, Albanese A, Ghika J, Schorderet DF. A family with segmental dystonia: evidence for polymorphism in GTP cyclohydrolase I gene (GCH I). Mov Disord 2000;15(Suppl 3):154–155.
101. Furukawa Y, Hornykiewicz O, Fahn S, Kish SJ. Striatal dopamine in early-onset primary torsion dystonia with the *DYT1* mutation. Neurology 2000;54:1193–1195.
102. Kish SJ, Shannak K, Hornykiewicz O. Uneven pattern of dopamine loss in the striatum of patients with idiopathic Parkinson's disease: pathophysiologic and clinical implications. N Engl J Med 1988;318:876–880.

103. Hornykiewicz O. Biochemical aspects of Parkinson's disease. Neurology 1998;51(Suppl 2):S2–S9.
104. Zhong X-H, Haycock JW, Shannak K, et al. Striatal dihydroxyphenylalanine decarboxylase and tyrosine hydroxylase protein in idiopathic Parkinson's disease and dominantly inherited olivopontocerebellar atrophy. Mov Disord 1995;10:10–17.
105. Wilson JM, Levey AI, Rajput A, et al. Differential changes in neurochemical markers of striatal dopamine nerve terminals in idiopathic Parkinson's disease. Neurology 1996;47:718–726.
106. Hyland K, Gunasekera RS, Engle T, Arnold LA. Tetrahydrobiopterin and biogenic amine metabolism in the *hph-1* mouse. J Neurochem 1996;67:752–759.
107. Sumi-Ichinose C, Urano F, Kuroda R, et al. Catecholamines and serotonin are differently regulated by tetrahydrobiopterin: a study from 6-pyruvoyltetrahydropterin synthase knockout mice. J Biol Chem 2001;276:41,150–41,160.
108. Ihara M, Kohara N, Urano F, et al. Neuroleptic malignant syndrome with prolonged catatonia in a dopa-responsive dystonia patient. Neurology 2002;59:1102–1104.
109. Bonafé L, Thöny B, Penzien JM, Czarnecki B, Blau N. Mutations in the sepiapterin reductase gene cause a novel tetrahydrobiopterin-dependent monoamine-neurotransmitter deficiency without hyperphenylalaninemia. Am J Hum Genet 2001;69:269–277.
110. Hyland K, Arnold LA, Trugman JM. Defects of biopterin metabolism and biogenic amine biosynthesis: clinical, diagnostic, and therapeutic aspects. Adv Neurol 1998;78:301–308.
111. Kitada T, Asakawa S, Hattori N, et al. Mutations in the parkin gene cause autosomal recessive juvenile parkinsonism. Nature 1998;392:605–608.
112. Ozelius LJ, Hewett JW, Page CE, et al. The early-onset torsion dystonia gene (*DYT1*) encodes an ATP-binding protein. Nat Genet 1997;17:40–48.
113. Nygaard TG, Marsden CD, Fahn S. Dopa-responsive dystonia: long-term treatment response and prognosis. Neurology 1991;41:174–181.
114. Steinberger D, Korinthenberg R, Topka H, et al. Dopa-responsive dystonia: mutation analysis of *GCH1* and analysis of therapeutic doses of L-dopa. Neurology 2000;55:1735–1737.
115. Nygaard TG, Duvoisin RC. Hereditary progressive dystonia/dopa-responsive dystonia. In: Joseph AB, Young RR, eds. Movement Disorders in Neurology and Neuropsychiatry. 2nd ed. Blackwell Science, Malden, MA: 1999;531–537.
116. Fink JK, Ravin P, Argoff CE, et al. Tetrahydrobiopterin administration in biopterin-deficient progressive dystonia with diurnal variation. Neurology 1989;39:1393–1395.
117. Kapatos G, Kaufman S. Peripherally administered reduced pterins do enter the brain. Science 1981;212:955–956.
118. Kaufman S, Kapatos G, Mclnnes RR, Schulman JD, Rizzo WB. Use of tetrahydropterins in the treatment of hyperphenylalaninemia due to defective synthesis of tetrahydrobiopterin: evidence that peripherally administered tetrahydropterins enter the brain. Pediatrics 1982;70:376–380.
119. Kondo T, Miwa H, Furukawa Y, Mizuno Y, Narabayashi H. Tetrahydrobiopterin therapy for juvenile parkinsonism. In: Segawa M, ed. Hereditary progressive dystonia with marked diurnal fluctuation. Parthenon, New York, NY: 1993;133–140.
120. Hoffmann GF, Assmann B, Bräutigam C, et al. Tyrosine hydroxylase deficiency causes progressive encephalopathy and dopa-nonresponsive dystonia. Ann Neurol 2003;54(Suppl 6):S56–S65.
121. Furukawa Y, Kish SJ, Fahn S. Dopa-responsive dystonia due to mild tyrosine hydroxylase deficiency. Ann Neurol 2004;55:147–148.
122. Furukawa Y, Filiano JJ, Kish SJ. Amantadine for levodopa-induced choreic dyskinesia in compound heterozygotes for *GCH1* mutations. Mov Disord 2004;19:1256–1258.

20

Whipple's Disease

John Lynch and Tim Lynch

PATIENT VIGNETTES

Patient 1: A 55-year-old-man developed right facial twitching followed 6 months later by somnolence, blurred vision, and imbalance. He noticed that the facial twitching spread to his neck and tongue, and his family noticed that it persisted in sleep. He then developed dysarthria and complained of poor memory, change in personality, malaise, intermittent fevers, increased sweating, and impotence over the ensuing 6 months. On initial assessment 1 year after the onset of facial twitching, orientation, memory, and language were normal. He was intermittently inattentive and had marked dysarthria resulting from rhythmic lingual retraction and masticatory myorhythmia coinciding with rhythmic contractions of the right side of the face, neck, chest, and the right arm. The contractions spread irregularly to the left side of the face, chest, arm, and leg. Vertical gaze was limited, but improved with the oculocephalic maneuver. Saccades were slow in all directions. Pendular vergence oscillations of the right more than the left eye (frequency = 1 Hz) occurred synchronously with masticatory and skeletal myorhythmia (i.e., oculofacial-skeletal myorhythmia). Muscle tone, strength, sensation, deep tendon reflexes, plantar responses, and postural stability were normal. His gait was mildly ataxic.

Routine laboratory, cerebrospinal fluid (CSF), and electroencephalogram (EEG) studies were normal. Brain magnetic resonance imaging (MRI) with gadolinium revealed a nonenhancing left frontal periventricular hyperintensity. Electromyographic analysis revealed 400-ms bursts of bilateral rhythmic activity. This activity originated at the level of cranial nerve VII, and spread rostrally to involve the muscles of the mastication, and caudally to involve muscles of the neck, arms, and legs.

Periodic acid-Schiff (PAS) and Grocott methenamine silver stains from a second duodenal biopsy demonstrated intracytoplasmic granular rod-shaped structures consistent with Whipple's bacillus. Central nervous system (CNS) Whipple's disease (WD) was diagnosed. He was treated with Trimethoprim-sulfamethoxazole (TPM-SMX) (1 double-strength [DS] tablet twice a day) for 2 years, which resulted in improvement in malaise and the ocular component of the myorhythmia. Ceftriaxone (2 g/day) was added for 9 months, with modest improvement in hemifacial spasms, malaise, and lethargy.

From: *Current Clinical Neurology: Movement Disorder Emergencies: Diagnosis and Treatment*
Edited by: S. J. Frucht and S. Fahn © Humana Press Inc., Totowa, NJ

Patient 2: A 47-year-old woman developed severe progressive insomnia unresponsive to medication, a 10-lb weight loss, diplopia, fever and submandibular lymph node enlargement. Past history was notable for arthritis without diarrhea.

On examination, vertical and horizontal saccades were slow, with diminished abduction of the left eye. Down gaze was full; up gaze was mildly limited. There were spontaneous, convergent nystagmoid movements in the right eye unaccompanied by miosis. These movements increased with downward moving opticokinetic stimuli.

Over the ensuing 8 months, a progressive opthalmoparesis resulted in complete loss of voluntary eye movements except for adduction of the right eye. She developed short-term memory loss, depressive symptoms, difficulty swallowing, blurred vision, intermittent hypersomnolence, and increased postural instability. On re-examination, she was intermittently unarousable, with hypomimia and severe dysarthria. Pendular vergence oscillations of both eyes synchronous with the masticatory myorhythmia (oculomasticatory myorhythmia [OMM]) were present. There was mild hypertonia, and normal strength and sensation. Deep tendon reflexes were brisk. Gait was slow, with shuffling, difficulty turning, and postural instability. Carbidopa/levodopa and prednisolone (20 mg daily) were prescribed without benefit.

Routine laboratory studies and EEG were within normal limits. CSF analysis revealed protein levels of 50 to 55 mg/dL with a normal glucose concentration, and 70 PAS-negative mononuclear cells. Brain computed tomography scans appeared normal and an MRI revealed an Arnold-Chiari type 1 malformation with no brainstem compression. Specimens obtained from two duodenal biopsies indicated mild chronic nonspecific duodenitis. No PAS staining or other changes consistent with WD were detected. Electron microscopy was not performed. CNS WD was diagnosed based on clinical findings (i.e., OMM and supranuclear gaze palsy) and subsequently confirmed by polymerase chain reaction analysis of the PAS-negative duodenal biopsies. Intravenous ceftriaxone (2 g daily) for 6 months resulted in complete resolution of OMM and improvement in the supranuclear gaze palsy and malaise. After switching to TPM-SMX (1 DS tablet twice a day), the supranuclear gaze palsy, lethargy, and malaise recurred. After years of follow-up, she was restricted to a wheelchair and fed by gastrostomy.

INTRODUCTION

Whipple's disease (WD) was originally described as a gastrointestinal (GI) disorder associated with arthralgia *(1)*. It can result in debilitating neurological dysfunction *(2,3)* and often has a relapsing course. It is caused by a bacilliform bacterium, *Tropheryma whippelii*. Infection can occur in several organs, including the GI tract, heart, lungs, kidney, brain, and skin. Fewer than 800 cases have been reported. Although WD is a relatively rare entity, its diagnosis may be made, or at least strongly suspected, from certain clinical features. Early diagnosis and treatment is essential to ensure good recovery.

Sequencing of polymerase chain reaction (PCR)-amplified bacterial 16s ribosomal RNA from infected tissue has led to characterization of the Whipple organism *(4)*. *Tropheryma whippelii* DNA has also been detected in the saliva of patients without Whipple's disease *(5)*. Overall, four different rDNA types are recognized in the proposed classification system for molecular variants of *T. whippelii*. It appears to be a unique member of the Actinomycetaceae family of bacteria *(6)*.

The disease has not been reproduced in animals and its pathophysiology is not completely understood. The host produces a cellular rather than humoral immune response that results in macrophage recruitment. The role of T-cell-mediated immune defects is uncertain. WD has been described in connection with acquired immunodeficiency syndrome and other conditions of immunosuppression.

The bacillus has morphological features of both Gram-positive and Gram-negative organisms. Determination of the DNA G + C content confirmed that it belongs to the high G + C Gram-positive bacteria *(7)*. It appears both intracellularly and extracellularly; infected macrophages are characteristically present. In most tissues, however, infection is not restricted to macrophages alone. Infected cells stain strongly with periodic acid-Schiff (PAS). Examination by electron microscopy demonstrates that the areas of intense PAS staining are packed with bacilli, some of which have degenerated. These areas usually have a distinctive sickle shape. Cells containing them are referred to as sickle particle cells.

Culturing the bacterium has been an elusive goal. In 1997, the bacterium was isolated and grown in human macrophages inactivated with interleukin-4 *(8)*. It has since been cultured from a patient with endocarditis resulting from WD *(9)*. Monoclonal antibodies to the immunodominant epitope of *T. whippelii*, which is an 84-kDa protein, have been developed *(10)*.

The epidemiology of WD is poorly understood. There seems to be a predominance of the systemic disorder in elderly men (8:1 male:female) and Caucasians, but this is less obvious in central nervous system (CNS) WD.

CLINICAL FEATURES

Systemic Disease

The symptoms of the systemic disease are weight loss, abdominal pain, diarrhea (often with steatorrhea), and migratory arthralgia. Arthralgia often antedates the GI symptoms. Malabsorption may be prominent. Low-grade fever, lymphadenopathy, increased skin pigmentation, and subcutaneous nodules, which histologically demonstrate septal panniculitis with a large amount of foamy histiocytes *(11)*, also occur. There has been a report of bone-marrow involvement *(12)*. Myocarditis, pericarditis, endocarditis, and coronary arterial damage *(13)* have been described. There have been cases of ocular (keratitis, uveitis, vitreous opacities) and neurological disease without evidence of systemic infection *(2,14)*.

Neurological Manifestations

The neurological disorder, which occurs in 6–43% of patients with WD, is usually a progressive encephalopathy, characterized by memory loss, personality change, and cognitive dysfunction *(2)*. Asymptomatic CNS infection may occur. Neurological symptoms predating other systemic features of WD occur in 5% of cases. Seizures, meningitis, strokes, peripheral neuropathy, myopathy, acute intracranial hypertension *(15)*, and rhythmic tremor of the palate and other cranial limb muscles with cerebellar ataxia *(16)* have been described. A novel association between juvenile dermatomyositis and WD has been reported *(17)*. Focal findings

may suggest discrete lesions and include ophthalmoplegia, motor and sensory signs, ataxia, and evidence of hypothalamic dysfunction, including hypersomnolence and hormone deficiencies. A combination of slow pendular vergence nystagmus (1 Hz), concurrent contraction of the masticatory muscles (oculomasticatory myorhythmia), and vertical supranuclear palsy has been described in WD *(3,18)*. Continuous smooth, rhythmic convergent eye movements characterize pendular vergence oscillations, with a frequency of 1 Hz and varying from 10 to 25 degrees of amplitude per eye, but never diverging beyond the primary position. The oscillations continue throughout sleep and may be subtle and asymmetric. Convergence and divergence are at the same speed and are not accompanied by miosis or accommodation. The anatomical basis for this apparently unique movement disorder is not known, but it may originate from the upper brainstem. The rhythmic myoclonus is characterized by repetitive contractions of facial, masticatory, and pharyngeal muscles with or without limb involvement. It continues throughout sleep and differs from oculopalatal myoclonus, which has a frequency of 2 Hz. Oculomasticatory myorhythmia in association with supranuclear palsy is pathognomonic of neurological WD.

EVALUATION (*SEE* TABLE 1)

Radiological Findings

Although magnetic resonance imaging (MRI) is worth pursuing, patients with CNS WD may have normal brain imaging. The role of MRI has been reviewed *(2)*. MRI is superior to computed tomography (CT) for detection of small lesions. These lesions, which occur in 53% of cases *(2)*, consist of T1 hypointensity and T2 hyperintensity, show no mass effect, and are located in the medial part of the temporal lobes, hypothalamus, and pons. They may enhance after infusion of contrast. There is associated atrophy in 42% of cases. Biopsy of these lesions has provided the diagnosis in several cases. Multiple mass lesions have rarely been described *(19)*. Spinal cord involvement with Whipple's disease is unusual *(20,21,21a)*. Involvement of the optic chiasm has only rarely been revealed by MRI *(22)*.

Laboratory Investigations

General laboratory studies usually reveal steatorrhea, impaired xylose absorption, anemia, and hypoalbuminemia. Diagnosis, however, is usually made by jejunal biopsy, which demonstrates the PAS-staining macrophages. Because PAS-positive macrophages may be found in other diseases and in other tissues in normal individuals, confirmation of the diagnosis is facilitated by detection of the actual bacillus with appropriate stains, or by electron microscopy or PCR amplification of 16s ribosomal *T. whippelii* RNA. Immunological detection of *T. whippelii* may now be possible *(9,10)*. However, *T. whippelii* occurs only rarely in intestinal mucosa that lacks histopathological evidence of WD *(14)*, which suggests that the human small intestinal mucosa is an unlikely reservoir for this organism *(23)*. Cerebrospinal fluid (CSF) examination may be normal or show a moderate pleocytosis

Table 1
Guidelines for Diagnostic Screening, Biopsy, and Treatment of Central Nervous System (CNS) Whipple's Disease (WD) *(2)*

Definite CNS WD

Must have any one of the following three criteria:

1. Oculomasticatory myorhythmia or oculofacial-skeletal myorhythmia
2. Positive tissue biopsy
3. Positive polymerase chain reaction (PCR) analysis

If histological or PCR analysis is not performed on CNS tissue, then the patient must also demonstrate neurological signs. If histological or PCR analysis is performed on CNS tissue, then the patient need not demonstrate neurological signs (i.e., asymptomatic infection).

Possible CNS WD

Must have any one of four systemic symptoms, not of another known etiology:

1. Fever of unknown etiology
2. Gastrointestinal symptoms (steatorrhoea, abdominal distension, or pain)
3. Chronic migratory arthralgias or polyarthralgias
4. Unexplained lymphadenopathy, night sweats, or malaise

Also must have any one of four neurological signs, not of another known etiology:

1. Supranuclear vertical gaze palsy
2. Rhythmic myoclonus
3. Dementia with psychiatric symptoms
4. Hypothalamic manifestations

(about 200 cells, mostly mononuclear) or protein levels up to 100 to 200 mg/dL. Immunoglobin G elevation has been reported in the CSF.

The definitive diagnosis of CNS WD is confirmed by finding PAS-containing macrophages in the brain, and by demonstrating the bacillus in these cells or by demonstrating a positive PCR assay for *Tropheryma whippelii (2)*. PCR can be used for the diagnosis of WD, including in patients with histologically negative jejunal biopsies *(6,14,24,25)*. PCR of blood from a suspected case is very useful, given its speed and ease. Its sensitivity has, however, been questioned, particularly when blood mononuclear cells are used for DNA extraction rather than whole blood. Differences in the published sensitivity and specificity may result from methodological factors, such as the technique of DNA extraction and the sequence of primers and PCR condition *(26)*. If the organism has been detected in a small bowel biopsy or in other tissues such as synovium and vitreous humor *(27)*, cerebral biopsy is not necessary.

TREATMENT (*SEE* TABLE 2)

There is no clear evidence that one antimicrobial agent is better than another in the treatment of CNS WD. Therapeutic trials without definite diagnosis have been attempted, with the usual pitfalls of misdiagnosis and mistreatment. Evidence for the sensitivity of *T. whippelii* to various antibiotics is anecdotal. Many agents have

Table 2
Suggested Guidelines for the Treatment of Central Nervous System Whipple's Disease

First Line

1. 1.2 g of penicillin G intravenously four times daily for 2 weeks followed by
2. 960 mg of trimethoprim—sulfamethoxazole by mouth twice daily for 9 months

Second Line

2 g of ceftriaxone once daily intramuscularly or intravenously for 6 months

Third Line

200 mg of doxycycline by mouth once daily for 6 months

been used, including doxycycline, ampicillin, chloramphenicol, penicillin, cotrimoxazole, trimethoprim sulphamethoxazole, ciprofloxacin, rifampicin, cefixime, erythromycin, intramuscular streptomycin, and intravenous ceftriaxone. Tetracyclines given alone tend to fail. High-dose penicillin, perhaps with streptomycin followed by oral trimethoprim/sulfamethoxazole, would appear to be a reasonable treatment based on reported successful treatment regimens. Third-generation cephalosporins are reported to be of benefit, sometimes as an adjunct to the previously mentioned combination. Treatment must be prolonged because recurrence has followed months of treatment and apparent resolution of disease. It has been suggested that to ascertain eradication of *T. whippelii* in the cerebrospinal fluid, PCR is more reliable than cytology *(28)*.

REFERENCES

1. Whipple GH. A hitherto undescribed disease characterized anatomically by deposits of fat and fatty acids in the intestinal and mesenteric lymphatic tissues. Bull Johns Hopkins Hosp 1907;18:382–391.
2. Louis ED, Lynch T, Kaufmann P, Fahn S, Odel J. Diagnostic guidelines in central nervous system Whipple's disease. Ann Neurol 1996;40:561–568.
3. Lynch T, Fahn S, Louis E, Odel JG. Oculofacial-skeletal myorhythmia in Whipple's disease. Mov Disord 1997;12:624–625.
4. Wilson KH Blitchington R, Frothingham R, Wilson JAP. Phylogeny of the Whipple's-disease-associated bacterium. Lancet 1991;338:474–475.
5. Dutly F, Hinrikson HP, Seidel T, Morgenegg S, Altwegg M, Bauereind P. *Tropheryma whippelii* DNA in saliva of patients without Whipple's disease. Infection 2000;28:219–222.
6. Relman DA, Schmidt TM, Mac Dermott RP, Falkow S. Identification of the uncultured bacillus of Whipple's disease. N Engl J Med 1992;327:293–301.
7. La Scola B, Fenollar F, Fournier PE, Altwegg M, Mallet MN, Raoult D. Description of Tropheryma whippelii Int J Syst Evol Microbiol 2001;51:1471–1479.
8. Schoedon G, Goldenberger D, Forrer R, et al. Deactivation of macrophages with interleukin-4 is the key to the isolation of Tropheryma whippelii. J Infect Dis 1997;176:672–677.
9. Raoult D, Birg ML, La Scola B, et al. Cultivation of the Bacillus of Whipple's Disease. N Engl J Med 2000;342:620–625.
10. Liang Z, La Scola B, Rao HD. Monoclonal antibodies to immunodominant epitope of Tropheryma whippellii. Clin Diagn Lab Immunol 2002;9:156–159.

11. Tarroch X, Vives P, Salas A, More J. Subcutanoeus nodules in Whipple's disease. J Cutan Pathol 2001;28:369–370.
12. Walter R, Bachmann SP, Schaffner A, Ruegg R, Schoeden G. Bone marrow involvement in Whipple's disease: rarely reported, but really rare? Br J Haematol 2001;112:677–679.
13. James TN. On the wide spectrum of abnormalities in the coronary arteries of Whipple's disease. Cor Artery Dis 2001;2:115–125.
14. Lynch T, Odel J, Fredericks DN, et al. Polymerase chain reaction based detection of Tropheryma whippelii in central nervous system Whipple's disease. Ann Neurol 1997;42:120–124.
15. Levy S, Degott C, Redondo A, Benhamou JP, Bernuau J. Acute intracranial hypertension and anicteric cholestasis revealing Whipple's disease without digestive involvement. Gastroenterol Clin Biol 2001;25:100–102.
16. Quinn N. Rhythmic tremor of the palate and other cranial limb muscles, with cerebellar ataxia: consider Whipple's disease. Mov Disord 2001;16:787.
17. Helliwell TR, Appleton RE, Mapstone NC, Davidson J, Walsh KP. Dermatomyositis and Whipple's disease. Neuromuscul Disord 2000;10:46–51.
18. Schwartz MA Selhorst SB, Ochs AL, et al Oculomasticatory myorhythmia: a unique movement disorder occurring in Whipple's disease. Ann Neurol 1986;20:677–683.
19. Wroe SJ, Pires M, Harding B, Youl BD, Shorvon S. Whipple's disease presenting with multiple intracerebral mass lesions. J Neurol Neurosurg Psychiatry 1991;54:989–992.
20. Kremer S, Besson G, Bonaz B, Pasquier B, Le Bas J-F, Grand S. Diffuse lesions in the CNS revealed by MR imaging in a case of Whipple disease. AJNR 2001;22:493.
21. Clarke CE, Falope ZF, Abdelhadi HA, Franks AJ. Cervical myelopathy caused by Whipple's disease. Neurology 1998;50:1505–1506.
21a. Messori A, Bella PD, Polonara G, et al. An unusual spinal presentation of Whipple disease. AJNR 2001;22:1004–1008.
22. Schnider P, Trattnig S, Kolleger H, Auff E. MR of cerebral Whipple disease. AJNR 1995;16:1328–1329.
23. Maiwald M, von Herbay A, Persing DH, et al. Tropheryma whippelii DNA is rare in the intestinal mucosa of patients without other evidence of Whipple disease. Ann Intern Med 2001;134:115–119.
24. Chan RY, Yannuzzi LA, Foster CS. Ocular Whipple's disease: earlier definitive diagnosis. Ophthalmology 2001;108(12):2225–2231.
25. Ramzan NN, Loftus E, Burgart LJ, et al Diagnosis and monitoring of Whipple's disease by polymerase chain reaction. Ann Intern Med 1997;126:520–527.
26. Coria F, Cuadrado N, Velasco C, et al. Whipple's disease with isolated central nervous system symptomatology diagnosed by molecular identification of Tropheryma whippelii in peripheral blood. Neuologia 2000;15:173–176.
27. Rickman LS, Freman WR, Gren WR, Feldman ST, Sullivan J, Russack V, Relman DA. Uveitis caused by *Tropheryma whippelii* (Whipple's disease). N Engl J Med 1995;332:363–366.
28. Von Herbay A. Whipple's disease. Histologic diagnosis after the discovery of *Tropheryyma whippelii*. Pathologe 2001;22:82–88.

Index