Movement Disorders
100 Instructive Cases

Edited by
Stephen G Reich MD
Professor of Neurology
The Clara Zappa-Saghy and Thomas H Regis Professor of Parkinson's Disease
Co-Director
The Maryland Parkinson's Disease and Movement Disorders Center
The University of Maryland School of Medicine
Baltimore, MD, USA

A practical and user-friendly, Movement Disorders: 100 Instructive Cases represents a unique opportunity for the neurologist to learn about interesting cases from the world's best clinicians. The first-of-its-kind book delivers a series of practical, interesting teaching vignettes directly applicable to caring for patients with these problems. Avoiding the formality of a traditional monograph, this accessible text adopts a casual tone with short chapters that are conducive to a "quick read," something that is of paramount importance to a busy practitioner or resident.

Including educational illustrative material such as radiology imaging, histopathology, and patient photographs, the text also provides a DVD containing videotapes of patients in order to fully appreciate the cases and enhance their teaching value.

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Movement Disorders
Dedication

To my parents, Henry and Edith Reich, and my wife, Dana
Movement Disorders
100 Instructive Cases

Stephen G Reich MD
Professor of Neurology
The Clair Zamoiski Segal and Thomas H Segal
Professor of Parkinson’s Disease
Co-Director
The Maryland Parkinson’s Disease
and Movement Disorders Center
The University of Maryland School of Medicine
Baltimore, MD
USA

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healthcare
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Contributors

J Eric Ahlskog MD PhD
Professor of Neurology
Mayo Medical School
Mayo Clinic Rochester, MN
USA

Imran Ali MD
Medical University of Ohio
Toledo, OH
USA

Jomana T Al-Hinti MD
Department of Neurology
University of Arkansas
College of Medicine
Little Rock, AR
USA

Thamer Al-Khairallah MD
Movement Disorders Clinic
Toronto Western Hospital
Ontario
Canada

Karen E Anderson MD
Maryland Parkinson’s and
Movement Disorders Center and
the University of Maryland
Huntington’s Disease Clinic
Baltimore, MD
USA

Susan Anderson MD
Department of Pediatrics
University of Virginia
Charlottesville, VA
USA

Saima Athar MD PhD
Movement Disorders Program
Department of Neurology
Emory University
School of Medicine
Atlanta, GA
USA

Yasuhiko Baba MD
Research Fellow in
Movement Disorders
Department of Neurology
Mayo Clinic
Jacksonville, FL, and
Assistant Professor
Department of Internal Medicine
Fukuoka University
Japan

Daniel G Baseman MD
University of Texas Health
Science Center San Antonio
Department of Radiation Oncology
San Antonio, TX
USA

KP Bhatia MD, DM FRCP
Sobell Department of
Movement Neuroscience
Institute of Neurology
University College of London
London
UK

Karen Blindauer MD
Assistant Professor of Neurology
Director of Movement Disorders
Program
Medical College of Wisconsin
Milwaukee, MI
USA
List of contributors

S Bohlhalter
Human Motor Control Section
National Institute of Neurological Disorders and Stroke
Bethesda, MD
USA

Yvette M Bordelon MD PhD
Assistant Professor
Department of Neurology
UCLA Medical Center
Los Angeles, CA
USA

Sylvia Bösch MD
Department of Neurology
University Hospital of Innsbruck
Austria

Allison Brashear MD
Professor and Chair of Neurology
Wake Forest University
School of Medicine
Winston Salem, NC
USA

Christine Brefel-Courbon MD
Service de Pharmacologie
Centre Hospitalier Universitaire de Toulouse
France

Helen Bronte-Stewart MD MSE
Stanford Movement Disorders Center
Stanford University
Palo Alto, CA
USA

Robbie Buechler MD PhD
Division of Neurology
Duke University Medical School
Durham, NC
USA

Richard Camicioli MD
Associate Professor of Medicine (Neurology), University of Alberta
Glenrose Rehabilitation Hospital
Edmonton
Canada

Kevin R Cannard MD FAAN
Associate Professor of Neurology
F Edward Hébert School of Medicine
USUHS, Bethesda, MD and Chief
Movement Disorders Service
Walter Reed Army Medical Center
Washington, DC
USA

Dzintra F Celmins MD
The Parkinson’s Disease and Movement Disorder Center of Albany Medical Center
Albany, NY
USA

K Ray Chaudhuri MD FRCP DSC
National Parkinson Foundation Centre of Excellence
Kings College Hospital
London
UK

Robert Chen MA MBBChir MSC FRCPC
Division of Neurology
Department of Medicine
Toronto Western Research Institute
University of Toronto
Ontario
Canada

Kelvin L Chou MD
NeuroHealth Parkinson’s Disease and Movement Disorders Center
Warwick, RI
USA

Joseph Classen
Associate Professor of Neurology
University of Wuerzburg
Wuerzburg
Germany

Cynthia L Comella MD
Professor
Movement Disorders Section
Rush University Medical Center
Chicago, IL
USA
Susan Criswell MD
Department of Neurology and
American Association Advanced
Center for Parkinson Research
Washington University School of
Medicine
St Louis, MO
USA

Günther Deuschl
Department of Neurology
University of Kiel
Germany

Richard B Dewey Jr MD
The Clinical Center for
Movement Disorders
Department of Neurology
UT Southwestern Medical Center
Dallas, TX
USA

Vandana Dhawan MBBS
Department of Neurology
King’s College and University
Hospital Lewisham
and Guy’s, King’s, St Thomas’
Schools of Medicine
London
UK

Ruth Djaldetti MD
Rabin Medical Center
Beilinson Campus, Petah Tikva
Israel and Sackler School of Medicine
Tel Aviv University
Israel

Joshua L Dowling MD
Associate Professor
Washington University School of
Medicine
Department of Neurosurgery
Washington University in
St Louis, MO
USA

KE Egger MD
Clinical Department of Neurology
Medical University Innsbruck
Austria

Steven Eisenschenk MD
Clinical Director
Adult Neurology Comprehensive
Epilepsy Program and Associate
Professor of Neurology
Department of Neurology
University of Florida
Gainesville, FL
USA

Lawrence Elmer MD PhD
Medical University of Ohio
Toledo, OH
USA

Murat Emre MD
Professor of Neurology
Behavioural Neurology and
Movement Disorders Unit
Department of Neurology
Istanbul Faculty of Medicine
Istanbul University
Turkey

Alberto J Espay MD MSc
Assistant Professor of Neurology
Movement Disorder Center
University of Cincinnati
Cincinnati, OH
USA

Nelly Fabre
Service de Neurologie
Centre Hospitalier Universitaire de
Toulouse
France

Stanley Fahn MD
Columbia University Medical Center
Center for Parkinson’s Disease and
Other Movement Disorders
New York, NY
USA
Hubert H Fernandez MD
Director
Clinical Trials for
Movement Disorders
University of Florida
Gainseville, FL
USA

Joseph H Friedman MD
NeuroHealth Parkinson’s
Disease and Movement Disorders Center
Warwick, RI
USA

Steven J Frucht MD
Division of Movement Disorders
Columbia University Medical Center
New York, NY
USA

Sarah Furtado MD PhD FRCPC
Movement Disorders Program
Department of Clinical Neurosciences
University of Calgary
Alberta
Canada

Yoshiaki Furukawa MD
Movement Disorders Research Laboratory
Center for Addiction and Mental Health – Clarke Division
Toronto, Ontario
Canada

Oscar S Gershanik MD
Professor and Chairman
Department of Neurology
Centro Neurologico Hospital Frances
Buenos Aires
Argentina

F Geser MD PhD
Clinical Department of Neurology
Medical University Innsbruck
Austria

Christopher G Goetz MD
Professor of Neurological Sciences
and Professor of Pharmacology
Rush University Medical Center
Chicago, IL
USA

Cyril Goizet MD
Service de Génétique Médicale
Hôpital Pellegrin-Enfants
Bordeaux
France

Jennifer G Goldman MD
Assistant Professor of Neurological Sciences
Rush University Medical Center
Chicago, IL
USA

Amrit K Grewal MD
Neurology Group of Bergen County
Ridgewood, NJ
USA

Stephen E Grill MD PhD
Parkinson’s and Movement Disorders Center of Maryland
Elkridge, MD
USA

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

Hasmet A Hanagasi MD
Associate Professor of Neurology
Behavioural Neurology and Movement Disorders Unit
Department of Neurology
Istanbul Faculty of Medicine
Istanbul University
Turkey
List of contributors

Sami I Harik MD  
Department of Neurology  
University of Arkansas  
College of Medicine  
Little Rock, AR  
USA

Madaline B Harrison MD  
Department of Neurology  
University of Virginia  
Charlottesville, VA  
USA

Noriaki Hattori  
Human Motor Control Section  
National Institute of Neurological Disorders and Stroke  
Bethesda, MD  
USA

Jason Hawley MD  
Chief of Neurology  
Carl R Darnall Army Medical Center  
Fort Hood, TX  
USA

Mark A Hellmann MD  
Department of Neurology  
Rabin Medical Center  
Beilinson Campus, Petah Tikva  
Israel and Sackler School of Medicine  
Tel Aviv University  
Israel

Stacy Horn DO  
Department of Neurological Sciences  
University of Pennsylvania  
Philadelphia, PA  
USA

Neng Huang MD PhD  
The Parkinson’s Institute  
Sunnyvale, CA  
USA

Howard I Hurtig MD  
Elliott Professor Neurology  
Department of Neurology  
Parkinson’s Disease and Movement Disorders Center  
Pennsylvania Hospital  
Philadelphia, PA  
USA

Keith Hyland PhD  
Department of Neurochemistry  
Horizon Molecular Medicine  
Atlanta, GA  
USA

Barbara Illowsky Karp MD  
National Institute of Neurological Disorders and Stroke  
Bethesda, MD  
USA

Sanjay S Iyer MD  
Director  
Carolinas Center for Parkinson and Movement Disorders, and  
Interim Chairman  
Department of Neurology  
Carolinas Medical Center  
Charlotte, NC  
USA

Samay Jain MD  
Clinical Fellow in Movement Disorders  
Columbia University Medical Center Neurological Institute  
New York, NY  
USA

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

Paul Jarman  
The National Hospital for Neurology and Neurosurgery  
London  
UK

HA Jinnah MD, PhD  
Associate Professor of Neurology  
Johns Hopkins School of Medicine  
Baltimore, MD  
USA
List of contributors

Keith A Josephs MD MST
Associate Professor of Neurology
Behavioral Neurology and
Movement Disorders
Mayo Clinic
Rochester, MN
USA

Jorge L Juncos MD
Movement Disorders Program
Department of Neurology
Emory University
School of Medicine
Atlanta, GA
USA

Morvarid Karimi MD
Department of Neurology
Washington University in
St Louis, MO
USA

Thaddeus Kelly MD PhD
Department of Pediatrics
University of Virginia
Charlottesville, VA
USA

Suketu M Khandar MD
University of California
San Francisco, CA
USA

Shannon Kilgore MD
Stanford Movement Disorders Center
Stanford University
Palo Alto, CA
USA

Christine Klein MD
Departments of Neurology and
Human Genetics
University of Lübeck
Germany

Galit Kleiner-Fisman MD FRCP
Parkinson’s Disease Research
Education, and Clinical Center
Philadelphia VA Medical Center, PA
USA

Timothy Kleinig PhD
Department of Neurology
Royal Adelaide Hospital
University Department of Medicine
University of Adelaide
Adelaide
Australia

Jeff Kraakevik MD
Department of Neurology
Portland VA Medical Center
Portland, OR
USA

Scott Kraft MD FRCP
Movement Disorders Program
Department of Clinical Neurosciences
University of Calgary, Alberta
Canada

Daniel Kremens MD
Parkinson’s Disease and
Movement Disorders Center
Pennsylvania Hospital
Philadelphia, PA
USA

Roger Kurlan MD
Professor of Neurology and
Center for Aging and
Developmental Biology
University of Rochester
School of Medicine and Dentistry
Rochester, NY
USA

Pierre Labauge MD PhD
Department of Neurology
CHU Montpelier-Nîmes
Nîmes
France

Edwin Landaker MD
Department of Neurology
University of Virginia
Charlottesville, VA
USA
List of contributors

I L Langford MS
Department of Neurology
University of Mississippi
Medical Center
Jackson, MS
USA

Anthony E Lang MD
Movement Disorders Clinic
Toronto Western Hospital, Ontario
Canada

Mark S LeDoux MD PhD
Professor
Neurology, Anatomy
and Neurobiology
University of Tennessee Health
Science Center
Memphis, TN
USA

Irene Litvan MD
Raymond Lee Professor of Neurology
Director
Movement Disorder Program
Department of Neurology
University of Louisville
KY
USA

Kelly E Lyons PhD
Department of Neurology
University of Kansas Medical Center
Kansas City, KS
USA

Neil Mahant MD
Movement Disorders Clinic
Toronto Western Hospital, Ontario
Canada

Bala V Manyam MD
Adjunct Professor of Neurology
Southern Illinois University
School of Medicine
Springfield, IL
USA

Zoltan Mari MD
Johns Hopkins
University School of Medicine
Baltimore, MD
USA

William J Marks Jr MD
University of California
San Francisco, CA
USA

David E Martino MD
Sobell Department of
Movement Neuroscience
Institute of Neurology
University College of London
London
UK
List of contributors

Masao Matsuhashi
Human Motor Control Section
National Institute of Neurological Disorders and Stroke
Bethesda, MD
USA

Eldad Melamed MD
Director
Department of Neurology
Rabin Medical Center
Beilinson Campus, Petah Tikva
Israel and Sackler School of Medicine
Tel Aviv University
Israel

Leonard Verhagen Metman MD PhD
Associate Professor
Department of Neurology
Rush University Medical Center
Chicago, IL
USA

Gabriel F Mizraji
The Institute of Cognitive and Behavioural Neurology (INECO) and Buenos Aires Memory clinic
Extrapyramidal Diseases Section
Neurology Department
Centro Neurologico
Hospital Frances
Buenos Aires
Argentina

Eric S Molho MD
The Parkinson’s Disease and Movement Disorder Center of Albany Medical Center
Albany, NY
USA

John C Morgan MD PhD
Movement Disorders Program
Department of Neurology
Medical College of Georgia, and Department of Veterans Affairs Medical Center
Neurology Service
Augusta, GA
USA

Joy Muthipeedika MD DM
Movement Disorders Program
Department of Clinical Neurosciences
University of Calgary, Alberta
Canada

Markus Naumann MD
Professor of Neurology
Director
Department of Neurology and Clinical Neurophysiology
Klinikum Augsburg
Augsburg
Germany

Virinder Nohria MD PhD
Department of Neurology
University of Virginia
Charlottesville, VA
USA

John Nutt MD
Department of Neurology
Portland VA Medical Center
Portland, OR
USA

Elizabeth O’Hearn MD
Neurology and Neuroscience
Johns Hopkins School of Medicine
Baltimore, MD
USA

Michael S Okun MD
Associate Professor of Neurology
Department of Neurology
University of Florida
Gainseville, FL
USA

William Ondo MD
Professor of Neurology
Baylor College of Medicine
Houston, TX
USA
Fabienne Ory MD
Service de Neurologie
Centre Hospitalier Universitaire de
Toulouse
France

Ronald F Pfeiffer MD
Professor and Vice Chair
Department of Neurology
The University of
Tennessee College of Medicine
Memphis, TN
USA

Rajesh Pahwa MD
Department of Neurology
University of Kansas Medical Center
Kansas City, KS
USA

Spiridon Papapetropoulos MD PhD
Assistant Professor
Department of Neurology
University of Miami
Miller School of Medicine
Miami, FL
USA

George W Paulson MD
Movement Disorders Division
The Ohio State University
Medical Center
Columbus, OH
USA

Elizabeth L Peckham DO
National Institute of Neurological Disorders and Stroke
Bethesda, MD
USA

Joel S Perlmutter MD
Department of Neurology
Mallinckrodt Institute of Radiology
Program in Physical Therapy
Department of Anatomy and Neurobiology
Washington University in
St Louis, MO
USA

Carlos Portera-Cailliau MD PhD
Department of Neurology
University of California
Los Angeles, CA
USA

Peter P Pramstaller MD
Department of Neurology
Central Hospital and
Institute of Genetic Medicine
EURAC-Research, Bolzano-Bozen
Italy

Werner Poewe MD
Professor
Department of Neurology
University Hospital of Innsbruck
Innsbruck
Austria

Michael Pourfar MD
Assistant Professor of Neurology
North Shore University Hospital
Manhasset, NY
USA

Juan G Puig MD
Professor of Internal Medicine
Hospital La Paz
Universidad Autonoma
Madrid
Spain

Niall Quinn MD
Sobell Department of Motor Neuroscience and
Movement Disorders
UCL Institute of Neurology
London
UK

Brad A Racette MD
Department of Neurology and
American Association Advanced Center for Parkinson Research
Washington University School of Medicine
St Louis, MO
USA
List of contributors

Jan Raethjen
Department of Neurology
University of Kiel
Germany

Alex Rajput MD FRCP
Associate Professor of Neurology
University of Saskatchewan
Saskatoon
Canada

Ali H Rajput MBBS FRCP
Professor Emeritus of Neurology
University of Saskatchewan
Saskatoon
Canada

Bhaskar Rao MD
Department of Internal Medicine
University of Louisville, KY
USA

Olivier Rascol MD PhD
Service de Pharmacologie
Centre Hospitalier Universitaire de Toulouse
France

Stephen G Reich MD
Professor of Neurology
The Clair Zamoiski Segal and Thomas H Segal
Professor of Parkinson’s Disease Co-Director
The Maryland Parkinson’s Disease and Movement Disorders Center
The University of Maryland
School of Medicine
Baltimore, MD
USA

Sharon C Reimold MD
Department of Cardiology
UT Southwestern Medical Center
Dallas, TX
USA

Fredy J Revilla MD
Assistant Professor of Neurology
Department of Neurology
University of Cincinnatti
Cincinatti, OH
USA

Irene Hegeman Richard MD
Associate Professor of Neurology and Psychiatry
University of Rochester
School of Medicine and Dentistry
Rochester, NY
USA

Sarah Pirio Richardson MD
Parkinson’s Disease and Movement Disorders Program
Department of Neurology
University of New Mexico
Albuquerque, NM
USA

David P Richman MD
University of California
Davis, CA
USA

David Riley MD
Neurological Institute
University Hospitals
Cleveland, OH
USA

Susie I Ro MD
Department of Neurology
Beth Israel Deaconess Medical Center
Boston, MA
USA

Robert L Rodnitzky MD
Professor and Chair
Department of Neurology
University of Iowa Carver
College of Medicine
Iowa City, IO
USA
Ramon L Rodriguez MD
Associate Professor
Director
Clinical Trials for Movement Disorders
Department of Neurology
University of Florida
Gainesville, FL
USA

Keith Saxon
Laryngeal and Speech Section
National Institute of Neurological Disorders and Stroke
Bethesda, MD
USA

Alfons Schnitzler MD
Department of Neurology
University Hospital Düsseldorf
Germany

Axel Schramm MD PhD
Department of Neurology
University of Erlangen
Germany

Kapil D Sethi MD FRCP
Movement Disorders Program
Department of Neurology
Medical College of Georgia, and
Department of Veterans Affairs Medical Center
Neurology Service
Augusta, GA
USA

Michael Samuel MD
Departments of Neurology
East Kent Hospitals
NHS Trust, and King’s College Hospital
London
UK

Ana Sanchez MD
Fellow
Epilepsy
University of Maryland School of Medicine
Baltimore, MD
USA

Joohi Shahed MD
Parkinson’s Disease Center and
Movement Disorders Clinic
Baylor College of Medicine
Houston, TX
USA

Kathleen M Shannon MD
Associate Professor
Department of Neurological Sciences
Rush University
Senior Attending Physician
Rush University Medical Center
Chicago, IL
USA

Hiroshi Shibasaki MD
Human Motor Control Section
National Institute of Neurological Disorders and Stroke
Bethesda, MD
USA

Lisa M Shulman MD
Associate Professor of Neurology
Co-Director
University of Maryland Parkinson’s Disease and Movement Disorders Center, University of Maryland School of Medicine
Baltimore, MD
USA

Andrew Siderowf MD MSCE
Parkinson’s Disease and Movement Disorders Center
Philadelphia, PA
USA

Carlos Singer MD
Professor of Neurology
Department of Neurology
University of Miami
Miller School of Medicine
Miami, FL
USA
List of contributors

Tarik Slaoui MD
Service de Neurologie
Centre Hospitalier Universitaire de Toulouse
France

Jason Speir MD
Movement Disorders Program
Department of Neurology
Medical College of Georgia, and
Department of Veterans Affairs Medical Center
Neurology Service
Augusta, GA
USA

Mark Stacy MD
Division of Neurology
Duke University Medical School
Durham, NC
USA

Michaela Stampfer-Kountchev MD
Department of Neurology
University Hospital of Innsbruck
Innsbruck
Austria

Thyagarajan Subramanian
Professor of Neural and Behavioral Sciences and Director
Movement Disorders Program
Penn State University
College of Medicine
Hershey, PA
USA

S H Subramony MD
Department of Neurology
University of Mississippi Medical Center
Jackson, MS
USA

Oksana Suchowersky MD FCPC
Movement Disorders Program
Department of Clinical Neurosciences
University of Calgary, Alberta
Canada

Dan Tarsy
Department of Neurology
Beth Israel Deaconess Medical Center
Boston, MA
USA

James Tetrud MD
The Parkinson's Institute
Sunnyvale, CA
USA

Philip Thompson PhD
Department of Neurology
Royal Adelaide Hospital
University Department of Medicine
University of Adelaide
South Australia

Lars Timmermann MD PhD
Department of Neurology
University Hospital Cologne
Germany

Rosa J Torres
Hospital La Paz
Universidad Autonoma
Madrid
Spain

Babak Tousi MD
Clinical Assistant Professor of Medicine
Cleveland Lerner College of Medicine
Case Western Reserve University
Cleveland, OH
USA

Joel M Trugman MD
Department of Neurology
University of Virginia
School of Medicine
Charlottesville, VA
USA

Ryan J Uitti MD
Department of Neurology
Mayo Clinic Jacksonville
Jacksonville, FL
USA
Alfonso Verdu MD
Pediatric Neurologist
Universitario Gregorio Marañon
Madrid
Spain

L Voulters MD
Department of Neurology
University of Mississippi
Medical Center
Jackson, MS
USA

Cheryl Waters MD
Neurological Institute
Columbia University
New York, NY
USA

Nidhi K Watson MD
Fellow
Department of Neurological Sciences
Movement Disorders Section
Rush University Medical Center
Chicago, IL
USA

Robert Weeks PhD
Department of Neurology
King’s College Hospital
London
UK

William J Weiner MD
Professor and Chairman
Department of Neurology
University of Maryland School of Medicine
Baltimore, MD
USA

Gregor K Wenning MD PhD
Clinical Department of Neurology
Medical University Innsbruck
Innsbruck
Austria

N Robb Whaley MD
Department of Neurology
Mayo Clinic Jacksonville
Jacksonville, FL
USA

Zbigniew K Wszolek MD
Consultant
Department of Neurology
Mayo Clinic
Jacksonville, FL, and
Professor of Neurology
Mayo Clinic College of Medicine
Rochester, MN
USA

Theresa A Zesiewicz MD
Associate Professor of Neurology
Parkinson’s Disease and Management Disorders Center
University of South Florida
Tampa, FL
USA
Preface

The case-by-case method is arguably the most important teaching tool in medicine. This is particularly true of neurology and especially the area of movement disorders where diagnosis largely depends on a careful, detailed history and examination coupled with pattern recognition. It is with this background in mind that *Movement Disorders: 100 Instructive Cases* was conceived. This is not intended to be a textbook but the number and diversity of cases covers a broad spectrum of movement disorders ranging from Parkinson’s disease and parkinsonian syndromes, to ataxia, to hyperkinetic disorders such as tremor, myoclonus, chorea and dystonia. While some cases are zebras, others demonstrate common movement disorders and the link is that all have at least one important teaching point. Although there is some duplication of cases, this can be justified as each author puts on his or her unique spin, but more importantly, repetition is one of the most valuable teaching and learning techniques.

I am appreciative to the many authors of this book who share my enthusiasm for teaching and learning, for contributing such “instructive” cases. Pete Stevenson, formerly with Martin Dunitz publishers, got this project started. I am particularly grateful for the editors at Informa who saw this to completion: Lindsay Campbell, Alexa Chamay Berrier, and Alan Burgess, for their patience and encouragement. I owe a debt of thanks to William J Weiner, chairman of Neurology at the University of Maryland, who helped turn this book from an idea into reality by his guidance, teaching, wisdom, enthusiasm and support—qualities he has consistently demonstrated since I came to the University of Maryland in 2002.

Truth be told, this book, with so many chapters, videos, figures and authors, could not have been completed if it were not for the outstanding organizational skills of my secretary, Ms Nandy Yearwood. My parents, Edith and Henry Reich, have had at the same time little and everything to do with this book and I am pleased to dedicate it to them with appreciation of their love and support. My wife, Dana Boatman, shares in the dedication. Unfailingly supportive, even when undeserved, she has read many of the chapters, listened patiently and enthusiastically to more details of *Movement Disorders: 100 Instructive Cases* than she ever wanted to know, and never doubted that this could be finished, even when I did. We are the proud parents of a son, Daniel, who serves to remind us daily that while professional accomplishments are important, some things are more important.

Finally, and most importantly, I know that I speak for all authors when I express tremendous gratitude to the patients who graciously allowed their cases and images to be shared in order to educate physicians in the care of patients with movement disorders.

*Stephen G Reich*
Familial dystonia, parkinsonism, ataxia, and dementia: what is it?

Christine Brefel-Courbon, Nelly Fabre, Fabienne Ory, Tarik Slaoui, Cyril Goizet, Pierre Labauge, and Olivier Rascol

CASE PRESENTATION

A right-handed woman was examined for the first time in 1986 at age 47 years. She complained of tremor, interfering with writing and other activities of daily life. She had a family history of an unknown movement disorder with probable autosomal dominant transmission (her father and a sister). Tremor was first noticed in the right arm at age 41 and gradually worsened, involving both sides within 1 year. On examination, the tremor was bilateral and complex, mainly affecting posture and action with a mild rest component which was more obvious in the lower limbs. Mild right hemi-parkinsonism was also present, with cogwheel rigidity at the wrist and loss of right arm swing while walking. Reflexes were pathologically brisk. There were no prominent cerebellar signs at this stage, except mild slurring of speech and a broad-based gait. Sensory examination, eye movements, and cognition were normal. The patient complained of several episodes of depression in past years and was depressed at the time of first examination.

Over the next few years, her condition progressively deteriorated. Cerebellar signs became more prominent, with dysarthria, ataxia, and dysmetria. Pyramidal signs also became obvious, with bilateral extensor plantar responses. At age 57 cognitive impairment was first noticed, with mild frontal deficits affecting immediate and visual memory and poor verbal fluency. At age 64 (see video, Case 1), she developed severe spontaneous abnormal movements, mainly of the dystonic type, predominating in the left hemibody. Dystonia was associated with some degree of choreic movement, mainly in the face and tongue. Severe parkinsonian signs (bradykinesia and rigidity) were present in the right hemibody. Gait was markedly unsteady, mainly because of left foot dystonia and postural instability, which did not allow assessment for cerebellar ataxia. There were marked frontal cognitive deficits (difficulties in memory, mental calculation, and attention) and behavioral changes. Within 2 years, she became bedridden and demented, with urinary incontinence, unintelligible speech, and severe dystonia.

Over the course of her illness, several medications were tried. At the beginning, propranolol produced partial benefit for the tremor. Levodopa was not effective.
Lateron, levotonine produced no improvement in cerebellar signs. Antidepressants induced a modest and transient benefit on mood. During the last 4 years, low doses of haloperidol had reduced the abnormal choreic movements.

Routine hematological and biochemical studies were normal except for mildly increased liver enzymes. Copper studies were normal. Liver ultrasound was normal. Oculography showed normal saccades, but abnormally slow, smooth pursuit. Autonomic function tests were normal. Brain magnetic resonance imaging (MRI) showed cortical and subcortical atrophy involving the cerebellum and brainstem, with abnormal T2 signal in the basal ganglia and a low signal ribbon all along the cerebral cortex suggesting iron overload (Figure 1.1).

Genetic investigations showed that her father (deceased), paternal aunt (deceased), one sister, one brother, and three cousins also presented a complex mixture of cerebellar, pyramidal, and ‘extrapyramidal’ motor and cognitive signs. Genetic tests for spinocerebellar ataxia (SCA) types 1, 2, 3, and 6, dentatorubro pallidoluysian atrophy (DRPLA), and Huntington’s disease were performed and all were negative.

The affected patient’s sister died. Autopsy revealed intranuclear iron inclusions in neurons and glia in most gray and white matter areas of the brain. Moreover, the same iron inclusions were observed in the skin (fibroblasts) and muscle. Molecular genetic study revealed a CT dinucleotide insertion (at position 498–499) mutation in exon 4 of the ferritin light polypeptide, leading to the diagnosis of ferritinopathy. Muscle biopsy was then performed in the patient and demonstrated intranuclear iron inclusions in fibroblasts. Genomic DNA was extracted from venous blood lymphocytes and the same mutation as found

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**Figure 1.1** MRI demonstrates abnormal T2 (A) bilateral hypointense caudate and lenticular signals associated with a central hyperintense lenticular signal and T1 (B) hyperintense lenticular signals.
in her sister was detected. The same mutation was also discovered in other clinically affected members of her family.

**DISCUSSION**

Here we describe a patient with a progressive neurological disease beginning with mixed tremor, followed by cerebellar dysfunction, parkinsonism, dystonia, and subcortical dementia. Investigations revealed iron accumulation in the basal ganglia, cortex, and in muscle. The family history was consistent with the diagnosis of hereditary iron overload disease. Neuroferritinopathy is a recently recognized rare autosomal dominant disorder that results in abnormal aggregates of iron and ferritin in the brain. Neuroferritinopathy has been associated with an adenosine insertion at position 460–461, or an insertion of two nucleotides at position 498–499, or a missense mutation in the L-ferritin gene.

Onset of the disease occurs between the second and the fifth decade of life. Abnormal movements (chorea, dystonia, bradykinesia, rigidity) and dysarthria are common. Postural tremor and cerebellar signs may also be observed. Cognitive impairment is generally limited to subcortical frontal lobe dysfunction, but can progress to dementia in some patients.

Other neurological diseases share clinical characteristics with neuroferritinopathy. Autosomal dominant cerebellar ataxias such as SCA2 and SCA3 and DRPLA include cerebellar ataxia, postural tremor, chorea, parkinsonism, and dementia. Pantothenate kinase-associated neurodegeneration (PKAN), formerly called Hallervorden–Spatz syndrome, a neurodegenerative disorder with iron accumulation, is also characterized by cerebellar ataxia, dystonia, parkinsonism, and dementia. Aceruloplasminemia, another neurodegenerative disorder with iron accumulation, is a rare recessive disease, responsible for involuntary movements, cerebellar ataxia, and dementia. Although genetic and pathophysiologic pathways of brain iron accumulation are heterogeneous, these overload diseases lead to similar clinical signs such as cerebellar ataxia, parkinsonism, abnormal movements, and dementia.

The diagnosis of neuroferritinopathy is not easy because of the heterogeneous clinical presentation. Serum ferritin does appear to be a good predictive test because ferritin levels have been reported low or normal in patients. However, in our family, iron deposits were observed outside the nervous system in the liver, kidney, muscle, and skin. Hence, muscle or skin biopsy could be helpful for diagnosis.

This case is instructive because it demonstrates the clinical and radiographic features of the rare disorder neuroferritinopathy, an autosomal dominant degenerative disease combining various degrees of cerebellar, parkinsonian, pyramidal, frontal, and choreodystonic signs. It is one of several disorders leading to pathological iron accumulation. Neuroferritinopathy can be diagnosed using skin or muscle biopsy along with molecular confirmation.
REFERENCES


Legend to video

Case 1  The video of the patient at age 64 demonstrates oromandibular dystonia, dysarthria, bradykinesia, and rigidity (right hemibody more than left), left hemidystonia, difficulty walking, postural instability, and saccadic pursuit eye movements.
Primary dystonia: a surgical disease?

Helen Bronte-Stewart and Shannon Kilgore

CASE PRESENTATIONS

Case 2.1

This 30-year-old Japanese man experienced difficulty writing with his right hand at age 7, which progressed to more severe dystonia of the right arm. At age 17, he had a left thalamotomy in Japan, which significantly improved his dystonia. By age 28, however, his left arm was as impaired as his right side had been. When excited, he occasionally had difficulty speaking in both English and Japanese. After a streptococcal pharyngitis, he developed severe neck and shoulder pain and retrocollis and his gait worsened. Trials of levodopa, benzodiazepines, and botulinum toxin offered minimal to no benefit. There was a strong family history of a movement disorder on the paternal side and his paternal aunt had also undergone thalamotomy.

Examination showed severe left arm, trunk, and neck dystonia, with rapid mobile dystonic movements of the head and left arm (see video, Case 2.1). He was unable to lie, sit, stand, or walk without disabling movements. The movement subscore of the Burke Fahn Marsden Dystonia Rating Scale (BFMDRS) score was 44. Magnetic resonance imaging (MRI) of the brain revealed only the left thalamotomy. Testing revealed a GAG946 mutation in one allele of the DYT1 gene.

The patient underwent right globus pallidus interna (GPI) deep brain stimulation (DBS). He experienced immediate but transient improvement for several days. His stimulator was turned on 1 week postoperatively. One month after starting DBS, he was back at work and exercising. He also had significant improvement in left hand function. The BFMDRS movement subscore was 1 at 18 months’ follow-up.

Case 2.2

This 21-year-old Hispanic female had had DYT1 dystonia since age 11 years. Her dystonia began with worsening handwriting and progressed to difficulty with movement of her left side. At age 18, she had sudden worsening of axial
dystonia and had since been unable to sit, stand, or walk erect. She became completely disabled. Family history was positive for two cousins, a paternal aunt, and her brother, all having dystonia. She had tried levodopa without benefit. Examination showed severe generalized dystonia of the neck, trunk, and limbs (see video, Case 2.2). The BFMDRS movement score was 84.

The patient underwent a right posteroventral pallidotomy. She noticed immediate improvement in her ability to lie straight and control her left hand. Within 6 weeks, she was able to walk without falling. Four months later, she was able to stand, as well as use her left hand to feed herself, provide personal hygiene, and write. She was offered a left GPi DBS procedure but requested a pallidotomy, which was performed four-and-a-half months after the right side procedure. Ten days later, she was able to ambulate normally. The patient noted some initial dysarthria not evident to others. By 3 months she was able to run, and there was no evidence of dystonia on examination. One year postoperatively, her speech was normal to the examiner, although the patient complained of difficulty projecting her voice. Her BFMDRS score remains 0 after 4 years.

**DISCUSSION**

Dystonia is a movement disorder characterized by involuntary, sustained muscle contractions with twisting, and repetitive movements. Dystonia may affect only certain regions of the body (focal dystonia) or may be generalized. Primary generalized dystonia is often hereditary; the DYT1 mutation is positive in more than 50% of early-onset cases. Secondary generalized dystonia usually results from a metabolic disorder or structural brain insult.

Drug treatment for generalized dystonia is often unsatisfactory or is limited by side-effects. Surgical treatments for dystonia, such as thalamotomy, pallidotomy, and DBS have improved in their benefit-to-risk ratio through a combination of technological advances and a better understanding of the role of the basal ganglia in dystonia. If surgery is contemplated, it is critical to determine whether the etiology of dystonia is primary or secondary. These two cases demonstrate that primary dystonia may respond well to either bilateral pallidotomy or DBS of the internal segment of the globus pallidus (GPi).

The excellent outcomes in these patients, both with DYT1 generalized dystonia, support a growing body of literature concerning the effectiveness of pallidotomy and GPi DBS for primary dystonia. Treatment of primary generalized dystonia with bilateral pallidotomy has shown a 60–80% improvement in the BFMDRS and a similar improvement in the Unified Dystonia Rating Scale (UDRS). Although there was no cognitive or bulbar compromise in our patient after bilateral pallidotomy, this has been reported and is the main reason why most centers now perform bilateral DBS for generalized dystonia. Several studies have shown that bilateral GPi DBS is a very effective treatment for primary generalized dystonia in adults and children. The BFMDRS movement scores improved from 47 to 100% after 12 months of DBS. Disability scores also improved significantly, and there were few side-effects. Axial and cervical dystonia have also responded well to bilateral GPi DBS. Most studies of pallidotomy and GPi DBS report a gradual and cumulative improvement in dystonia, unlike the immediate improvement seen after DBS for Parkinson’s disease.
Secondary dystonias do not appear to respond as well to pallidotomy and GPi DBS compared to primary dystonias.\textsuperscript{7,16,17} An exception to this appears to be tardive dystonia, with recent reports suggesting benefit from GPi DBS.\textsuperscript{18–20} Limited data suggest that the ventrolateral thalamus may be a more promising target for the treatment of secondary dystonias, but more careful, prospective, randomized studies are needed.

These two cases are instructive because they demonstrate the clinical features of DYT1 dystonia, but, moreover, emphasize the potential of surgical therapy, either pallidotomy or GPi DBS, to offer significant improvement.

REFERENCES
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Legend to video

Case 2.1 This video shows a 30-year-old man with DYT1 positive generalized dystonia before deep brain stimulation of the right globus pallidus interna (GPI) and 18 months after the procedure. The patient had had a left thalamotomy in Japan at the age of 17.

Case 2.2 This video shows a 21-year-old woman with DYT1 positive generalized dystonia before, and 10 days and 1 year after, bilateral pallidotomy. Note the early improvement in the patient’s clinical signs.
A curable form of dystonia not to be missed

Stephen E Grill

CASE PRESENTATION

A 46-year-old woman was seen for a movement and gait disorder. She was the product of a full-term, normal pregnancy. She was delayed in her motor milestones and did not sit or walk until age 19 months, yet her language and cognitive milestones were normal. During childhood, she did not keep up with her friends in sports activities and tended to walk ‘hunched over’, with inversion of the feet. She denied muscle weakness. At age 14, she underwent a pneumoencephalogram and electroencephalogram (EEG), which were normal. She was placed on ephedrine, which she thinks helped minimally. Her life was restricted and she used a wheelchair, especially for long distances.

Her medical history includes only congenital ptosis and hypertension. Family history is significant for a nephew diagnosed with dystonia at the age of 11, who was noticed to have an ‘unusual’ gait at the age of 5 years. He also had congenital ptosis. She also has twin sons, diagnosed with a movement disorder, who were confined to wheelchairs.

On examination, she had left ptosis. There was an extra digit on the left foot, which was webbed, and the 4th and 5th digits on the right foot were also webbed. Speech was clear. Neck and shoulder movements were normal. There was increased tone in all extremities, with cogwheeling of the right arm. There were dystonic postures and movements of all limbs. When writing, the right hand involuntarily flexed, and simultaneously there was increased foot inversion. The gait was difficult, with flexion of the trunk and severe bilateral inversion and circumduction of the feet (see video, Case 3).

She was begun on carbidopa/levodopa 25/100, half a tablet twice a day, and noticed dramatic improvement in all of her symptoms over the next few weeks. When seen in follow-up 6 years later, she no longer used her wheelchair. She went back to school, earned her master’s degree, and was working as a marriage counselor. Her handwriting was greatly improved. She still had some difficulty with her gait, particularly when fatigued. Examination revealed mild dystonic finger movements but her handwriting was significantly improved. The gait was slow and there was slight right foot circumduction.
The carbidopa/levodopa was increased to 25/100, one tablet twice a day (see video).

Her nephew had also been started on carbidopa/levodopa, with improvement of his gait, and her two sons were also taking carbidopa/levodopa and were walking and no longer confined to wheelchairs.

DISCUSSION

This patient has dopa responsive dystonia (DRD), a disorder which typically presents in the first decade of life. DRD is a progressive disorder preferentially affecting the legs and which may eventually spread to other muscles. The dystonia and gait disorder often have diurnal variations, worsening in severity during the latter half of the day. Parkinsonian features of rigidity and bradykinesia and the marked response to levodopa may incorrectly lead to a diagnosis of juvenile Parkinson’s. Because of the abnormal gait and the presence of hyperreflexia, children with DRD may be incorrectly diagnosed with spastic diplegia.

Dopa responsive dystonia is an autosomal dominantly inherited disorder with incomplete penetrance, which is higher in females. The cause is mutations in the guanosine triphosphate (GTP) cyclohydrolase I (GCH1) gene, located on chromosome 14. GCH1 is the rate-limiting enzyme in the synthesis of tetrahydrobiopterin, an essential cofactor for tyrosine hydroxylase, which in turn is the rate-limiting enzyme in dopamine synthesis. Hence, DRD is due to functionally low dopamine levels.

The diagnosis of DRD is based on the clinical characteristics as well as a striking response to small doses of levodopa with nearly complete resolution of symptoms. Because the phenotype can result from one of several mutations, using genetic analysis as a screening test is difficult. Since both fluorodopa- and 2β-carbomethoxy-3β-(4-iodophenyl)tropane (β-CIT)-positron emission tomography (PET) are normal in DRD, they can be used to differentiate it from juvenile Parkinson’s, but this is rarely necessary.

This case is instructive by demonstrating the importance of always considering dopa responsive dystonia in children as well as adults with dystonia, parkinsonism, or a gait disorder. The diagnosis of DRD hinges on demonstrating a significant response to levodopa, which is often dramatic.

REFERENCES

Legend to video

Case 3 Prior to treatment with levodopa, the gait is severely dystonic with bilateral foot inversion and circumduction, involuntary flexion of the trunk, and dystonia of the fingers. When writing, there is involuntary, dystonic wrist flexion. After treatment with levodopa, the gait is markedly improved with only mild foot inversion. The finger and hand movements are also much improved and the handwriting appears normal.
A neurology consultation for Parkinson’s on the psychiatry service

J Eric Ahlskog

CASE PRESENTATION

A 52-year-old woman with a 12-year history of Parkinson’s disease (PD) was referred with severe anxiety, depression, and parkinsonism. She was initially evaluated in the emergency room and then admitted to the psychiatric unit. The psychiatric evaluation documented a tearful anxious demeanor, variable agitation, tremulousness, a very soft voice, slow, stiff movements, and an unsteady, shuffling gait. She also complained of dyspnea and cramps. She was noted to have vegetative signs of depression with insomnia, anorexia, and 12-pound weight loss. The psychiatric diagnosis was agitated depression.

She had a 4-year history of depression and anxiety, increasing since her divorce 2 years previously. She lived alone. As recently as 6 months prior, her psychiatric problems and PD had been only intermittently disabling; she had still been able to dine out with friends plus engage in a variety of hobbies, including gardening, cooking, and crafts. This lifestyle, however, had been increasingly disrupted by bouts of anxiety that started to recur on a regular basis; in the past year she had been briefly hospitalized elsewhere several times for ‘panic attacks’.

She most recently had been admitted to her community hospital several weeks previously because of marked anxiety attacks associated with shortness of breath. At that time, she had been on carbidopa/levodopa 25/100, two tablets every 3–4 hours (800–1000 mg daily) and 1.75 mg pergolide daily for her parkinsonism; her psychiatric symptoms had been treated with serzone, nortriptyline, and alprazolam. Because of concern that levodopa was causing or exacerbating her anxiety and agitation, her community physicians reduced the dosage to 300 mg daily. Pramipexole was initiated in place of pergolide, but seemingly increased her anxiety. She was switched to ropinirole, slowly raised to 10 mg daily, plus entacapone 200 mg four times daily. Her psychiatric symptoms persisted and she was switched from serzone to paroxetine 20 mg daily; lorazepam 0.5 mg every 8 hours was added to the alprazolam 0.5 mg twice daily. After discharge and while maintained on these medications, her psychiatric
symptoms continued to escalate, as did her parkinsonism, leading to the current psychiatric hospitalization.

Shortly after the current admission, the psychiatric nursing staff documented that she was ‘increasingly anxious and started hyperventilating … unable to get her breath.’ She ambulated with a walker and could barely move her right leg at times, and sometimes would ‘freeze up’, and complained of ‘cramping pain all over her body’. They noted a helpless demeanor, poor eye contact, a flat affect, and variability in her ability to walk and speak. She complained that paroxetine made her ‘nervous’, stating that her depression was reactive to the physical disability; consequently, the psychiatry staff held her paroxetine. They switched her to clonazepam 0.5 mg three times daily in place of the lorazepam and alprazolam. Based on her observation that ropinirole and entacapone had not been helpful, they were discontinued, and she was treated with carbidopa/levodopa monotherapy, raising the dose to one-and-a-half tablets of 25/100 (immediate-release), four times daily.

Admission blood work, including arterial blood gases, was normal, as was a chest X-ray, electrocardiogram, pulmonary function tests, and computed tomography (CT) head scan. An internal medicine consultation was unremarkable and no primary cardiopulmonary cause was found for her complaints of dyspnea, including no evidence of pergolide-related lung or heart disease. She had previously had an unremarkable magnetic resonance imaging (MRI) of the brain.

The neurology department was consulted, finding her slightly tearful, mildly agitated, and complaining of extreme nervousness, shortness of breath, tremor, and stiffness. She reported a several-year history of fluctuations in her levodopa response; however, by history, her favorable responses to levodopa had attenuated in the last couple of months.

She was examined 5 hours after her last dose of carbidopa/levodopa. She had prominent facial hypomimia and severe hypokinetic dysarthria with hypophonia. She required assistance to rise from her wheelchair. She had marked gait freezing and retropulsion, and even with assistance was barely able to walk. Moderate limb rigidity and reduced speed and amplitude of alternate motion rate were noted, left more than right. Her prominent upper limb rest tremor abated with posture and action.

In summary, this lady had been severely disabled by a combination of anxiety, sometimes panic, dyspnea, and parkinsonism. The symptoms evolved from paroxysmal to nearly persistent with recent medication changes.

DISCUSSION

At the time of the initial neurologic consultation, she was subsequently administered two-and-a-half carbidopa/levodopa 25/100 (immediate-release) tablets and re-examined an hour later. By that time, she could rise and walk without assistance, her tremor had abated, and her parkinsonism was markedly improved. Moreover, she also reported a marked change in her psychiatric symptoms, with near resolution of the anxiety, as well as the dyspnea. It was therefore suspected that her psychiatric symptoms and dyspnea had their basis in PD and appeared to be levodopa responsive. This is in contrast to the initial
concern of her physicians that her PD drugs were exacerbating her anxiety. She was discharged a few days later on a more aggressive carbidopa/levodopa schedule, plus low dose paroxetine and an unchanged clonazepam dosage. She returned a few weeks later, reporting marked improvement in all of her symptoms, confirming that her anxiety and dyspnea were levodopa responsive PD symptoms. A therapeutic dose of a dopamine agonist (pramipexole) was later added to better control her response fluctuations. She was last seen in the clinic 4 years later, with symptoms still largely controlled, although with occasional, but tolerable off-states; her social and recreational life had returned.

A wide variety of non-motor symptoms occur in PD, which are levodopa responsive; anxiety and related symptoms, as well as dyspnea, are among the more common. An important clue is fluctuation of symptoms, whether motor or non-motor, especially if time-locked to levodopa off-states. In this case, observation after a supra-threshold dose of carbidopa/levodopa at the time of the neurologic consultation provided important evidence.

![Diagram](image)

Figure 4.1 An insufficient levodopa dose, as shown by the lower curve (dashed), does not improve Parkinson’s symptoms because it fails to elevate brain levodopa and dopamine levels above the hypothetical threshold. A supra-threshold dose (upper curve) leads to resolution of symptoms, but with later recurrence when the levels decline. The appropriate treatment strategy is to determine a levodopa dose that consistently exceeds this threshold and then administer it at overlapping intervals that minimize infra-threshold symptoms. © Mayo Clinic, 2005.
When PD patients are doing very poorly, as in this woman’s case, treatment is best focused on carbidopa/levodopa. Her carbidopa/levodopa had been reduced and she was nearly continuously in a levodopa off-state with both motor and non-motor problems, including anxiety, panic, and dyspnea. PD patients with levodopa fluctuations often experience symptoms in a somewhat all-or-none manner, as if there is a levodopa dose threshold. Thus, the most severely fluctuating patients often report being either ‘on’ or ‘off’, without much in between. If underdosed (below threshold), the symptoms are fully present, whereas a levodopa dose that exceeds the threshold leads to complete resolution; this is illustrated in Figure 4.1. The appropriate initial strategy is to identify a levodopa dose that consistently kicks in, and then administer that dose at intervals that match the response duration. Adjunctive drugs can subsequently be added to smooth and improve that response, including dopamine agonists or catechol-O-methyltransferase inhibitors.

This case is not meant to imply that all anxiety in PD is levodopa responsive or that depression is best treated with adjustment of PD drugs. However, it is crucial to recognize that certain non-motor symptoms may be levodopa responsive and consider that when appropriate.

This case is instructive because it illustrates several issues important to PD treatment, including the following:

- PD not only is a motor disorder, but also includes a variety of non-motor symptoms.
- Anxiety and dyspnea are among the common disabling non-motor symptoms.
- Anxiety is rarely caused or exacerbated by PD drugs, despite the fact that they stimulate catecholamine systems.
- These non-motor PD symptoms are often very levodopa responsive.
- The non-motor symptoms may fluctuate with the motor symptoms of parkinsonism, and the temporal association is an important clue. Patients often fail to recognize this temporal relationship.
- Both motor and non-motor symptoms may sometimes respond to dopamine replacement therapy in an all-or-none manner, as if there is a dose threshold. Off-phase symptoms may become persistent if PD drugs (especially levodopa) are reduced below threshold.
- A single supra-threshold dose of carbidopa/levodopa, followed by observation in the office or at the bedside, may help to confirm the origin of levodopa responsive non-motor symptoms.
- When PD symptoms are severe and patients are underdosed, optimization of carbidopa/levodopa schedules is an appropriate first step.

REFERENCES

Facial twitching: what is it and how do you treat it?

Carlos Portera-Cailliau

CASE PRESENTATION

A 55-year-old woman presented for a second opinion regarding a diagnosis of hemifacial spasm (HFS) because the spasms seemed to be spreading to the contralateral side. The patient’s symptoms had begun 3 years previously with intermittent twitching of the left eyelid. She was diagnosed with blepharospasm. Several months following this diagnosis she began to experience twitching of the left eyebrow, cheek, lip, and chin. She had never been exposed to dopamine receptor blocking drugs. Brain magnetic resonance imaging (MRI) with contrast revealed no abnormalities or enhancement within the facial nerve on the left side, but a prominent blood vessel was described around the root exit zone. In the absence of other symptoms in her neck, trunk, limbs, or contralateral face, she was diagnosed with left HFS.

Within a year of the initial symptoms, she was referred to an ophthalmologist for botulinum toxin injections, which were administered every 3 months and initially provided almost complete relief of her symptoms for at least 2 months. The only side-effect was a mild left facial droop, so she later began to receive injections of small amounts of botulinum toxin into muscles of the right face, presumably to make her face more symmetric. In the few months preceding her visit to our institution, the patient began to experience twitching of the right eye. The last injection of botulinum toxin had been one-and-a-half months prior to our initial evaluation. The patient had several questions. What was her diagnosis? Were her symptoms truly spreading to the previously normal, right side of the face, and was that typical of HFS? Was there a role for surgery in the treatment of HFS?

On examination at her first visit (see video, Case 5, first segment), the patient had occasional contractions of muscles around her chin and the corner of her mouth on the left side (one every several seconds), which occurred every time she blinked. There were no muscle contractions on the right side. There was no evidence of tremor or other involuntary movements elsewhere in the face, neck, trunk, or limbs. A lower motor neuron facial paresis was apparent on the left face. The rest of the neurological examination was normal. Given the paucity of signs and symptoms, due to recent botulinum toxin injections we asked the patient to return to the clinic at a later date, before her next set of injections, as it
was not possible for us to determine the nature of the problem or whether it was bilateral.

The patient returned to the clinic 6 weeks later. Subjectively, she had felt an increase in facial twitching on the left side, but none on the right. On examination (see video, second segment), she had frequent (once per second) contractions of muscles in the upper and lower left face. The facial spasms were more noticeable than in the previous visit and involved the eyelid, the perioral region, and the chin synchronously. We observed no muscle contractions on the right side of the face. There was still a left facial droop, which we attributed to the residual effects of botulinum toxin. Our final diagnosis was left hemifacial spasm.

DISCUSSION

Hemifacial spasm is characterized by involuntary tonic and clonic contractions of muscles innervated by the facial nerve.\(^1\) It is an uncommon movement disorder, with an annual incidence of almost 1 per 100,000. The prevalence of HFS in women is nearly twice that in men.\(^2\) Most cases of HFS are sporadic, though familial occurrences have been described.\(^3\) Patients usually present in their fifth decade of life. In most patients, the initial complaint is of forceful, unilateral eye closure due to contraction of the orbicularis oculi muscle. This can interfere with vision and cause embarrassment. During a period of months to years, other muscles innervated by the ipsilateral facial nerve, including muscles in the cheek, perioral region, and chin, become involved in a synchronous manner. Tinnitus may occur as a consequence of stapedius muscle contraction. Bilateral HFS can occur years after the initial onset of symptoms, but is relatively uncommon.\(^4\) When bilateral, the facial contractions on both sides are asynchronous. The facial spasms are aggravated by stress and fatigue, and may persist during sleep. HFS is a chronic condition that rarely resolves spontaneously. Lower motor neuron facial weakness can be seen in long-standing cases, as well as synkinesia.

It is important to distinguish HFS from other involuntary facial movements such as myokymia, tics, blepharospasm, psychogenic facial spasms, focal seizures, and tardive dyskinesia.\(^5\) Establishing the correct diagnosis is critical, to institute the appropriate treatment. A careful neurologic examination will suffice in most cases. If the patient is already receiving treatment, it may be useful to ask the individual to return to the office for a second visit after treatment has been withheld or after its effects have worn off, as in the case presented here. HFS is caused most commonly by an irritative lesion of the facial nerve, such as an atherosclerotic or ectatic intracranial artery that compresses the ipsilateral 7th cranial nerve.\(^6,7\) Less frequently, the underlying cause of irritation is a multiple sclerosis plaque or a mass lesion such as a tumor, cyst, or aneurysm. Thus, neuroimaging is recommended for all patients with HFS with high resolution MRI and magnetic resonance angiography (MRA).\(^6\)

Treatment options for HFS include oral medications, botulinum toxin injections, and decompressive surgery.\(^8\) The efficacy of oral medications is transient, and their use is limited by side-effects. Carbamazepine, anticholinergics, baclofen, clonazepam, gabapentin, and haloperidol have been studied in small clinical
Facial twitching

trials, but large placebo-controlled trials of oral drugs have not been carried out in HFS. The treatment of choice for HFS is injection of botulinum toxin to the affected facial muscles. A small number of placebo-controlled double-blind studies have shown that botulinum toxin results in good to excellent improvement in symptoms in 75–100% of patients. The mean duration of benefit is 3 months. The drug is well tolerated, with infrequent and transient side-effects (diplopia, facial weakness, dry eyes, ptosis). Immunoresistance to botulinum toxin is rare in HFS patients, presumably because of the low doses administered. Microvascular decompression of the facial nerve at the cerebellopontine angle results in marked improvement in a majority of patients. However, recurrence rates of up to 20% and surgical side-effects and complications (e.g. hearing loss) may be unacceptable to some patients.

This case is instructive because it:

- demonstrates the utility of having patients return to the office when medications have worn off, to help establish the diagnosis, or side-effects;
- is a representative example of hemifacial spasm, which is a peripheral nerve movement disorder, manifested by involuntary contraction of muscles on the same side of the face; HFS can significantly affect quality of life by interfering with vision and for many patients is also a source of embarrassment;
- illustrates that botulinum toxin is an effective, long-lasting, and well-tolerated treatment for HFS;
- exemplifies that HFS is most often caused by compression of the 7th cranial nerve by an intracranial artery and that surgical intervention to decompress the nerve can be curative.

REFERENCES

Legend to video

Case 5  A 55-year-old woman with a 3-year history of facial twitching. The first videoclip segment was recorded shortly after treatment with botulinum toxin injections to the affected facial musculature. It reveals mild left hemifacial spasm (HFS). Note also the presence of mild facial paresis (decreased nasolabial fold) and synkinesia (synchronous contraction of several facial muscles) on the affected side. The second videoclip segment was recorded several weeks later, after the effects of the last botulinum toxin injections had worn off. The facial muscle contractions are now more apparent, helping to establish the diagnosis of HFS. Note the paradoxical elevation of the lid despite spasm of the orbicularis oculi (i.e. pathological cocontraction of antagonist muscles).
CASE PRESENTATION

This patient was first seen at age 38 years for evaluation of ballistic movements of the right upper extremity. At age 10 he had suffered a closed-head injury resulting in severe tremor of the right upper extremity. Five years later, he underwent ligation of the left anterior choroidal artery, a then controversial procedure to treat movement disorders. Postoperatively he had a right hemiparesis that slowly evolved into continuous jerking movements of the right upper extremity. In the years following the surgery, the patient suffered two subdural hematomas, resulting in a temporal contusion and a partial temporal lobectomy. Because of falling, he is wheelchair dependent.

On examination there was continuous jerking of the right arm that he attempted to control by sitting on it or grasping it with his left hand. The affected limb was flexed at the shoulder, elbow, and wrist with extension of the metacarpophalangeal, proximal interphalangeal, and distal interphalangeal joints. There was an intermittent flexion–extension tremor involving both the forearm flexor/extensor muscles, biceps, and triceps. There was mild retrocollis and left torticollis, and he had difficulty sitting secondary to truncal extension. His speech was nearly unintelligible, but he followed simple commands without difficulty. There were no cranial nerve deficits, except for a brisk gag reflex. He was unable to perform rapid alternating movements with the right hand and leg. Left-sided testing demonstrated bradykinesia. There were no sensory deficits. He had bilateral flexor plantar responses (see video, Case 6, first segment).

Medication trials with trihexyphenidyl, baclofen, levodopa, haloperidol, and clonazepam resulted in little, if any, symptomatic improvement. Botulinum toxin type A injections to the affected extremity reduced the severity of the spasms and allowed for improvement in control of the right upper limb. Even though there were no significant functional gains (see video, second segment), the degree of improvement was deemed sufficiently beneficial for the patient to continue receiving injections of botulinum toxin.

DISCUSSION

Ballism, a term coined by Kussmaul, is a hyperkinetic movement disorder characterized by irregular, involuntary violent flinging of the limbs, and may be
Movement Disorders

categorized topographically as hemiballism (one side of body), monoballism (one extremity), paraballism (lower limbs), or rarely bilateral ballism. Jules Bernard Luys, a French neurologist, first associated this movement disorder with an infarction of the subthalamic nucleus (STN) in the late 1800s.

The STN is a lens-shaped structure surrounded by myelinated fiber tracts. Anteriorly, it is separated from the globus pallidus (GP) by the internal capsule, lying adjacent to the fields of Forel, and the posterior lateral hypothalamic and the red nucleus. Its ventrolateral border is the cerebral peduncle and the substantia nigra, while dorsally it is separated from the ventral thalamic nuclei by parts of both the fasciculus lenticularis and the zona incerta. Within the basal ganglia, the STN receives inhibitory input from the external segment of the GP, and sends excitatory (glutaminergic) reciprocal output to both the medial and lateral segments of this basal ganglionic nucleus. γ-Aminobutyric acid (GABA) plays a major role not only in STN physiology but also in modulating its rate and pattern of discharges, including recently discovered bursting activity.

In animals, ballism, as well as choreic and athetoid movements of the contralateral hemibody, is elicited after lesions or the topical application of GABAergic agonists in the STN.

The vascular supply to the STN is from both anterior (anterior choroidal and posterior communicating arteries) and posterior (posterior choroidal) circulation. The antitremor effects of anterior choroidal artery ligation might have been related, at least in part, to infarction of the STN and related structures. Previous reports suggest that more than 25% of the STN must be compromised for the occurrence of abnormal movements. However, more recent authors have suggested that focal transient dyskinesias may be evoked with lesions that involve only 4% of the nucleus. In addition to lesion size, small lesions in STN efferent fibers induce ballism, while lesions involving the inner part of the pallidum or the fields of Forel do not induce involuntary movements.

Ballismus has been estimated to occur in 1 in 500,000 in the general population. A review of movement disorders in a large tertiary, mainly outpatient, referral center found 21 cases of ballismus in 3084 subjects. Any lesion interfering with the afferent or efferent STN pathways may induce ballism. Structural lesions causing ballismus have also been associated with the globus pallidus, ansa lenticularis, and the thalamus. Stroke is the most common cause of ballismus (typically hemiballismus) and accounts for 60–80% of cases. It may also be caused by severe hyperglycemia, postpartum hypovolemia, or other metabolic disorders.

Management of ballismus should be directed at the underlying cause, such as steroids for autoimmune disease, surgery for abscesses, or simply supportive care. Stroke-related ballism is often self-limited. Persistent or severe hemiballismus may require pharmacologic or surgical treatment. Therapeutic intervention includes dopamine receptor blocking drugs, such as haloperidol, fluphenazine, perphenazine, chlorpromazine, pimozide, risperidone, tiapride, olanzapine, and clozapine. Tetrabenazine (a monamine depleter) has also been used effectively in non-remitting cases. Alternative approaches include clonazepam, pregabide, valproic acid, and gabapentin. Dressler and others have also used botulinum toxin for ballismus. Surgical interventions have been successful
for ballismus, including stereotactic thalamotomy to either the ventrolateral (VL) or ventrointermediate (VIM) nucleus. Pallidotomy as well as high frequency stimulation of the VL complex of the thalamus has also been successful in treating ballismus.\(^5\)

This case is instructive for several reasons. First, it demonstrates the clinical features of ballismus and emphasizes the importance of first defining the phenomenology when evaluating a patient with a movement disorder. Second, it stimulates a review of the anatomy, pharmacology, differential diagnosis, and treatment of hemiballismus. Third, it demonstrates that botulinum toxin is a therapeutic option for the treatment of ballismus. Last, it emphasizes that for patients who are very debilitated, and whose overall condition is not amenable to treatment, targeting a single problematic area can nevertheless be beneficial and improve quality of life.

**REFERENCES**


**Legend to video**

**Case 6** In the first segment, this patient exhibits a number of neurologic abnormalities. He is confined to a wheelchair, but is most disabled by the ballistic right arm. He has little ability to voluntarily move the limb, and tries to control it by holding it with his left hand, placing it under his right leg, or wedging it against the side of the wheelchair. In the second segment, 3 months after botulinum toxin injection the patient continues to show some benefit. His right upper limb movements are not as violent and he is able to open and close the right hand to command. Although he did not notice any functional improvement in the right limb, he was nevertheless satisfied enough with the improvement to continue receiving botulinum toxin for many years, which allowed him greater freedom to use his non-affected side.
A woman who can walk but not stand

Theresa A Zesiewicz and Stephen G Reich

CASE PRESENTATION

A 74-year-old woman was referred for ‘difficulty standing’, which began insidiously 5 years previously and gradually progressed to the point of being unable to stand for more than ‘a few seconds.’ The patient had to sit in the shower, and lean against a wall while brushing her teeth to avoid unsteadiness. She was unable to wait in a line and described a feeling of ‘having to sit down’ while standing. The patient was unaware of tremor of the lower extremities while standing until the referring neurologist pointed it out to her. She developed anxiety about standing and walking. Having previously been diagnosed with primary orthostatic tremor, she had experienced either side-effects or limited benefit from brief trials of clonazepam, valproic acid, propranolol, levodopa, primidone, gabapentin, and levetiracetam.

On examination, there was no tremor while the patient was sitting down. Motor examination revealed normal upper and lower extremity strength, tone, and bulk, and the knee jerks were 3+. There was a low amplitude postural and kinetic tremor of both upper limbs. After standing for about 10 seconds, there was a fine, rapid tremor in the lower extremities with an urge to sit (see video, Case 7). Gait was normal.

Suspecting that her prior trial of clonazepam was inadequate, the patient was re-challenged with it, but found side-effects to be intolerable. She was subsequently re-challenged with gabapentin and experienced modest improvement with 3600 mg/day.

DISCUSSION

Orthostatic tremor (OT) is characterized by tremor of the legs while standing accompanied by a feeling of instability. The tremor usually appears after standing for several seconds or up to 1 minute. Both tremor and unsteadiness are resolved by walking, sitting, or leaning against a wall. The sense of uneasiness upon standing often overshadows that of the tremor, although patients rarely fall. Orthostatic tremor may negatively impact on a patient’s quality of life, causing difficulty in performing normal daily activities and impairing social
activities. Patients may avoid situations where they are forced to stand, such as shopping, waiting in lines, and washing dishes. Some patients become so phobic about standing that the condition may be misdiagnosed as psychogenic. Orthostatic tremor usually affects middle-aged or elderly persons, and may progress slowly. Legs are most commonly affected, but tremor may also occur in the arms and cranial muscles.

The diagnosis of OT is suggested by the unique patient history of not being able to stand but having no difficulty walking. There are few clinical findings in orthostatic tremor except for a visible and, occasionally, palpable fine rippling of the leg muscles upon standing. Electromyography (EMG) recordings demonstrate high-frequency (13–18 Hz) burst firing in weight-bearing muscles. This EMG pattern is most common in the legs, but can also occur in the trunk and upper extremities when they are used to support the body weight. Auscultation over affected lower limbs may reveal a rhythmical thumping sound, and the condition is often better diagnosed by palpation rather than visually.

Orthostatic tremor is occasionally associated with other neurologic features, referred to as ‘orthostatic plus’ syndrome, in contrast to primary orthostatic tremor in which tremor is the only manifestation. One natural history study of 41 patients found that 75% had primary orthostatic tremor, with tremor as the only manifestation of the disorder, while 25% of patients had additional neurologic findings including parkinsonism, restless legs syndrome, tardive dyskinesia, and orobuccal dyskinesia. The age of onset in primary orthostatic tremor patients was significantly younger compared to those with orthostatic tremor-plus syndrome. Orthostatic tremor has also been associated with cerebellar and pontine lesions, polyradiculopathy, hydrocephalus, aqueductal stenosis, vascular parkinsonism, and head trauma.

Although there is some controversy about a possible relationship between orthostatic tremor and essential tremor (ET), they are generally considered to be distinct disorders. Orthostatic tremor has a higher frequency than ET, a poorer response to beta-blockers and alcohol, and usually no associated family history. The etiology of orthostatic tremor is unknown. It is postulated that a central oscillator in the posterior fossa generates the tremor. The cerebellum or the bilaterally projecting brainstem centers that regulate stance and tone may be involved. Positron emission tomography (PET) in orthostatic tremor patients demonstrated abnormal bilateral and contralateral lentiform and thalamic activation. A potential role of the dopaminergic system in orthostatic tremor has also been proposed, as single photon emission computed tomography (SPECT) scans using $[^{123}I]$FP-CIT ($[^{123}I]$-labeled $N$-(3-fluoropropyl)-2β-carbomethoxy-3β-(4-iodophenyl)tropane) found a marked reduction in striatal tracer binding.

Most of the recommendations on treatment of orthostatic tremor come from non-controlled studies. Clonazepam is generally considered to be the treatment of choice, although the longevity of the therapeutic effect is disputed. Other potential therapies include: gabapentin, levodopa, pramipexole, phenobarbital, valproic acid, and primidone.
This case is instructive because it presents the typical historical and physical findings of primary orthostatic tremor, including the pathognomonic history of unsteadiness upon standing relieved by walking or sitting down.

REFERENCES


Legend to video

Case 7 After standing for approximately 10 seconds, the patient develops a tremor of the lower extremities and must sit down as she is clearly distressed. A slight tremor of the hands is also visible. The ankle–foot orthosis was found by the patient to improve her ability to stand but there was no foot drop.
A child with a severe movement disorder on the psychiatry unit

Cynthia L Comella

CASE PRESENTATION

The patient is a 9-year-old African-American girl with a history of left foot inversion when walking that began at the age of 7 years. Over the next 2 years, symptoms spread to the right leg and torso with extension of the trunk and bilateral inversion of the feet. In order to alleviate her symptoms, the patient would kneel and press her head against the floor, resulting in calluses on her forehead. During the year prior to presentation she required a wheelchair. The patient did very well in school despite her impairments. She was experiencing tremendous stress at home and was diagnosed as having a conversion disorder. She was admitted to the child psychiatry unit and treated with psychotherapy and anxiolytics. She did not improve. A neurologist visiting the unit to consult on another patient observed her and recommended a consultation with the movement disorders service.

On examination, the patient’s cognitive, cranial nerve, sensory, and cerebellar examinations were normal. Motor examination showed stereotypic movement of the trunk and legs, with sustained extension of her trunk and neck, extension of the legs, and inversion of the feet. She was unable to walk secondary to the marked spasms. Family history was negative for neurological disease. She was diagnosed with generalized dystonia (see video, Case 8). Testing for the DYT1 gene was positive. She was treated with trihexyphenidyl, escalated slowly to 80 mg per day, baclofen to 110 mg per day, and lorazepam 4 mg per day. She received small doses of botulinum toxin to cervical muscles. She has done well with treatment, and is now ambulatory with only mild, intermittent dystonic posturing of her trunk.

DISCUSSION

This case highlights several important issues. The misdiagnosis of her condition as a psychogenic conversion disorder led to years of ineffective treatment. Some of the clinical features of a psychogenic movement disorder include bizarre movements, suppression of movement with distractibility, abrupt onset,
inconsistency, other non-organic signs, and selective disabilities.\(^1\) Many have a history of a precipitating event, and often there is either an associated psychiatric condition, such as depression, or identifiable gain. Psychogenic movement disorders, now referred to as functional movement disorders, can be exceedingly difficult to diagnose, and suspected cases should always be evaluated by an expert. Although psychogenic movement disorders can occur in children, this patient did not demonstrate the diagnostic features.

Dystonia is defined as a clinical syndrome with involuntary sustained muscle contractions usually producing twisting and repetitive movements or abnormal postures.\(^2\) There may be overlying spasms that can appear tremor-like. Primary dystonia has no other neurological or physical abnormalities and is diagnosed solely by examination. Physicians unfamiliar with the clinical features are at risk of misdiagnosis, especially in the context of increased stress, as was experienced by this patient. Childhood-onset dystonia usually presents as an action dystonia, manifested as a foot inversion when walking or running. However, within 5 years, the dystonia typically generalizes, with spread to the other leg, torso, and other body regions.\(^3\) Symptom onset in late childhood and adolescence affecting the limb or neck is associated with a slightly better prognosis. In adults, dystonia typically begins in the neck, eyes, face, or limbs, and usually remains focal, although there may be spread of dystonia to contiguous areas. Permanent remissions are rare.

There are no confirmatory laboratory tests for primary dystonia. In children, and adults younger than 26 years, with primary dystonia, testing for the DYT1 gene is recommended.\(^4\) Most cases of early-onset torsion dystonia are caused by a 3-base pair deletion (GAG) in the coding region of the DYT1 gene (TOR1A) on chromosome 9q34, leading to an abnormality in the protein, torsin A. Although this patient was not Ashkenazi Jewish and had no family history, she was shown to carry the DYT1 gene. In fact, many non-Jewish individuals with young-onset dystonia have this mutation. The DYT1 gene is only 30–40% penetrant (only 30% of those carrying the gene will manifest symptoms),\(^5\) and hence the lack of a family history is not unusual. Importantly, if DYT1 gene testing was negative in this patient, the diagnosis of dystonia would still have been correct based on the clinical findings. Dystonia is a disorder with genetic heterogeneity in which many genes have not yet been identified and others cannot be assessed using commercially available tests.

The treatment of childhood-onset generalized dystonia is primarily with oral pharmacological agents or deep brain stimulation surgery. In childhood-onset generalized dystonia, especially if the DYT1 gene is not found, the first treatment is levodopa. Dopa responsive dystonia (DRD) is an autosomal dominant dystonia with reduced penetrance. DRD has a wide spectrum of clinical presentations, and in addition to dystonia there may also be parkinsonism. Some children with DRD are misdiagnosed as having cerebral palsy. DRD is caused by a wide variety of mutations in the GCH1 gene in about 50% of cases. GCH1 encodes guanosine triphosphate (GTP) cyclohydrolase I, a rate-limiting enzyme in the synthesis of tetrahydrobiopterin (BH4) from GTP. This leads to a marked reduction in central dopamine.\(^6\) This disorder is exquisitely responsive to low doses of levodopa, with essentially complete remission of symptoms for many years.
In addition to DRD, Wilson’s disease is another potentially curable cause of dystonia in children and young adults and should be considered in all cases.

In patients without a response to levodopa, anticholinergic drugs, such as trihexyphenidyl and benztropine, can be very effective and are the only drugs that have been evaluated in controlled studies.\(^7\) Anticholinergic therapy often requires large doses for effect (greater than 10 mg and up to 120 mg of trihexyphenidyl). These large doses are usually well tolerated in children, but are difficult to administer in adults because of the frequent occurrence of dose-limiting side-effects. Oral baclofen has also been shown in open label studies to be effective in children at doses from 40 to 320 mg, although of limited benefit in adults. Botulinum toxin can be used for localized areas of dystonia, as was seen in this patient in the cervical area, but is not feasible as a primary treatment for dystonia involving multiple body areas due to dosing limitations.\(^8\)

Recently, deep brain stimulation with bilateral implantation of microelectrodes into the globus pallidus has shown promise for the treatment of generalized dystonia.\(^9\) This approach is currently recommended only for those patients who fail pharmacological treatments because there is the potential risk of surgical complications. The long-term outcome of DBS for dystonia is not yet known.

This case is instructive for several reasons. First, it demonstrates the typical features of DYT1 dystonia. Second, it emphasizes that dystonia may be misdiagnosed if the characteristic clinical features are not recognized. Third, it illustrates that the most important initial diagnostic considerations in children and young adults with dystonia include DYT1, dopa responsive dystonia, and Wilson’s disease. Last, this patient’s dramatic improvement confirms that there are a variety of therapeutic interventions than can effectively treat dystonia and improve functioning.

REFERENCES

Legend to video

Case 8  The first segment shows the patient as seen on the child psychiatry ward. She demonstrates involuntary movements with back arching, neck arching, and posturing of her extremities that are consistent with a diagnosis of dystonia. She was later found to have the DYT1 gene mutation. The second segment shows the patient after starting on low doses of the anticholinergic agent, trihexyphenidyl. There is some improvement in the movements, although they remain disabling. At this time, the extension of the head (retrocollis) was a major disabling feature. The third segment shows the patient on high doses of trihexyphenidyl after receiving local injections of botulinum toxin for her retrocollis. She is able to walk, and is doing well in rehabilitation. The fourth segment shows the patient 3 years after diagnosis and treatment. She has remained on the trihexyphenidyl and has not required additional treatment with botulinum toxin for retrocollis. She continues to have some mild symptoms of dystonia but is functioning well in school and has tolerated the medications without significant side-effects except for dry mouth.
Progressive slowing and gait disorder

Richard Camicioli

CASE PRESENTATION

An 86-year-old man was referred to the movement disorders clinic for evaluation of progressive gait and balance impairment leading to restriction in his activities. The gait impairment had begun gradually 1 year before and had progressed insidiously. Upper extremity function was preserved. He had pain in the back and left knee for which he took analgesics. Memory loss and problem-solving difficulties, noted by family members, impaired instrumental activities of daily living. Cognitive decline had progressed along with the gait impairment. There was occasional freezing. The patient was also more irritable and talked about dying. He had some urinary urgency. He had smoked for 70 years and drank two alcoholic beverages a day. His only medication was occasional oxycodone. He had a history of a lumbar laminectomy and enucleation of one eye.

On initial assessment his Mini Mental State Examination (MMSE) score was 21/30. He was off by several days on the date, but knew the month and year. He could count backwards from 20 to 0 by ones and recite the months of the year backwards. He recalled 3/5 elements of a learned address. Verbal fluency was eight animals in 1 minute. The cranial nerves were normal. He had normal strength and bulk. There was paratonia in the upper and lower extremities. He had slowing of hand opening and closing movements and foot tapping. Coordination was normal. Vibration sense was slightly diminished and some position sense errors were made in the feet, but otherwise sensation was normal. Tendon reflexes were normal. There was a right extensor plantar response and a downgoing left plantar response. The patient had to push himself up from a chair to stand. He was mildly stooped. He had increased sway when standing with eyes closed and feet together, but did not fall over. He fell when pulled backwards. There was hesitancy on initiation of gait, and irregular stepping on a variable base. He turned en bloc. Arm swing was relatively preserved.

Investigations included magnetic resonance imaging (MRI) of the brain which showed high signal changes in the corona radiata. (Figure 9.1)

Over the next year he developed further difficulty in initiating walking, and worsening of freezing. Subsequently, he developed dysarthria acutely
accompanied by further worsening in his gait. Urinary urgency worsened and cognitive function also declined. These interfered significantly with activities of daily living.

His MMSE score remained 21/30. He had dysarthria but no other cranial nerve abnormalities. His gait had worsened, with freezing and widening of his base (see video, Case 9). He had repeat MRI and work-up for large vessel vascular disease and was found to have a 60–70% stenosis of the right carotid artery. He had a large volume lumbar puncture (LP) without improvement in gait. A repeat MMSE was 22/30. He learned how to use a motorized scooter.

Over the next year, his gait remained stable, but he had further cognitive decline, with a MMSE score of 14/30, and he was begun on donepezil. The patient’s wife had the impression of global cognitive improvement. He developed excessive daytime sleepiness and was begun on modafinil with some improvement. The patient did not have a trial of levodopa.

**DISCUSSION**

This patient was diagnosed as having vascular parkinsonism and vascular dementia. He demonstrated many red flags suggesting that parkinsonism was not the result of Parkinson’s disease: late age of onset; disproportionate involvement of gait with early freezing; no tremor; concurrent cognitive impairment; symmetrical bradykinesia and increased tone; early impairment of postural righting reflexes, not explained by other causes; and an upgoing toe.

Cerebrovascular disease, including subcortical white matter high signal change, is associated with cognitive impairment, dementia, parkinsonism, gait impairment, and depression. These features can overlap, as illustrated by this case. Clinical criteria for vascular parkinsonism have been proposed recently, but no consensus statement has been made. Proposed criteria include¹ the presence of parkinsonism (bradykinesia and at least one of: rest tremor, rigidity, or postural instability) and cerebrovascular disease (defined by clinical or radiological evidence of relevant cerebrovascular disease). There should be a relationship between the parkinsonism and cerebrovascular disease, based on the presence of acute or progressive signs contralateral to an appropriate lesion involving the basal ganglia and its connections (thalamus or frontal cortex) or an insidious onset with severe subcortical white matter disease. A documented cerebrovascular event is not necessary.

In our case, although the patient showed moderate white matter disease, the temporal relationship between cerebrovascular events and gait disorder was initially not clear (Figure 9.1). A repeat MRI scan after an acute deterioration, which was superimposed on a more insidious decline, showed a pontine an infarct, associated with worsening gait.

Patients with vascular parkinsonism may also have vascular dementia. While DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition) criteria suggest that memory impairment is included as a key cognitive domain for dementia, other domains such as executive function are often prominent in vascular dementia. The presence of symmetrical parkinsonism without tremor, or of gait impairment in the setting of dementia, is also supportive of the
Progressive slowing and gait disorder

Our patient illustrates a common clinical scenario in which cognitive and gait impairment coexist, highlighting the overlap between vascular dementia and parkinsonism with a prominent gait disorder. In some cases of vascular dementia, the gait disorder occurs first, before evidence of dementia.

Laboratory investigations for suspected vascular parkinsonism or vascular dementia should include evaluation of vascular risk factors, as well as investigations addressing reversible causes. Imaging is necessary since clinical features overlap with normal pressure hydrocephalus. A large volume removal of spinal fluid is a consideration. This might lead to an improvement in normal pressure hydrocephalus (NPH) and in some patients with vascular gait impairment. Separation between vascular parkinsonism and NPH remains problematic: patients with NPH have gait disorder, dementia, and incontinence, which can be seen in vascular parkinsonism. The presence of hydrocephalus on brain imaging is necessary for NPH. In vascular parkinsonism, there is evidence of vascular disease in the basal ganglia or more diffusely in the white matter, as observed in our case. An adequate trial of dopaminergic medications, preferably levodopa/decarboxylase inhibitor (up to 1 g/day of levodopa) should be considered, since some patients with presumed vascular parkinsonism may improve. The presence of an infarct in the nigrostriatal pathway was predictive of a good response to levodopa. Our patient did not have a trial of levodopa. Physiotherapy may be helpful. A home safety evaluation and assessment for assistive devices is important.

Figure 9.1 Axial fluid attenuated inversion recovery (FLAIR) MRI shows cortical and subcortical atrophy with confluent white matter high signal changes periventricularly and in the deep subcortical white matter.
This case is instructive because it demonstrates the features of vascular parkinsonism and reviews clinical and radiologic findings that support the diagnosis.

REFERENCES


Legend to video

Case 9  Gait of the patient shows hesitancy with initiation, a wide base, feet slightly out-turned, and decreased stride length. There is asymmetry in stepping and preserved arm swing.
CASE PRESENTATIONS

Case 10.1
In her 50s, this woman noticed a tremor of the right upper limb. Five years later she developed a tremor in the left arm, and subsequently the lips and chin. She was evaluated at age 66 years. The video (Case 10) shows a postural and kinetic tremor of the upper limbs which improved 30 minutes after drinking 1 ounce of alcohol. She was prescribed propranolol 60 mg per day. She died at age 69 of chronic myelogenous leukemia. Pathological examination of the brain revealed no abnormalities.

Case 10.2
A 57-year-old woman had the onset of bilateral upper limb action tremor. At age 67 years, she had a prominent postural and kinetic tremor in the upper limbs, jaw tremor, and resting tremor in the upper limbs. She was taking Parnate® (tranylcypromine) for ‘depression’. Her father had ‘shaking palsy’. She was diagnosed with tremor-dominant Parkinson’s disease. The Parnate was discontinued and she was started on levodopa 500 mg, six times per day. Five months later, she reported significant improvement in her tremor and had ‘virtually no signs of parkinsonism’. Over the years, the resting tremor worsened and she developed cogwheeling at the wrists but no bradykinesia. She declined to discontinue levodopa. The video, taken at age 84 years, shows a pronounced postural and kinetic tremor in both upper limbs, lip and jaw tremor, and resting tremor in all limbs. Posture was erect and there was no bradykinesia. She died at age 92. Brain autopsy was unremarkable, including the substantia nigra.

Case 10.3
At age 50, this woman had onset of tremor in her head and both upper limbs. She did not tolerate propranolol or primidone. At age 60, she developed resting tremor in the left hand. There was some improvement on amantadine and ethopropazine. However, both medications caused hallucinations and were
therefore discontinued. On examination there was a resting and postural tremor in the upper limbs and less so in the lower limbs, and ‘yes’ type head tremor. There was loss of left arm swing (bradykinesia) and rigidity on the left side. She was diagnosed with essential tremor (ET) and parkinsonism. Sinemet® (levodopa/carbidopa) 100/25 mg three times per day produced some improvement, but within 1 year she developed left foot dyskinesia. She died at age 79. Autopsy showed Lewy body pathology of Parkinson’s disease.

**DISCUSSION**

Tremor is the cardinal feature of essential tremor (ET) and is present in the majority of patients with Parkinson’s disease (PD). Although the distinction between ET and PD is usually easy, in some cases it is challenging. These three patients illustrate distinct clinical phenotypes of ET. Essential tremor is characterized by tremor during action, i.e. postural and kinetic tremor.¹ Case 10.1 had classical ET, but not all ET cases improve with alcohol, and tremor due to other causes may also improve with alcohol.² Although rest tremor is typical of Parkinson’s disease, it may also be seen in ET. In an autopsy study, 30% of longitudinally followed ET patients developed resting tremor late in the course.³ The resting tremor in case 10.2 represents a natural evolution of ET rather than parkinsonism.

Parkinson’s disease is a clinical diagnosis based on the presence of two of the following three features: resting tremor, bradykinesia, and rigidity.⁴ The ‘ratchet-like’ sensation felt when the examiner performs passive movement of the joint, when associated with increased tone, is called cogwheel rigidity, which is a feature of PD. When tremor is present at a joint, it may interrupt the passive movement intermittently to give a sensation of cogwheeling (as in case 10.2). In such cases, the tone should be tested at a joint where there is no tremor. When making a second diagnosis of PD in a patient with ET, all three cardinal features (bradykinesia, rigidity, resting tremor)⁵ must be unequivocal and preferably asymmetrical. The additional clinical diagnosis of PD was made in case 10.3. She improved on levodopa, but developed dyskinesia, a strong indication of striatoni-gral tract dysfunction. The definitive diagnosis of PD is based on Lewy body inclusions.⁶ In a large autopsy study, 5% of ET cases had Lewy body pathology of PD – a rate similar to that in the general elderly population.⁷

These three cases are instructive because they present the varied phenotype of essential tremor including some clinical ‘exceptions’. The latter include the occasional unilateral onset of ET (case 10.1); the presence of a resting tremor in cases of long-standing ET not due to concurrent parkinsonism (case 10.2); and last, the fact that some patients with ET go on to develop PD (case 10.3), but the diagnosis should be supported by not only the characteristic clinical features, but also a beneficial, sustained response to levodopa, ideally with the eventual development of motor fluctuations and dyskinesias, to be even more confident of PD.
REFERENCES


Legend to video

Case 10  The first case demonstrates a postural and kinetic tremor of the upper limbs which attenuates 30 minutes after drinking 1 ounce of alcohol, evidenced by improved ability to pour from a pitcher. The second case, filmed when the patient was 84 years old, demonstrates a pronounced postural and kinetic tremor in both upper limbs and a resting tremor in all limbs, as well as a lip and jaw tremor. The last case was filmed when the patient was 61 years old. There is a prominent resting and postural tremor in the upper limbs and less so in the lower limbs, as well as a ‘yes–yes’ type of head tremor. There is loss of left arm swing and she has rigidity of the left side.
CASE PRESENTATION

A teenage boy had a long history of Gilles de la Tourette’s syndrome, beginning at age 4 with waxing and waning repetitive movements of facial, neck, and extremity muscles. In his early years, eye blinking, neck jerks, and throat clearing predominated, though rapid eyebrow twitches, arm thrusting, and multiple animal sounds (squeaks, chirps, growls) appeared, disappeared, and reappeared. At the onset of puberty, more complex movements developed with spinning, repetitive hopping, and dance-like hip/trunkal thrusting. Though he was never free of movements, regular seasonal variations occurred, the early fall and early summer being most problematic times. Prior to each movement, he experienced a tense internal feeling that was relieved when he performed the movement or emitted the noise, and he could suppress the movements adequately well at school to avoid incessant teasing.

At age 14, a neurological consultation with a movement disorder specialist documented mildly dysmorphic facial features and a tall slender adolescent. Multiple tics were present in the examining room, and when the patient was asked to sit by himself quietly in a room while a video camera recorded his movements, eye, facial, neck, and extremity tics were frequent, along with multiple repetitive noises. He was briefly treated with pimozide 2 mg at bedtime for 6 months with improvement, but stopped the medication thereafter because he and his family felt that treatment was not needed.

At age 16, the patient experienced increasing frequency of tic movements that required significant mental energy to keep the tics suppressed. The patient and family requested that treatment be re-initiated. Based on the positive past effects of pimozide, the same drug was prescribed (2 mg at bedtime). Three weeks later, he reported marked improvement in the tics and more ease in controlling them. Vocalizations were still present and of equal frequency to his pre-medication state, but the sounds were softer and more easily disguised.

Six weeks after starting the neuroleptic, the family telephoned with concerns that tics had again become problematic and that they had increased the pimozide to 4 mg at bedtime over the past 2 weeks. Their son had developed a new ‘body
tic' and a ‘kicking tic’. They described the trunk jerking forward and both legs kicking. Like his other tics, he felt tense inside until he moved and then felt immediately better. As with his tics, once this relief occurred, however, he felt an internal tension start to develop within seconds or minutes and build again until he moved his trunk and feet. His other tics remained better controlled than before neuroleptic therapy and he was sleeping better at night. Based on this description, by telephone, the neurologist increased the neuroleptic with the family’s encouragement to 6 mg at bedtime. A follow-up appointment was offered in 1 week, but scheduled for 6 weeks later when the family was to return from their summer holiday.

The patient arrived for his follow-up appointment, but preferred to wander about the hallways rather than sit in the waiting room until his name was called. When the neurologist called him to the room, he asked to remain standing and paced about the room, though he was pleasant and pleased overall, especially because his involuntary vocalizations were less pronounced than before treatment. When asked to sit so that the neurologist could examine him, he cooperated, but rocked his trunk forward and backward, explaining that this new ‘tic’ was the only remaining problem. He explained that the rocking motion and leg paddling movements of hip and leg flexion/extension had not responded to the increase in neuroleptic dosage, and wondered if he should increase the medication further. Video recording demonstrated both motor and vocal tics, but in addition, frequent restless truncal and lower extremity stereotypic movements that had never been part of the patient’s tic repertoire (see video, Case 11).

The neurologist noted several issues: first, the new movements had occurred within the context of starting the neuroleptic; second, they emerged as the well-documented tics of the past dramatically improved; third, the patient was restless and had difficulty sitting in his chair, a behavior quite distinct from his past visits to the neurologist’s office; fourth, though he was emphatic that the new movements were associated with an urge to move and with relief after moving just like his tics, the teenager admitted that he initiated these movements himself as opposed to his usual tics that ‘seemed to come from inside my body by themselves’.

The visual observation of the movement and the history suggested to the neurologist that this new ‘tic’ was not a tic, but rather neuroleptic-induced akathisia. The neuroleptic dose was decreased to 3 mg at bedtime, and within 3 weeks, the trunk and leg movements abated. The original tics did not increase and the patient became more comfortable living with his tics. He remained on the lower neuroleptic dosage for 6 months, but because of increased vocalizations and more complex tics at the start of a new part-time job, the dose needed to be slightly increased to 4 mg at bedtime. The akathisia re-emerged, but responded to propranolol at low doses. Six months later, because the tics were adequately controlled, the neuroleptic was decreased again and eventually stopped.

DISCUSSION

Akathisia can occur in primary neurological diseases such as Parkinson’s disease, but most commonly is a side-effect of neuroleptic drugs that block dopamine receptors. The risk for developing akathisia increases as the dose
and antipsychotic potency of the neuroleptic increase, and newer generation (atypical) neuroleptics are not devoid of risk. As in this case, akathisia is usually a subacute syndrome and occurs within the first days or weeks of neuroleptic introduction or after an increase in the neuroleptic dosage. Tardive akathisia, a variant of tardive dyskinesia, can also occur after chronic therapy.\(^2\)

The primary symptom of akathisia is an internal restlessness that patients discover can be relieved by movement. As in the present case, this restlessness may not be perceived as different from the ‘urge’ that precedes a tic and is relieved after the tic. In contrast to tics, however, akathisia most often involves the trunk and legs, rather than the cervical–cranial muscles that are typically most prominent for tic involvement.

Whereas D2 dopaminergic receptor blockade was originally hypothesized to be the cause of akathisia, this disorder has a less predictable pharmacology than acute neuroleptic-induced dystonia. Noradrenergic and opioid influences play a likely role in the pathophysiology, because \(\beta\)-noradrenergic blockers and opioid antagonists are often effective therapies if the neuroleptic cannot be withdrawn.\(^3\)

The emerging field of pharmacogenomics has studied genetic markers to identify subjects at risk for neuroleptic-induced akathisia. In this light, particular emphasis has been placed on the dopamine D3 receptor gene. Subjects whose alleles are homozygous for the Ser9Gly polymorphism of this gene have been reported to be twice as likely to develop akathisia as subjects with other polymorphisms.\(^4\) This same pattern has been reported in studies of tardive dyskinesia, suggesting a molecular biological link between the two conditions and reinforcing clinical observation that akathisia is a predictor of tardive dyskinesia risk.\(^5\)

This case is instructive because it emphasizes the need for continual vigilance regarding the array of neuroleptic-induced movement disorders, ranging from the akathisia of this case to acute dystonias, subacute parkinsonism, and tardive syndromes, whether choreic, dystonic, akathitic, or tic-like in phenomenology.\(^1\) Clearly, the patient, family, and experienced movement disorder specialist at first incorrectly ascribed the new clinical problem to tics. Though the clinician questioned the patient on characteristics typical of tics, the overlap between subjective accompaniments of akathisia and tics confused the diagnosis. Likewise, the patient’s ability to suppress the movements of akathisia confounded the specificity of this symptom as diagnostic of tics. The anatomical distribution of the trunk and legs in retrospect was important, though the patient had experienced arm, leg, and truncal tics before. The emergence of the akathisia in the context of improvement in the patient’s original tics might have suggested a different mechanism, but tics naturally wax and wane, with one typically improving as another crescendos.

The case especially underscores the value of on-site visual observation, which immediately established the diagnosis. The motor restlessness of the patient in the waiting room and his unnatural standing rather than sitting in the doctor’s office steered the neurologist to the distinctive qualities of akathisia. The rapid response to a reduction in neuroleptic dose...
reassured the patient and family, and the efficacy of propranolol when the neuroleptic was increased helped to maintain the patient’s otherwise high level of function. The pharmacogenomic data on akathisia and risk of tardive dyskinesia prompted particularly careful follow-up regarding the potential risk of tardive dyskinesia and the later decision to reduce and eventually discontinue therapy once the tics had remained controlled for 6 months.

REFERENCES

Legend to video
Case 11 The tape shows the young man with Gilles de la Tourette’s syndrome seated in a video-recording room without the physician present. Though he had few tics in the presence of his neurologist, when sitting quietly by himself many tics emerged, including neck, eye, and face tics along with vocalizations. In addition, the rocking motions and leg paddling movements of akathisia also occurred. These latter movements developed in the context of starting and increasing neuroleptic doses, whereas the other tics improved with neuroleptic therapy.
How to roll-out the work-up when the patient’s brain has ‘rocks’

Bala V Manyam

CASE PRESENTATION

A 67-year-old woman presented to her physician with a history of muscle stiffness, slowness of movements, and occasional tremor, mostly in the evening. The patient’s mental status examination and speech were reported to be normal. Her gait was slow and cautious. A diagnosis of Parkinson’s disease was made and she was started on carbidopa/levodopa 10/100, gradually increased to six tablets a day. There was little benefit, and she complained of increasing stiffness as well as slowness in her activities of daily living. She subsequently developed kyphosis from vertebral collapse secondary to osteoporosis. This was followed by progressive difficulty of gait with frequent falls, resulting in several fractures. She developed dysphagia and her speech began to deteriorate and was difficult to understand. There was further deterioration of her activities of daily living. Her memory became progressively worse. The dosage of carbidopa/levodopa was increased to 25/250 three times a day.

The medical history revealed that several years ago she had developed sudden, transient difficulty speaking, considered to be a small stroke. She was on warfarin for deep vein thrombophlebitis. There was history of hepatitis but details were not available. Her other medications included ranitidine, furosemide, and primidone 50mg per day. The reason for primidone was not clear. The family history was notable for parkinsonian features in her father. He had had an X-ray of the skull, but the report could not be traced and no autopsy was performed. The patient’s paternal aunt had a history of dementia. The patient’s 55-year-old daughter had a history of lightheadedness and ‘some calcium problem’ and was undergoing further work-up, but no additional details were available.

When evaluated at age 78 at a movement disorders clinic, the neurologic examination revealed a score of 18 on the Mini Mental State Examination (MMSE). There was mild rigidity and bradykinesia but no tremor. There was moderate kyphosis and she walked with a simian posture and shuffling gait. On the pull-test there was mild retropulsion, but she corrected herself from falling. Cranial nerves, strength, reflexes, and sensory examination were unremarkable. A computed tomography (CT) scan of the head was performed which
showed extensive calcification of the dentate nuclei, basal ganglia, thalamus, and centrum semiovale (Figure 12.1). Laboratory studies revealed normal calcium, phosphorus, albumin, vitamin B₁₂, and thyroid function. A CT scan of the patient’s daughter revealed bilateral, symmetric calcium deposits similar to the patient.

**DISCUSSION**

This patient presented with atypical parkinsonism prompting a CT scan of the head which revealed extensive calcification of the basal ganglia, dentate nuclei, thalamus, and corona radiata. Similar changes were observed in her daughter. The red flags suggesting that parkinsonism was not due to Parkinson’s disease (PD) in this patient included early falls, lack of response to levodopa, early bulbar dysfunction with dysphagia and dysarthria, and dementia earlier in course, compared to PD.

There are multiple causes for this degree of intracranial calcification (Table 12.1).¹² The major differential diagnosis in this case is hypoparathyroidism, which was ruled out. There was no evidence of a developmental disorder or a systemic disease known to be associated with intracranial calcification, and therefore this patient fits into the category of ‘primary striopallidodentate calcinosis’, and when familial, this is also known as Fahr’s disease.¹³ Even though, this eponym may be inaccurate and undeserved,¹ it remains the most well-known designation for symptomatic, intracranial calcification when no other cause is apparent. Fahr’s disease is typically autosomal dominant, but all forms of inheritance have been described. To date, there is no gene identified for Fahr’s disease, but one family with autosomal dominant inheritance has been found, linked to chromosome 14q. Yet, this linkage was not found in other families, confirming genetic heterogeneity.⁵–⁷

The clinical features of Fahr’s disease are also heterogeneous, and may vary within families including individuals with extensive calcification who are asymptomatic. The most common manifestations are movement disorders, typically

![Figure 12.1 CT scan of the brain showing extensive calcification of the dentate nuclei, basal ganglia, thalamus, and centrum semiovale.](image-url)
Table 12.1 Bilateral brain calcifications are reported in all of the following conditions. (References can be found in the original source. Reproduced with permission)

<table>
<thead>
<tr>
<th>Striopallidodentate calcinosis</th>
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<tr>
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<td>Heredofamilial disorders</td>
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<td>COFS syndrome with familial 1:16 translocation</td>
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<td>lipomembranous polycystic osteodysplasia (AR)</td>
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<td>tapetoretinal degeneration (AD)</td>
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parkinsonism, but there may be hyperkinetic disorders such as dystonia, chorea, and tremor. Other manifestations include dementia, dysarthria, and ataxia.\textsuperscript{1,4}

Approximately 6\% of all CT scans demonstrate intracranial calcification, typically punctate involvement of the globus pallidus in individuals after the age of 50, and this is generally considered to be an age-related phenomenon and clinically irrelevant.\textsuperscript{1} More extensive calcification should prompt further evaluation, with the initial focus on calcium, phosphorus, and parathyroid metabolism. The differential diagnosis of intracranial calcification is extensive, but general categories include developmental disorders, endocrine and other metabolic causes, degenerative diseases, and infectious, vascular, and toxic etiologies.\textsuperscript{1,2} As many of the disorders are familial, it is important to examine other family members and have them undergo a CT scan, even if asymptomatic.

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<th>Table 12.1</th>
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AR, autosomal recessive; COFS, cerebro-oculofaciosteletal; AD, autosomal dominant; AIDS, acquired immunodeficiency syndrome; MELAS, mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke.
This case is instructive for several reasons. First, it emphasizes that cases of atypical parkinsonism require further evaluation, including cranial imaging. Second, it demonstrates an unusual cause of parkinsonism: Fahr’s disease, or primary familial striopallidodentate calcification. Lastly, it brings up a discussion of the extensive differential diagnosis of intracranial calcification.

REFERENCES

When sorrows come, they come not as single spies, but in battalions.¹

CASE PRESENTATION

In 1986, this 60-year-old sheriff developed tremor-predominant Parkinson’s disease, a form that has a relatively good prognosis. He did well using first selegiline and then modest doses of levodopa/carbidopa. By 1994 his chief complaint was back and leg pain severe enough to stop the golf he had always enjoyed. As the man who still holds the record for the longest touchdown run (99 yards) at his University he was stoic, but disappointed to be told that pain was simply to be expected in anyone who has Parkinson’s disease. He went to a movement disorders center for a second opinion and was told that while dull ache in hips, back, and shoulders, and even a diagnosis of bursitis, was indeed common in Parkinson’s disease, his severe pain, which he noticed while standing, and could relieve by sitting or by bending forward, was not a part of the disease. Lumbar magnetic resonance imaging (MRI) revealed that he had spinal stenosis, and referral to a neurosurgeon led to decompressive surgery. When the surgeon said, ‘Get out of bed’, the day after surgery, the patient said, ‘No way’, but did as he was told, and found his pain totally relieved. The Parkinson’s disease did not complicate surgery or the anesthesia.

In 1996 he discovered a black mole on his right forearm, and a pathologist reported that the lesion was an ulcerated spindle cell melanoma. A second lesion on the back was a melanoma in situ. With no family history of cancer, and following wide removal of the cancer, the couple were optimistic for their future. Nevertheless, they discussed whether or not the use of levodopa, which is intrinsic to the tyrosine pathways involved with melanoma, could enhance the risk or accelerate the growth of a melanoma. One year later, at the time of a routine visit to the movement disorder center, his right axillary fossa was swollen by a hard and almost fist-size mass. This was removed, and four of the lymph nodes included metastases from the melanoma. After this surgery, which also went well, he was noted for the first time to have dyskinesia. For the melanoma he received α-interferon and local radiation, and after 8 years there was no further recurrence.

The case was characterized by exceptionally attentive care by the family doctor, the surgeon, and the oncologist in the small Ohio town. Nevertheless, various
symptoms required continued management; for example, the ‘parkinsonologist’ was telephoned when the patient became transiently confused with visual hallucinations. For this symptom small doses of quetiapine were useful. Amitriptyline 25 mg at bedtime was employed briefly for a transitory and mild depression. The discovery of swollen red ankles led to temporary discontinuance of pergolide and of amantadine; the latter can cause livedo reticularis. Attention to his venous stasis and infection, and elevation of his legs, relieved the swelling. Drooling responded to benztropine and then to procyclidine in small doses. ‘Freezing’ and a tendency to fall led to recent use of a walker with wheels, again helpful. Wheeled walkers seem a good choice for many patients with Parkinson’s disease, but do not increase the speed of walking, nor do the walkers entirely prevent falls or gait hesitancy.

The melanoma has not recurred and Parkinson’s disease also seems stable, and at present he takes levodopa 400 mg, as well as variable, but always minimal, doses of agonists, amantadine 200 mg, procyclidine 10 mg, and 50 mg of quetiapine. The patient cannot walk readily due to imbalance, and because of this the couple has missed going out much of the time. He did attend a recent reunion of his college class at which time he was honored, and also attended a meeting with fellow ex-servicemen. He continues to defeat his devoted wife at games of cribbage, and inspires others with his uncomplaining grace in the face of his increasing motor incapacity during the almost two decades he has had Parkinson’s disease.

DISCUSSION

A review of this patient’s long course with Parkinson’s disease is instructive for many reasons, aside from the importance of a loyal spouse and attentive local physicians:

1. Pain, although not uncommon in the back and shoulders, is not a major feature of Parkinson’s disease. Lack of arm swing, stiffness, and perhaps even sudden withdrawal from large amounts of levodopa whenever the patient is ‘wearing off’ may increase pain, but if severe pain is present other disorders should be suspected. Having Parkinson’s disease is no protection from cancer, heart disease, and other ailments of the elderly, and, of course, is certainly no protection from the depression so common when a person who was never ill before develops Parkinson’s disease.

2. Spinal stenosis is common, and the clinical observations may include back and leg pain made worse by standing and walking and relieved by bending forward to open up space around the compressed lumbar nerve roots, or sitting. Decompressive surgery can be helpful.

3. Life with Parkinson’s disease can continue for decades and be full and meaningful despite additional disorders and continued parkinsonian symptoms.

4. This lesson is the most relevant one for this case. Levodopa is a substrate for the formation of melanins, since tyrosine is converted to levodopa and then to dopaquinone followed by further oxidation to produce melanin. Some clinicians have therefore been hesitant to use the drug in any patient with a strong family history of skin cancer. A few clinicians would also stop the drug if melanoma appeared, although abrupt cessation of levodopa after
years of therapy can be hazardous and produce dysphagia, aspiration, or even a central fever. The Physician’s Desk Review still includes a warning about the use of levodopa when melanoma is present. The most recent review,\textsuperscript{4} utilizing experience with 54 patients with both Parkinson’s disease and melanoma, states: ‘It did not appear that the Parkinson’s disease patients on levodopa therapy were predisposed to melanoma, nor did levodopa therapy appear to exaggerate melanoma if it were previously present’. This patient’s story is another example that patients need to be involved when there is potential therapeutic hazard, even though there is no need to ‘show every tooth of the dragon’. A caution about melanoma is not, however, one that must be mentioned to every patient as therapy begins, nor is it necessary to discontinue the useful drug if melanoma appears.

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Ear clicking after a stroke
Jennifer G Goldman

**CASE PRESENTATION**
A 47-year-old man presented one-and-a-half years after a right midbrain hemorrhage (Figure 14.1) with involuntary left-side jerking movements, a left hemisensory deficit, and gait difficulty. Since the stroke, he also experienced vertigo, diplopia, dysarthria, and sleep apnea. Several months into rehabilitation, he noticed clicking noises in his ears. On examination, there was dysarthria, dysmetric saccades, nystagmus, marked left hemisensory deficit to proprioception and vibration, left sided dyssynergia, dysmetria, and ataxia. Isolated rhythmic contractions of the soft palate at about 2 Hz were seen, characteristic of palatal tremor (see video, Case 14).

**DISCUSSION**
Palatal tremor is a rare but fascinating movement disorder characterized by rhythmic movements of the soft palate and, in some cases, other brainstem, trunk, and limb muscles. Early descriptions of palatal tremor date back to cases reported in the late 19th century. Although various terminologies such as palatal tremor, palatal myoclonus, palatal nystagmus, and brainstem myorhythmia have been applied over the years, the term palatal tremor, more recently, has been adopted to reflect the underlying rhythmicity of movements.

Palatal tremor can be categorized as either essential (EPT) or symptomatic (SPT).\(^1\text{-}^3\) EPT, occurring in about 25% of cases, is characterized by the absence of central nervous system lesions, structural brainstem changes, and identifiable causes. Rhythmic contractions of the tensor veli palatini, a soft palate muscle innervated by the 5th cranial nerve, are present and frequently accompanied by ear clicks. In EPT, ear clicks may be the presenting symptom and are likely produced by opening and closing of the eustachian tube, at a mean frequency of less than 120 clicks/minute. Apart from palatal contractions, neurological examination in EPT is normal. In contrast, SPT typically follows a brainstem or cerebellar lesion such as a stroke. Other symptomatic causes include neurodegenerative disorders such as progressive supranuclear palsy and spinocerebellar ataxia, encephalitis, psychogenic disorders, and rare disorders such as the syndrome of progressive ataxia and palatal tremor, which can be hereditary or sporadic.\(^4\text{-}^5\)
SPT involves rhythmic contractions of the levator veli palatini, a soft palate muscle thought to be innervated by the 7th cranial nerve; palatal movements occur at a mean frequency faster than in EPT, typically greater than 120 clicks/minute. Rhythmic jerking movements of other brainstem and limb muscles often accompany the palatal tremor; for example, pendular nystagmus, lower facial muscle contractions, head or limb tremor of similar frequency, and even laryngeal or pharyngeal movements affecting air-flow may be present. Although ear clicks may occur in SPT, patients are more likely to present with signs and symptoms of brainstem and cerebellar dysfunction, and SPT is often asymptomatic.

Although little is known regarding the pathophysiology of EPT, the anatomical circuitry and pathology of SPT is well described. SPT is produced by damage in the dentatorubro-olivary pathway, also known as the Guillain–Mollaret triangle. This triangular circuit links the dentate nucleus of the cerebellum to the contralateral red nucleus (via the superior cerebellar peduncle) and inferior olive (via the central tegmental tract), looping back to the contralateral dentate nucleus (via the inferior cerebellar peduncle). In SPT, hypertrophic inferior olive degeneration occurs as a result of brainstem or cerebellar lesions interrupting the Guillain–Mollaret triangle. Microscopically, enlarged neurons with cytoplasmic vacuolation, astrocytic hypertrophy, and gliosis are seen.
Neuroimaging with T2- and proton-density-weighted magnetic resonance imaging (MRI) demonstrates hyperintense signal and enlargement of the inferior olivary nucleus, as seen in this patient’s fluid attenuated inversion recovery MRI (Figure 14.2). Whereas inferior olivary hypertrophic degeneration develops about 3 weeks after the lesion, clinical manifestations of SPT may not develop until 2–49 months later, and radiological changes of olivary hypertrophy may be delayed by 6 months and persist for 3–4 years. Structural neuroimaging is normal in EPT, but functional MRI studies have demonstrated activation of the inferior olive and cerebellar dentate nuclei. Physiologically, an autonomous oscillator that synchronizes firing of inferior olivary neurons governs palatal tremor. The persistence of palatal rhythmic contractions in SPT during sleep and coma demonstrate the oscillator’s resistance to deactivation by forces weaker than motor cortex stimulation. However, the exact physiological role of the inferior olive and its interactions with the brainstem and cerebellum remain to be defined in palatal tremor.

Management of palatal tremor has included several pharmacological and surgical techniques studied in small numbers of patients with variable efficacy. Many patients may not require treatment unless the ear click is bothersome, and

Figure 14.2  Fluid attenuated inversion recovery MRI brain performed about 1 year after the hemorrhage demonstrates increased signal intensity and enlargement of the right inferior olive.
in some cases, other brainstem and cerebellar features overshadow both the ear click and palatal tremor. Medications reported to be effective range from benzodiazepines, anticonvulsants, anticholinergic and dopaminergic agents, to 5-hydroxytryptophan and sumatriptan. Surgical treatments such as sectioning the levator veli palatini and tensor veli palatini muscles have afforded partial relief of ear clicks. More recently, treatment with low doses of botulinum toxin injected into the palatal muscles has been effective, although possible side-effects of dysphagia should be noted.

This case is instructive because it demonstrates the typical history, physical findings, and imaging of symptomatic palatal tremor due to a brainstem hemorrhage.

REFERENCES


Legend to video

Case 14 The examination demonstrates clinical correlates of his brainstem hemorrhage including dysarthria, dysmetric saccades, nystagmus, rhythmic contractions of the soft palate, and left sided dyssynergia, dysmetria, and ataxia. The second and third segments show additional examples of symptomatic palatal tremor.
Atypical parkinsonism and cerebellar ataxia

Karen Blindauer

CASE PRESENTATION

A 47-year-old African-American woman had developed mild vertigo 5 years ago. It was intermittent initially, and gradually became more constant after about a year. At the same time she noticed slurred speech, diplopia, and micrographic, tremulous handwriting. Over the next year she developed progressive loss of balance, tremor in both hands, which was worse with activity, and impaired mobility. It was more difficult to arise from a chair and get out of the car. She experienced transient dysphagia, which resolved. Her family noted a dramatic change in personality; she became less motivated and less interactive. The family history is negative for any neurological or psychiatric disease.

On examination she was alert and oriented with a flat affect. There were slow saccades with normal extraocular movements except for right gaze-evoked nystagmus, subtle left facial weakness, nasal speech, and a slight perioral tremor. There was mild left upper extremity rigidity and slight weakness of the interossei and tibialis anterior muscles. Deep tendon reflexes were 2+ throughout except for the Achilles reflex, which was absent bilaterally. Plantars were flexor bilaterally. There was an asymmetric bilateral upper extremity postural and kinetic tremor, mild left upper extremity ataxia and dysdiadochokinesia, and mild bradykinesia in all extremities noted with finger, hand, foot, and toe tapping. She was able to rise off of the chair without difficulty. Her gait was wide based and ataxic, with a reduced stride length and restricted arm swing bilaterally. She retropulsed with recovery on pull testing. The sensory examination was normal.

An extensive work-up included, but was not limited to, the following. Magnetic resonance imaging (MRI) of the brain and cervical spine was normal. Neuropsychological testing revealed mildly slow processing speed and executive dysfunction, implying a subcortical and/or frontal pathological process. Cerebrospinal fluid (CSF) protein, glucose, cell count, Lyme titer, and immunoglobulin G (IgG) synthesis rate were all normal. Serum lactate, pyruvate, ceruloplasmin, angiotensin converting enzyme (ACE), Lyme titer, antineuronal antibody, and anti-Purkinje cell antibodies were normal or negative. Twenty-four hour urine copper was normal. Nerve conduction studies and electromyography (EMG) were normal.
She received a trial of carbidopa/levodopa 25/100 dosed three times daily and noted a significant improvement in her tremor, mobility, and gait.

DISCUSSION

This patient presented with a combination of parkinsonism, cerebellar signs, and cognitive impairment. With one exception, an extensive work-up was negative. The serum Hereditary Ataxia Panel (Athena) was positive for SCA17, with 47 CAG/CAA repeats (normal ≤ 42).

Spinocerebellar ataxia (SCA) type 17 is an autosomal dominant ataxia caused by the pathological expansion of the CAG/CAA repeat in the TATA-binding protein gene. The normal allele length is 25–44 repeats, and the expanded allele contains 43–63 repeats. A repeat length of 43–47 is in the indeterminate or not fully penetrant range. A median age of onset of 23 years has been described, and the correlation between CAG/CAA repeat length and age at disease onset appears weak. Clinical features of SCA17 include varying combinations of the following signs and symptoms: progressive gait and limb ataxia, depression, schizophrenic symptoms, dementia (early in disease course or rapidly progressive or frontal lobe type), parkinsonism, dysphagia, slow saccades, focal or generalized dystonia, hyperreflexia, spasticity, choreiform movements, myoclonus, and seizures. A clinical presentation compatible with typical Parkinson’s disease or Huntington’s disease has also been described. The phenotype may vary considerably among members of the same family. The prominent dementia and psychiatric abnormalities help to distinguish SCA17 from some of the other inherited spinocerebellar ataxias.

Other SCAs that may present with atypical parkinsonism and rarely even typical Parkinson’s disease include SCA2, SCA3, and SCA8. Other extrapyramidal signs and symptoms can also be seen in SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA12, and SCA21.

This case is instructive because it illustrates the importance of including inherited spinocerebellar ataxia in the differential diagnosis of atypical parkinsonism or frontal lobe dementia with ataxia, even in patients with a negative family history for any neurodegenerative disorders. Confirming an autosomal dominantly inherited ataxia provides the patient with a definitive diagnosis, which has prognostic implications, and informs family members of their risk of developing the same disease.

REFERENCES

CASE PRESENTATION

A 51-year-old man presented at age 37 years with slowness in his left hand. He was diagnosed with idiopathic Parkinson’s disease (PD) and started on levodopa with excellent benefit. Within 4 years, however, he started to complain of left foot inversion upon awakening. This was relieved by taking his morning dose of levodopa but would return before his next dose was due. In fact, the left foot inversion became the first sign of the levodopa effect wearing off at each dose. The abnormal postures gradually spread to other parts of the body, including the right leg, upper extremities, neck, and face. They also became increasingly painful and distressing. The intervals between individual doses of levodopa had to be progressively shortened in order to abort the pain and functional disability resulting from these abnormal fixed involuntary movements. Around the same time, he also developed peak-dose dyskinesias. At age 46, because of unsatisfactory control of his parkinsonian symptoms, despite optimal medical therapy, as well as levodopa-induced dyskinesias and increasingly painful abnormal postures, the patient underwent staged bilateral deep brain stimulation of the subthalamic nucleus (STN DBS). This resulted in marked improvement that has been sustained over the ensuing 4 years.

DISCUSSION

Dystonia can be the heralding sign of PD, especially in patients with young-onset disease. More frequently, though, it occurs as a levodopa-induced phenomenon during the course of chronic treatment. Dystonia is usually associated with the ‘off’ state when levodopa levels are low. ‘Early-morning dystonia’ occurs upon awakening and ‘end-of-dose dystonia’ is experienced at the end of each levodopa dose.1,2 ‘Off’ dystonia typically involves the lower extremities with curling of the toes, inversion of the foot, and cramping of the calf, but it can be present in the trunk, face, neck, and upper extremities as well, as was the case in our patient (see video, Case 16, first segment). It can be extremely painful and often interferes with gait. The first and most prominent presentation of ‘off’ dystonia is usually on the side with the most severe parkinsonism,2 which is typically the side initially affected. Dystonia can also occur at peak dose of levodopa, but in that case usually affects the craniocervical region more than the legs, is not...
painful, and is often associated with chorea in the extremities. Although the pathophysiology of ‘off’ dystonia is not fully known, it appears to be related to abnormal low-frequency irregular firing of globus pallidus interna neurons.3

The medical approach to treatment of ‘off’ dystonia hinges on minimizing the amount of time the patient spends in the ‘off’ state. Therefore, regular levodopa is preferable over slow release preparations. Dissolving levodopa in carbonated beverages may further expedite its absorption and more rapidly terminate the painful dystonia.1 Subcutaneous administration of apomorphine may provide the most rapid relief of the ‘off’ dystonia. When dystonia and other fluctuations cannot be adequately controlled with medical therapy in a patient who still has high quality ‘on’ time, immediate and sustained benefit can be obtained with STN DBS, as shown in our patient.4,5

ACKNOWLEDGMENT

This article is dedicated to the memory of Nidhi Watson, our Movement Disorder fellow who passed away in 2007.

This case is instructive because it describes the varied expression of dystonia in PD, a common, painful, and disabling phenomenon that can often be improved with medical and surgical interventions.

REFERENCES


Legend to video

Case 16 The first segment shows pre-STN DBS in the ‘off’ state (12 hours after last levodopa dose). Severe ‘off’ dystonia is present in the lower extremities with inversion of the right foot and extension of the left leg associated with rapid dystonic movements. His neck is turned forcefully to the right with jaw opening. The patient’s eyebrows are raised in a fixed manner. Both arms show evidence of dystonia, worse on the left with flexion at the elbow and clawing of the hand. The second segment shows the patient pre-STN DBS after his usual dose of levodopa. The ‘off’ dystonia has largely resolved, and is replaced by a levodopa-induced peak-dose dyskinetic gait. The third segment shows the patient post-STN DBS in the ‘off’ state (12 hours after levodopa dose but with continuous STN stimulation). The ‘off’ dystonia is largely resolved except for mild lip tightening.
A man with Parkinson’s catching a few ‘Z’s’

Andrew Siderowf

CASE PRESENTATION

The patient presented to the neurology service at the age of 46 years having noticed resting tremor and clumsiness in his left hand for 6 months. There was no history of sleep disturbance or psychological symptoms. The patient worked as a manager for a beverage company, drank socially, did not smoke, and had no family history of Parkinson’s disease. Neurological examination at initial presentation demonstrated resting tremor and cogwheel rigidity in the left arm. Finger-tapping was slow in the left hand. There was cogwheel rigidity in the right arm and left leg. The remainder of the neurological examination was normal. Since the patient was right-handed and was not functionally impaired by his symptoms, no therapy was initiated.

Six months later, the patient returned to the clinic with increased tremor in his left hand that was interfering with his ability to make presentations at work. Treatment was initiated with pramipexole, and titrated to a dose of 1 mg three times a day. The patient returned to the clinic 4 months later complaining of excessive daytime somnolence (EDS), and brought with him the email message shown in Figure 17.1. He had fallen asleep while composing the message with his hand on the ‘z’ key and typed several rows of ‘z’s’ before his finger fell off the key. He underwent an overnight polysomnographic study which demonstrated decreased sleep latency and periodic leg movements, but no apnea. He was subsequently switched to ropinirole and then pergolide at therapeutic doses, but continued to have daytime drowsiness. Additional medication trials included carbidopa/levodopa alone and in combination with low-dose agonist therapy. He also had trials of caffeine, modafinil, and methylphenidate without effect. Ultimately, he underwent deep brain stimulation (DBS) surgery and was able to discontinue dopaminergic medications. Following DBS, his daytime drowsiness improved significantly, but did not completely resolve.

DISCUSSION

This patient’s case illustrates the problem of excessive daytime somnolence (EDS) in Parkinson’s disease (PD). Disorders of sleep and wakefulness are very
common in PD patients, and a number of different problems may be observed. Of these, EDS has received considerable attention following the report of eight patients receiving dopamine agonist therapy who fell asleep while driving. However, other sleep problems occur in PD, including sleep fragmentation due to night-time wearing-off, periodic leg movements, vivid dreaming, rapid eye movement (REM) behavior disturbance, and obstructive sleep apnea. In one survey, 76% of PD patients reported at least one problem related to sleep and 18% took a sleeping medication.

These various night-time sleep problems may contribute to EDS, but EDS may occur for other reasons. It is well-accepted that patients with more long-standing PD and those with dementia are more likely to have EDS. However, in a large-scale epidemiological study of non-demented, independent patients conducted at Canadian PD centers, no other clinical risk factor for EDS was identified. This study found that patients with higher scores on two validated sleep scales, the Epworth Sleepiness Scale (ESS) and the Sleep Composite Score, were at significantly higher risk of EDS.

Substantial controversy exists regarding the role of dopaminergic therapy in the etiology of EDS. The Canadian study found increased EDS in patients treated with any antiparkinsonian medication compared to untreated patients, and a dose–response effect such that patients receiving higher cumulative medication dosages were more likely to experience EDS. However, there was no difference between classes of dopaminergic medications (levodopa versus dopamine agonists). This finding is in contrast to results from clinical trials comparing the dopamine agonists ropinirole and pramipexole to levodopa, in which higher rates of somnolence were observed in subjects randomized to a dopamine agonist. In the case described above, problematic daytime drowsiness did not resolve until DBS surgery was performed, allowing the discontinuation of dopaminergic medications.

The occurrence of daytime drowsiness raises several practical issues. The first question is how doctors can screen PD patients for EDS. The most important consideration is simply to bring up the subject of daytime sleepiness with patients, since they may not realize that it is related to PD. Another approach is to use a sleepiness scale as part of a waiting-room questionnaire. One of the key
findings of the Canadian study is that the ESS is a potentially useful screening test. It is a brief questionnaire that can easily be administered in the office. Using a cut-off of 7, the ESS was 75% sensitive for major daytime drowsiness.

A second practical issue is how to counsel patients receiving dopaminergic therapy about the risks of EDS, particularly when driving. In the Canadian study, falling asleep at the wheel was uncommon (3.8%), but one could argue that this frequency is still too high, considering the risk of harm with each episode. It is clear that patients should be educated about the symptoms of EDS, and the particular situation of EDS while driving should be discussed. Some experts have argued that patients starting dopaminergic therapy should not drive for a period of time to determine whether they will experience daytime drowsiness. However, there is no consensus on this point. Furthermore, there are no uniform recommendations on whether patients with PD, regardless of treatment, should be reported to the state department of motor vehicles.

The third practical issue is how to treat PD patients with EDS. An overnight polysomnographic study may be useful to determine whether ineffective nighttime sleep, particularly sleep apnea, is contributing to EDS. Addressing ‘sleep hygiene’ with patients, including the importance of regular bedtime and wake-up time, avoidance of caffeine toward the end of the day, and regular exercise, is also important. Caffeine in the morning may be helpful in keeping some patients awake. Stimulants traditionally used to treat narcolepsy, including methylphenidate, may be used for EDS associated with PD. Modafinil is another wakefulness-promoting agent that may have a slightly better side-effect profile than methylphenidate, but is expensive.

This case is instructive because it emphasizes that excessive daytime sleepiness is common in PD and has many potential causes, particularly antiparkinsonian medications such as dopamine agonists. Other considerations include a nocturnal sleep disorder, such as sleep apnea, restless legs syndrome (RLS), or insomnia associated with depression. Sleep disorders may also reflect an intrinsic aspect of PD itself. When a cause of EDS can be identified, specific therapy should be described, such as continuous positive airway pressure (CPAP) for apnea, or treatment of RLS. Lowering the dosage of dopaminergic drugs is a potential treatment, but may not be tolerated due to worsening of parkinsonism. In some cases, such as the one described above, DBS may be considered as a draconian dopaminergic drug-sparing approach to treat medication-induced EDS.

REFERENCES

A 44-year-old man with dizziness since the teens

Robert L Rodnitzky

CASE PRESENTATION

This 44-year-old man began to experience episodes of vertigo, dysarthria, and ataxia while a teenager. The spells typically occurred during physical exertion such as bowling. Later, in his 20s and 30s, they occurred while under pressure at his job in a factory. At first, each episode lasted 15–20 minutes, but over time, they began to last as long as 1–2 hours. The episodes occurred at an average frequency of 4–6 times per year, with no residual symptoms between attacks. He was evaluated by the neurology department in his 20s, but no diagnosis could be made. He was then referred to otolaryngology who attributed his spells to a cholesteatoma, which was not found after exploratory surgery. Other diagnoses considered included basilar invagination, convulsive disorder, and anxiety attacks. Further history revealed that his mother had similar spells, which were especially common while working but were reduced in frequency after her retirement. His daughter, age 20, experienced similar episodes occurring twice a week and lasting approximately 15 minutes. Examination of the patient revealed no neurologic abnormalities with the exception of gaze-evoked nystagmus on right or left horizontal gaze.

DISCUSSION

This patient was diagnosed as having episodic ataxia type 2 (EA2). He was treated with acetazolamide, and after reaching a dosage of 250 mg twice a day, had no further episodes of ataxia, dysarthria, or vertigo. Episodic ataxia type 2 is an autosomal dominant disorder clinically characterized by paroxysmal ataxia, vertigo, and nystagmus, typically occurring at the rate of one or two times per month but occasionally as often as several times per week. The episodes are often triggered by physical or emotional stress, as well as by alcohol or caffeine consumption. A characteristic attack lasts several hours but occasionally can persist for 1 or more days. Initially, affected individuals are normal between attacks, but many patients eventually develop persistent nystagmus and/or ataxia over time. Gaze-evoked nystagmus and primary position downbeat nystagmus are the two most typical eye findings in these patients. Weakness during
an attack and dystonia between attacks\(^1\) are two additional possible neurologic features.

EA2 is caused by a mutation in the CACNA1A gene on chromosome 19, which encodes an essential subunit of the voltage dependent P/Q-type calcium channel. The P/Q calcium channel is richly concentrated in cerebellar Purkinje cells, probably accounting for the predominance of cerebellar symptoms in this condition. The most common mutation is a non-sense mutation that results in an abnormally truncated protein product. More than 17 different mutations have been associated with the EA2 phenotype. Two other neurologic conditions are allelic to EA2 but are associated with different mutations of the same calcium channel gene. A trinucleotide expansion in the gene results in autosomal dominant spinocerebellar ataxia type 6 (SCA6), while certain missense mutations of the same gene are associated with familial hemiplegic migraine. Not unexpectedly, there is occasional crossover between the three clinical conditions associated with mutations of the CACNA1A gene.\(^1\) Thus, SCA6 patients sometime experience episodic rather than slowly progressive ataxia, especially at the onset of their illness. Conversely, EA2 patients occasionally present with slowly progressive ataxia. Additionally, some patients with EA2 experience episodes of hemiplegia, presumably representing the crossover between EA2 and familial hemiplegic migraine.

EA2 is clinically distinguished from episodic ataxia type 1, a disorder of the potassium channel, by the absence of myokymia, the duration of each attack (hours vs minutes), and the lower frequency of attacks (several per month or year vs several per day). Response to therapy is often useful in distinguishing the two forms, since EA2 is much more likely to improve with acetazolamide. The full spectrum of genetic abnormalities associated with EA2 is moderately complex.\(^1\) Some unaffected family members of EA2 patients have been found to harbor the typical CACNA1A mutation, demonstrating that this gene is not fully penetrant. Conversely, a small number of families with the EA2 phenotype linked to chromosome 19 do not carry an identifiable mutation of the CACNA1A gene, and still other affected families are not linked at all to chromosome 19. Lastly, some EA2 patients with the typical CACNA1A mutation have parents who do not carry this mutation, suggesting that a spontaneous mutation has occurred in the proband.

Although this patient was diagnosed on the basis of a typical clinical history, examination, and family history, the diagnosis of EA2 can be aided by genetic testing. Diagnostic sequencing of the entire CACNA1A gene is commercially available; however, it is clear that the abovementioned genetic complexity of this disorder needs to be fully understood in order for there to be meaningful interpretation of the resultant genetic analysis. Additional supportive, but not definitive, diagnostic evidence of EA2 is cerebellar vermis atrophy on magnetic resonance imaging (MRI).\(^2\)

The most effective therapy for EA2 is acetazolamide, which presumably acts by normalizing the elevated pH that is present in affected central nervous system tissue, particularly the cerebellum.\(^3\) This treatment is extremely useful in preventing or modulating the paroxysmal attacks in this illness, but it does not improve symptoms such as progressive ataxia, nystagmus, or dystonia that persist between attacks. In patients whose attacks are not improved by
acetazolamide, 4-aminopyridine has been found to be useful, possibly through the mechanism of restoring the inadequate release of γ-aminobutyric acid (GABA) in Purkinje cells to normal levels.3

This case is instructive for several reasons. First, it illustrates that recurrent symptoms that are relatively common, such as vertigo, can easily be dismissed as being clinically unimportant, especially if they are self-remittent and unassociated with apparent sequelae. Second, it presents the typical clinical phenotype of episodic ataxia type 2, and leads to consideration of its genotype, pathophysiology, and treatment. Third, since most cases of EA2 demonstrate autosomal dominant inheritance, this case emphasizes that a thorough family history is often the critical clue that prompts inclusion of this condition in the differential diagnosis.

REFERENCES
Weakness, ataxia, and myoclonus in a 68-year-old woman

Yvette M Bordelon and Stanley Fahn

CASE PRESENTATION

A 68-year-old retired nursing professor presented to the Columbia University Movement Disorder clinic with a 1-year history of progressive extremity weakness and gait disorder. Her initial symptoms were low back pain, left leg weakness causing her to trip occasionally, and gait incoordination. An outpatient evaluation conducted at a medical center near her home led to the diagnosis of ataxia. Brain magnetic resonance imaging (MRI) and lumbar puncture were normal. Over the next 5 months, there was deterioration in her coordination and progressive bilateral lower extremity weakness, resulting in difficulty arising from a chair or bed. An exaggerated startle response and jerks of her trunk and limbs began and she started falling.

As part of the work-up of a second neurologic opinion, repeat brain MRI was normal, as were an electroencephalogram and a fluorodeoxyglucose-positron emission tomography (FDG-PET) scan of the brain. A computed tomography (CT) scan of the chest, abdomen, and pelvis revealed no malignancy, and anti-Hu and anti-Yo antibodies were not found. Acetylcholine receptor antibodies were absent and Whipple’s testing was negative. She was treated initially with clonazepam, which helped with the jerking movements, but the dose was later decreased due to depression. Baclofen was then added with no further benefit.

Her medical history included a lumbar laminectomy 25 years previously and surgery for thoracic outlet syndrome 15 years previously. There was no history of depression, anxiety, or other psychiatric disorder. There was no history of alcohol, tobacco, or drug use. There was no family history of ataxia, myoclonus, motor neuron disorder, or other neurologic disorder. She had an identical twin sister who was healthy.

In the 3 months prior to the clinic visit at Columbia University she felt that there had been no further neurologic deterioration. There was persistent weakness of her legs, with difficulty walking and climbing stairs, and weakness of her left arm. She used a cane for ambulation. She fell approximately once per week. Jerking of her body and limbs continued and was intrusive at times. She and her husband had recently sold their home and moved into a one-floor apartment, making it easier for her to walk around the house.
On examination, mental status was normal and there were no cranial nerve deficits. Strength was normal in the upper extremities. She had difficulty arising from a chair, but strength was normal in the lower extremities with give-way weakness of hip flexion bilaterally. While supine she was unable to lift her legs off the table. Hoover sign was positive bilaterally. Sensation to light touch, temperature, and vibration was normal. Deep tendon reflexes were 2+ throughout, with downgoing toes. There was no dysmetria or dysdiadochokinesis. Intermittent myoclonic-like jerks were observed in arms, legs, and trunk. They occurred at rest and in response to sensory stimuli. There was also enhanced startle myoclonus involving the trunk and limbs. Her gait was wide-based with mild ataxia. Frequent myoclonic jerks interrupted her gait and made tandem gait impossible (see video, Case 19).

**DISCUSSION**

Given the examination findings, negative work-up, and negative family history, we felt that the most likely diagnosis was a psychogenic movement disorder. The patient was referred to a psychiatrist who felt that there was evidence of a conversion disorder but did not uncover any psychological stressors at the initial visit. Electrophysiologic testing revealed intermittent moderate-to-long duration (150–1500 ms) electromyogram (EMG) discharges of the bilateral pectoralis, left vastus lateralis, and right hand; there were also head oscillations of variable frequency (4–7 Hz). The irregular EMG burst patterns were not affected by posture and were completely abolished with distraction. The study suggested a non-pathophysiologic origin of this movement. She was admitted to hospital for treatment of her psychogenic movement disorder, further psychiatric evaluation and treatment, and intensive physical and occupational therapy.

The patient met with the psychiatrist on a daily basis, and during the course of her hospitalization significant psychological stressors were revealed, including depression and anxiety over her husband’s failing health and over her mother’s dementia. She was the sole caregiver for her mother and overwhelmed with the responsibility. The movement disorder team met with her daily and set goals for her productivity in physical and occupational therapy. Over the course of 4 days the patient showed steady improvement. She spent 1–2 hours per day in physiotherapy and occupational therapy and was taught relaxation, desensitization, and strengthening exercises. An additional 5–6 hours per day were spent with self-directed exercises recommended by the therapists. The antidepressant venlafaxine was started, and baclofen and clonazepam were slowly titrated off. On the day of discharge the patient was ambulating independently with a normal stance and stride without ataxia and she was able to tandem. She arose from a chair easily and climbed stairs with no impairment. The myoclonus and enhanced startle response had resolved.

There is a paucity of information on the incidence, characteristics, and, particularly, treatment of psychogenic movement disorders. Estimates of the occurrence of psychogenic movement disorders in neurology clinics range from 2.6 to 25%, with females constituting the majority of cases.¹ The most common psychogenic movement disorders are dystonia, tremor, gait abnormalities, myoclonus, and paroxysmal dyskinesias.²
The diagnosis of psychogenic movement disorders may be problematic, as organic illness must be considered and ruled out. A non-organic cause for a movement disorder can be proven only when it resolves with psychotherapy, hypnotherapy, physical therapy, or placebo. Historical and clinical characteristics supporting the diagnosis of psychogenic movement disorder include: (1) temporality: abrupt onset, static course, spontaneous remissions, and/or paroxysmal in nature; (2) inconsistent movements changing in pattern, distribution, and severity over time; (3) decrease or disappearance of movements with distraction and increase with attention; (4) movements and postures that do not fit into recognized physiologic or pathologic patterns; (5) presence of additional types of movement that are not consistent with a known movement disorder, particularly: rhythmical shaking, bizarre gait, deliberate slowness, bursts of verbal gibberish, excessive startle; (6) entrainment of the psychogenic tremor or movement to the rate of voluntary movement the patient is asked to perform; and (7) response to placebo, suggestion, or psychotherapy. 1,3

Psychogenic movement disorders may be classified by psychiatric diagnosis. Conversion disorder consists of physical symptoms linked to psychological factors, yet the symptoms are not consciously produced. Somatization disorder involves multiple and varied complaints over several years, typically involving several different organ systems, and, like conversion, are considered subconscious. Factitious disorder is characterized by volitional production of symptoms due to a pathological, psychological need. If the movement disorder is voluntarily feigned purely for secondary gain such as monetary rewards, avoidance of work or other responsibilities, or evasion of criminal prosecution, the disorder is diagnosed as malingering.

There is no current consensus on the appropriate treatment for psychogenic movement disorders and no controlled clinical trials have been conducted to date. A study conducted at Columbia University Medical Center found complete symptom remission in 25% of cases and significant symptom relief in another 21% of cases in patients undergoing inpatient psychiatric, neurologic, and rehabilitative treatment. 2 It is generally accepted that a multidisciplinary approach is most beneficial in the treatment of psychogenic movement disorders, coordinating neurologic and psychiatric care with rehabilitation. Medications treating underlying psychiatric diagnoses such as depression and anxiety should be used as indicated, and behavioral and relaxation techniques incorporated if necessary. This approach has been undertaken in an inpatient setting with some success, as noted above, but coordinating similar care in the outpatient setting may also be beneficial.

This case is instructive for several reasons. First, it shows a patient with a previously undiagnosed complex neurologic disorder achieving significant functional improvement after diagnosis and treatment for a psychogenic movement disorder. Second, it emphasizes the use of positive criteria on which to base the diagnosis of a psychogenic movement disorder. Third, it demonstrates that a psychiatric diagnosis may not be apparent during the initial assessment of a suspected psychogenic disorder, and that that should not rule out the diagnosis.
REFERENCES


Legend to video

Case 19 The first segment shows a 68-year-old woman with a 1-year history of weakness, ataxia, and myoclonus examined on the first day of hospitalization for treatment of a psychogenic movement disorder. Note wide-based, ataxic gait, frequent, diffuse myoclonic jerks, enhanced startle myoclonus, and proximal lower extremity weakness when attempting to stand. The second segment shows examination on hospital day 4 after intensive physical and occupational therapy and psychiatric evaluation and treatment. Note marked improvement of gait, and resolution of myoclonus and lower extremity weakness when standing and climbing stairs.
Chorea and action-induced myoclonus

Karen E Anderson and William J Weiner

CASE PRESENTATION

The patient was first seen at age 37 years. According to history provided by his prior physicians, dystonia had developed in his trunk and limbs in his late 20s along with gait impairment, leading to a medical discharge from military service. There were some abnormal movements in the face, described as tics by prior physicians. He was unable to work following discharge from the service and, according to prior clinical descriptions, probably had some cognitive impairment by age 30. Multiple diagnostic evaluations, including structural brain imaging, electroencephalograms (EEGs), electromyograms (EMGs), thyroid function tests, and testing for human immunodeficiency virus (HIV) and sexually transmitted disease failed to reveal the cause. The patient was finally diagnosed with Huntington’s disease (HD) by a neurologist who confirmed the clinical diagnosis with genetic testing, after at least 7 years of symptoms. The patient’s fraternal twin brother also has a clinical diagnosis of HD, but, due to insurance limitations, has not undergone genetic testing. As both were adopted, no other family history is known.

The patient was taking valproate 500 mg twice a day for a possible seizure disorder. The seizures were described as brief, episodic, myoclonic movements involving his arms and upper body. He had a depressed mood with irritability, neurovegetative symptoms, and anhedonia, which was successfully treated with 40 mg fluoxetine daily. On examination the patient was a poor historian, unable to give details of his illness and specifics about his current daily activities. He had slow saccades both vertically and horizontally, generalized bradykinesia, truncal dystonia, and moderate dysarthria. There was minimal chorea, limited mostly to his face and hands. There were occasional myoclonic jerks at rest. He had mild rigidity in his limbs and neck. Gait was wide-based, slow, and unsteady, with a lurching quality. He had impaired retention of new information and difficulty with executive tasks requiring set switching. He had been living semi-independently, sharing an apartment with his twin, under close supervision by an intensive case manager.

Several months after the initial evaluation by us, he began falling frequently. He lost weight and became disheveled, and there was concern that he was no longer able to care for himself, even with supervision. His twin also had a
decline in function at that time, and they were both admitted to a nursing home experienced in the care of HD patients. He gained weight, his gait stabilized, and there was some improvement in his speech and swallowing. His mood remained good, and he was cooperative with the staff. However, the myoclonus became more prominent with any directed movement, such as extending the arm to pick up an object (see video, Case 20). Any sustained action, such as attempting to hold a cup to his lips, also resulted in significant, debilitating myoclonic jerks. His ability to care for himself became severely impaired. The etiology of the myoclonus was unclear. Epilepsy and motor impersistence, both of which are seen in HD, were considered in the differential.

The patient was started on clonazepam 0.5 mg each morning, eventually reaching clonazepam 1 mg three times a day, along with the valproic acid; however, the patient’s myoclonus worsened, causing further disability. By age 39, approximately 12 years into the illness, he was no longer able to feed, groom, or dress himself, primarily due to impairment from the action myoclonus. Clonazepam and valproic acid were gradually withdrawn, and levetiracetam was added and titrated to 1000 mg twice a day. There was no improvement in the myoclonus, which became so prominent that any action by the patient and attempts by the staff to assist him (e.g. transferring him from a chair to the bed) were difficult. Levetiracetam was increased to 1500 mg twice a day with no benefit. The patient now requires complete assistance with all activities and has no independent function. His brother, whose HD symptoms have also progressed, has some myoclonic jerks, but they are not as pronounced as those seen in the patient.

**DISCUSSION**

Chorea and dystonia are the motor hallmarks of adult-onset HD. Most patients also have slow saccades, impaired fine motor control and dysarthria. Intellectual impairment, including memory and executive dysfunction, is seen in most patients. Psychiatric symptoms, including depressed mood, are very common.

Myoclonus has been described in HD, but is generally associated with juvenile cases, which are also more likely to develop seizures.\(^1 \, 2\) This patient had a more juvenile-appearing form of HD, despite definite adult onset of symptoms, given the pronounced bradykinesia, dystonia, and relative paucity of chorea when he was first seen in the middle stages of the illness. Thompson et al. described three HD patients in whom cortical myoclonus was the predominant feature of the illness.\(^3\) As with our case, all had onset of motor abnormalities prior to age 30. There are often other reports of action myoclonus as a relatively rare feature of HD.\(^4 \, 6\)

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This case is instructive because it demonstrates that myoclonus can occur in HD, independent of seizures. Although it usually occurs in the advanced stages, myoclonus may appear early, and is rarely the predominant motor abnormality in HD.
REFERENCES


Legend to video

Case 20  At rest, there are minimal abnormal movements aside from a resting tremor of the left lower extremity. There is severe dysarthria. With any attempt at directed movement, such as reaching for an object, the debilitating myoclonus becomes evident as does bradykinesia and incoordination.
A case of seizures, orofacial dyskinesias, and peripheral neuropathy
Carlos Singer and Spiridon Papapetropoulos

CASE PRESENTATION

A 31-year-old woman presented to us with a 7-year history of neurological complaints. She was a product of a normal, but somewhat difficult birth, and during the first year of her life she had experienced febrile seizures. At the age of 24 years she experienced the first grand-mal seizure of her adult life. She was not aware of any other seizures, with the possible exception of a single episode of a metallic taste and a few staring spells. She was subsequently placed on successive antiepileptics (including phenytoin, carbamazepine, phenobarbital, and gabapentin) that she had to discontinue due to side-effects (i.e. drowsiness, allergic skin reactions, elevated liver enzymes). Finally she was placed on sodium valproate that was well tolerated at a dose of 750 mg/day.

At the age of 27, she started experiencing problems with oral manipulation of food (mainly lack of control of her tongue), as well as swallowing and speech difficulties. She also developed sialorrhea, involuntary vocalizations, and lip biting. By the age of 29 she started experiencing gait and balance problems accompanied by impaired dexterity, especially of the left upper limb. It was at that time that her husband started noticing ‘restlessness’ as well as signs of cognitive impairment (mainly memory and sense of direction). Her syndrome progressed to involve involuntary movements of the trunk and limbs as well as the orolingual areas. Her cognition deteriorated to a point that she could no longer keep her job as a dental assistant, and her husband had to take over her financial affairs (although she performed well on the Mini Mental State Examination (MMSE) test, 28/30), and she could no longer drive or ride a bicycle.

When she was first evaluated at our movement disorders clinic at the age of 31, her seizures were relatively stable on gabapentin (2 g/day) and extended release carbamazepine (900 mg/day). Neurologic examination revealed mild slowness of saccades, hypophonic and nasal speech with hypokinetic articulation, rest tremor of the tongue (about 4 Hz), and occasional drooling. Intelligibility was compromised by about 10–20%. She had difficulty in keeping the tongue protruded. There was facial grimacing with forehead contractions, occasional
Movement Disorders

dystonia of the lower face, lip protrusions, and lip biting. She also displayed irregular rapid movements of the trunk and upper and lower extremities, proximal more than distal, which she successfully suppressed for minutes at a time. A very mild milkmaid’s grip was noted bilaterally. There was a fine postural tremor of the left upper extremity. There was a slight increase in tone of the right upper extremity with reinforcement maneuvers. Mild bradykinesia was noted (left > right). There was an inconsistent decrease in sensation to pinprick on the left foot, with preservation of vibration and position sense. Deep tendon reflexes were 1+ throughout with reinforcement. Both toes were downgoing. Gait revealed an asymmetry with more time spent in bringing the right leg forward as compared to the left. There was reasonably good arm swing (see video, Case 21).

Review of her prior laboratory tests revealed an elevated creatine phosphokinase and nerve conduction studies showing a sensorimotor axonal neuropathy. Additional laboratory findings included normal complete blood count (CBC), normal copper studies, and absence of the Huntington’s disease CAG expansion (20 and 18 repeats, normal ≤26). Swallowing studies revealed disordered propagation and decreased clearing of the oropharynx suggestive of neuromuscular dysfunction. Brain magnetic resonance imaging (MRI) revealed atrophy of the head of the caudate with abnormal signal intensity involving the caudate and putamen.

When last seen at the age of 35, her syndrome had progressed little. She complained of forgetfulness, and her speech was slurred with hypokinetic articulation and elements of nasality and stuttering. Intelligibility was compromised by only about 5–10%. There was tongue tremor with protrusion and involuntary guttural sounds, trunk and limb involuntary movements, speech impairment (mainly hypokinetic), and mild bradykinesia on finger tapping (left > right). Her gait was asymmetric and mildly wide-based. She still had preserved postural stability in the anterior/posterior direction. There were no signs of pyramidal involvement and she had preserved reflexes.

DISCUSSION

The diagnosis of this patient was made by a blood smear examination with Giemsa–Wright stain. It revealed 4% acanthocytes (from Greek ‘acantho’ which means spiky) (Figure 21.1). In a wet-preparation slide (1:1 dilution of blood in saline), 58% of the erythrocytes had these features (for details see reference 1). Molecular genetic analysis revealed two heterozygous mutations of the ChAc gene (EX70_73del mutation and EX53_7339_7340insT).

Neuroacanthocytosis (NAC) is an uncommon neurodegenerative disorder first described more than 30 years ago by Critchley et al. The disease typically begins between ages 25 and 45 with the gradual onset of a variety of neurological difficulties (see below) associated with aberrant erythrocyte morphology. Although it is mainly transmitted in an autosomal recessive pattern, dominant, X-linked (termed ‘McLeod’s syndrome’), and sporadic forms of NAC have been reported, all with similar clinical phenotypes.

The classic clinical picture of NAC includes a movement disorder, seizures, and a peripheral neuropathy. The movement disorder is characterized by trunk and limb chorea, orofacial dyskinesias, and tics of the orofacial region
associated with lip and tongue biting. There are also a variety of neuropsychiatric manifestations such as cognitive deterioration accompanied by mood and behavioral symptoms and occasionally thought disorder.\(^6\)

NAC can be mistaken for Huntington’s disease (HD) both clinically and radiologically.\(^7\) It has been suggested that especially in atypical cases of HD, NAC should be included in the differential diagnosis and ruled out by appropriate smear testing.\(^8\) Acanthocytosis is also found in a smaller percentage of cases with abetalipoproteinemia (ABL),\(^5\) pantothenate kinase-associated neurodegeneration (PKAN), and Huntington’s disease-like 2 (HDL2).\(^9\) MRI findings in NAC usually reveal caudate and sometimes more generalized atrophy with dilatation of the anterior horns. Furthermore, symmetrical abnormalities in the basal ganglia, with increased signal on T2-weighted sequences from the caudate and putamen nucleus, have been reported.\(^10\) These findings are very similar to those observed in HD.\(^7\)

The clinical and radiological similarities between HD, NAC, McLeod’s syndrome, and ABL and the presence of mutations leading to abnormal protein expression such as chorein, XK, and huntingtin, may allow identification of the pathogenetic mechanisms of neurodegenerative processes of the basal ganglia that lead to the development of these inherited disorders.\(^5\)

We describe the case of a patient with NAC who presented with a 3-year history of seizures before she ever developed the more classic movement disorder. For this period of time the diagnosis of neuroacanthocytosis was not considered. Although seizures are rarely the presenting symptom in NAC, a few such presentations have been reported in the literature.\(^11\) Interestingly, our patient suffered several side-effects from antiepileptic drugs (AEDs), and when the movement disorder first appeared it was initially attributed to the AEDs (for review of AED-induced motor disorders see reference 12) and diagnosis was delayed once again.

Another point of interest in our case is the presence of mild–moderate asymmetric parkinsonism characterized by bradykinesia and gait/posture abnormality. Although the movement disorder in NAC is predominantly hyperkinetic (chorea, tics, dystonia, and dyskinesias), several cases with a combination of hyper- and hypokinetic symptoms have been reported.\(^13,14\)

![Figure 21.1](image)

(A) Normal blood smear. (B) Our patient’s blood smear showing increased number of acanthocytes.
Our case also illustrates the importance of using the proper laboratory testing. Reported percentages of acanthocytes in affected individuals’ blood vary widely, but are usually in the 5–50% range. As there is no standard clinical method for performing an acanthocyte count, it is not clear how much variability can be accounted for by differing laboratory procedures. In some cases a simple dried blood smear might not be diagnostic, since it may reveal a normal acanthocyte count. In such cases dilution in normal saline (one drop of blood and one drop of saline), \textit{in vitro} aging of the red cells, and contact with glass may cause a great proportion of these patients’ red cells to develop multiple spiny or rounded projections. In our specific case, we personally enlisted the assistance of the pathology department, reviewed with them the literature on proper laboratory testing, and were present during the performance of the test.

\textbf{This case is instructive because it demonstrates many of the clinical features of neuroacanthocytosis including its workup. Special attention should be paid to the correct laboratory techniques for demonstrating acanthocytes before genetic confirmation is considered.}

\textbf{REFERENCES}


Legend to video

Case 21 The video demonstrates some of the cardinal features of our patient’s neurological examination. During her symptom description her hypophonic and nasal speech with hypokinetic articulation is noted. There is mild slowness of saccades, rest tremor of the tongue (about 4Hz), and occasional drooling. Throughout the examination her orobuccolingual symptoms are present. There is mild bradykinesia revealed by finger tapping (left > right). Gait is asymmetric with more time spent in bringing the right leg forward as compared to the left. There is reasonably good arm swing.
A case of intermittent chorea induced by coffee

D Martino, P Jarman, and KP Bhatia

CASE PRESENTATION

A 36-year-old left-handed truck driver was admitted to the National Hospital for Neurology and Neurosurgery, London, for paroxysmal involuntary movements of his limbs. Episodes had begun at the age of 6 years, and were characterized by choreic and dystonic movements which could occur either on his right or left side, or on both. They lasted from 5 minutes to several hours, with the average duration being 1 hour. The movements were precipitated by caffeine, alcohol, emotional stress, and, less frequently, temperature changes or fatigue, whereas sudden movement or physical exercise had no effect. The frequency of attacks had diminished throughout the years: during childhood, they were daily, and at the time of observation ranged from three per week to one every 3 weeks. He often felt a sensation of inner tension preceding the movements. During episodes his speech would become slurred, and on occasion his gait would be affected. After an attack, he felt fatigued, but consciousness was always preserved, both during and following movements. He reported the ability to abort attacks in their early stages with short periods of sleep. Between attacks the patient was completely well and his neurological examination was normal. He tried several medications, including levodopa, clobazam, clonazepam, and phenytoin, none of which provided substantial benefit.

His developmental milestones were normal. He did not smoke or use recreational drugs, and drank alcohol only sporadically. His medical history was unremarkable. There was a family history of a similar movement disorder occurring in several generations (Figure 22.1) with an apparent autosomal dominant mode of transmission. In most affected family members the attacks began in early childhood.

During admission, he underwent a number of investigations, which were all normal, including routine blood chemistries, cell blood counts, plasma amino acids, and brain imaging. Cerebrospinal fluid (CSF) routine tests were normal. Additionally, CSF was collected at baseline (14.00) when symptom-free and during an attack (19.00) induced by fasting and drinking a cup of coffee, to measure dopamine and serotonin metabolites. The dopamine metabolite homovanillic acid showed a 3.2-fold increase to the top end of the reference range during the
attack, whereas the serotonin metabolite hydroxyindoleacetic acid increased 2.5-fold to just above the reference range.

The patient was video-recorded during an episode, triggered by four cups of strong coffee (see video, Case 22). While sitting with his arms in resting position, subcontinuous, jerky, dystonic movements of the left leg with inversion and anteroflexion of the left foot, and more rapid, brisk movements of mixed (choreiform and dystonic) quality, mainly in extension of the left hand, could be seen. Occasional jerks of the right arm and shoulder and of the trunk were present, although the distribution of involuntary movements was strongly asymmetrical. Choreic movements in the left hand and fingers were worsened by the outstretched arm posture. Performance on finger tapping was poor on the left, due to the superimposed choreiform jerks. On gait examination, the patient tended to drag the left leg due to dystonic posture, and there was bilateral foot dystonia with toe extension.

**DISCUSSION**

This patient suffers from a paroxysmal disorder of involuntary movements, occurring during the waking state and with preserved consciousness. Episodes began during childhood, and their phenomenology and precipitants have remained substantially the same throughout the years; his neurological examination has always been normal between attacks. These features are typical of the group of disorders named paroxysmal dyskinesias. 1

Paroxysmal dyskinesias are classified, according to the precipitating factor, into three main types: paroxysmal kinesigenic dyskinesias (PKD), paroxysmal non-kinesigenic dyskinesias (PNKD), and paroxysmal exercise-induced...
dyskinesias (PED).\textsuperscript{1} Another type previously referred to as hyponogenic (or nocturnal) paroxysmal dyskinesia is now recognized to be a form of mesial frontal lobe epilepsy. The absence of attacks induced by sudden movement or prolonged exertion in our patient excludes the diagnoses of PKD and PED. Instead, his history and the nature of the movements are typical for the PNKD variety, first described in 1940 by Mount and Reback,\textsuperscript{2} who called this disorder ‘familial paroxysmal choreoathetosis’, already emphasizing its frequent familial presentation.

PNKD may begin from 2 months to 50 years of age, although the majority of cases have their onset in childhood or adolescence.\textsuperscript{3} Although attacks may occur spontaneously, they are more often exacerbated by stress, excitement, alcohol, caffeine, chocolate, smoking, cold, or heat. Most patients, like ours, report more than one precipitant.\textsuperscript{3} Although physical stress or fatigue may cause an attack in PNKD, this should be differentiated from either PKD, in which attacks are shorter and provoked immediately after the beginning of a complex movement (e.g. arising from a chair), or PED, whose attacks are exclusively triggered by exercise. Attacks in PNKD are typically less frequent than in PKD, ranging from two per month to 20 per day; as in our patient, attack frequency tends to diminish with age. Attacks usually last minutes to hours. Sleep benefit and diurnal variations in frequency and severity of attacks have been reported. Drug treatments are difficult and antiepileptics are not effective as they are in PKD, but could be tried. Benzodiazepines such as clonazepam may help. Other options include levodopa, and paradoxically also dopamine receptor blocking agents. Most patients, however, learn to avoid precipitants, and drug treatment is not always necessary. Sporadic cases of PNKD should be investigated to rule out possible causes of secondary PNKD of which multiple sclerosis, transient ischemic attacks or stroke, trauma, and hypo/hyperglycemia are the most frequent.\textsuperscript{1}

Familial PNKD has an autosomal dominant inheritance with high penetrance. Its genetic cause has recently been defined in a single PNKD locus on chromosome 2q33–36.\textsuperscript{4} Familial PNKD seems very homogeneous, both clinically and genetically. Only two missense single-nucleotide mutations in exon 1 of the brain-specific isoform (MR-1L) of myofibrillogenesis regulator 1 (MR1) gene, mapping at the same locus, have been documented in 58 typical patients from 10 unrelated families, including the original family reported by Mount and Reback.\textsuperscript{5} The MR1 is homologous to the hydroxyacylglutathione hydrolase gene, which detoxifies methylglyoxal;\textsuperscript{5} interestingly, this is a by-product of oxidative stress present in coffee and alcoholic beverages, which are among the main precipitants of PNKD attacks. Genetic analysis of our patient and affected living relatives confirmed the presence of a missense mutation on exon 1 of the myofibrillogenesis regulator gene (MR1).
REFERENCES


Legend to video

Case 22 This video episode was triggered by four cups of strong coffee. While sitting with his arms in resting position, subcontinuous, jerky, dystonic movements of the left leg with inversion and anteroflexion of the left foot, and more rapid, brisk movements of mixed (choreiform and dystonic) quality, mainly in extension of the left hand, may be seen. Occasional jerks of the right arm and shoulder and of the trunk are present, although the distribution of involuntary movements is strongly asymmetrical. Choreic movements in the left hand and fingers are worsened by the outstretched arm posture. Performance on finger tapping is poor on the left, due to the superimposed choreiform jerks. On gait examination, the patient tends to drag the left leg due to dystonic posture, and there is bilateral foot dystonia with toe extension.
A curable cause of dystonia

Joel M Trugman, Keith Hyland, and Yoshiaki Furukawa

CASE PRESENTATION

The index case in this family was first evaluated at 6 months of age for developmental motor delay and truncal hypotonia. By age 1 year she had generalized dystonia with episodes of dystonic limb spasms accompanied by upward ocular deviations (oculogyric crises) lasting minutes to hours. By age 3 years, the child had achieved no significant motor milestones. Examination at that time showed poor head control, inability to roll over or sit independently, and no speech production. Generalized dystonia, symmetric hyperreflexia, and bilateral extensor responses were noted (see video, Case 23).

Diagnostic evaluation performed between 6 months and 3 years of age included the following normal tests: serum copper and ceruloplasmin, lactic acid, very long chain fatty acids, arylsulfatase A, urine organic acids, chromosome analysis, and cranial magnetic resonance imaging (MRI). Plasma amino acids at age 6 months were normal except for a very mild elevation in phenylalanine (131 µmol/l, reference range 42–120 µmol/l). Plasma phenylalanine levels measured at other times between the ages of 6 months and 4 years were normal.

The mother had a history of leg and forearm muscle cramps and a tendency for flexion-inversion of the feet. She developed generalized dystonia at age 19 after taking oral contraceptives, which resolved after their discontinuation. On examination at age 28, she had bilateral foot dystonia and mild spasticity and hyperreflexia in the legs. The maternal grandmother complained only of mild muscle cramps, but examination at age 54 demonstrated dystonic inversion of the right foot with mild spasticity and hyperreflexia in the legs. The maternal great-grandmother had childhood-onset leg dystonia, which compromised her ability to walk to elementary school. She became minimally symptomatic in early and mid-adulthood but developed tremor after age 60. On examination at age 84, she had dystonic inversion of her left foot, tremor of both arms and the left foot, and mild generalized rigidity.

Because of the findings suggesting dopa responsive dystonia (DRD) in the mother, grandmother, and great-grandmother, the index case was treated with levodopa beginning at age 3. Carbidopa/levodopa was begun at a minimal levodopa dose (8mg/day) causing mild generalized dyskinesia. The dose of levodopa was increased slowly to 20mg four times per day over a 2-year
Movement Disorders

period, and the child showed a gradual, steady, and remarkable improvement in motor function. With levodopa, she developed speech (simple words) and purposeful arm reaching movements; she also developed the ability to sit independently and then scoot on her buttocks. The dystonic posturing of her legs and paroxysmal dystonic limb spasms with oculogyric crises improved. At age 5, however, the child experienced a 2-week period of lethargy and regression in motor skills, accompanied by an increased plasma phenylalanine level (968 µmol/l, reference range 38–73 µmol/l), indicating the development of significant hyperphenylalaninemia (HPA). At this point treatment with oral tetrahydrobiopterin (BH4) was begun. She soon developed the ability to walk. Speech and motor function improved steadily. At age 7 she was speaking in full sentences with mild dysarthria. At age 11, ‘eye rolling’ episodes were noted to persist, although in milder form lasting minutes. Wearing-off of medication effect, manifest as fatigue and muscle spasms in the limbs and jaw (worsened dystonia), has been obvious and somewhat problematic. At age 14, the most recent follow-up, the patient was maintained on levodopa (350 mg/day), entacapone (800 mg/day), and BH4 (650 mg/day), in four divided doses. Examination shows that cognition is normal; speech is mildly slurred but easily understood. She has normal strength and muscle tone with generalized fidgetiness and choreic dyskinesia in the limbs. Dystonic posturing in the limbs is absent at rest and present to a minimal extent with action. Tendon reflexes are normal and plantar responses are flexor. She walks independently with mild jerky dyskinesia.

The mother and grandmother of the index case were also treated for DRD with levodopa (200-300 mg/day) and had near-complete resolution of symptoms and signs.

DISCUSSION

Guanosine triphosphate cyclohydrolase I (GTPCH) is the enzyme that catalyzes the first step in the biosynthesis of tetrahydrobiopterin (BH4) from GTP (Figure 23.1). BH4 functions as an obligatory cofactor for three related hydroxylases: tyrosine hydroxylase (TH) and tryptophan hydroxylase (TRH), located primarily in the brain and critical for dopamine and serotonin synthesis, and phenylalanine hydroxylase, located mainly in the liver, mediating the metabolism of phenylalanine to tyrosine. BH4 deficiency presents clinically with symptoms and signs of basal ganglia dopamine deficiency due to impaired TH activity and with hyperphenylalaninemia (HPA) due to impaired phenylalanine hydroxylase activity.

Autosomal recessive GTPCH deficiency, described in 1984, is a rare enzyme deficiency presenting with HPA and severe neurological dysfunction in the newborn period. The syndrome of childhood-onset dystonia responsive to levodopa, described by Segawa et al in 1976 and later termed dopa responsive dystonia (DRD), was determined in 1994 to be caused by heterozygous mutations in the GTPCH I (GCH1) gene, and is appropriately termed autosomal dominant GTPCH deficiency.

The index case and family presented here taught us much about GTPCH deficiency. The mother, grandmother, and great-grandmother appeared to have
A curable cause of dystonia

Figure 23.1  Simplified tetrahydrobiopterin (BH4) biosynthetic pathway and BH4-dependent hydroxylation of aromatic amino acids. GTPCH, GTP cyclohydrolase 1; PTPS, 6-pyruvoyltetrahydropterin synthase; SR, sepiapterin reductase; PAH, phenylalanine hydroxylase; TPH, tryptophan hydroxylase; TH, tyrosine hydroxylase; DHPR, dihydropteridine reductase; AADC, aromatic L-amino acid decarboxylase.

typical DRD. The child, however, had a syndrome that was outside the spectrum of DRD with neurological features suggestive of autosomal recessive GTPCH deficiency (developmental motor delay, early truncal hypotonia, lack of speech development, oculogyric crises), but without overt hyperphenylalaninemia.

In evaluating this family, we first did a cerebrospinal fluid (CSF) analysis on the index case, which showed low concentrations of both BH4 and neopterin (BH4 5.0 nmol/l, reference range 9–40 nmol/l; total neopterin 2.5 nmol/l, reference range 7–65 nmol/l), confirming a severe central nervous system (CNS) BH4 deficiency. We then asked the following questions: if the index case and family members have BH4 deficiency, why is there not overt hyperphenylalaninemia and is there a defect in phenylalanine metabolism? To address these we challenged patients with an oral phenylalanine load (100 mg/kg body weight) and followed serum levels of phenylalanine and tyrosine for 6 hours. In patients with DRD, phenylalanine levels stayed elevated for a prolonged period of time and tyrosine levels did not rise appropriately as compared to controls. This defect was corrected by pretreatment with BH4. In the index case the defect was more profound than in the DRD patients. We demonstrated that patients with DRD do, in fact, have a systemic BH4 deficiency; it is not severe enough to cause hyperphenylalaninemia, but a subclinical impairment in phenylalanine hydroxylation can be demonstrated.
Finally, molecular genetic analysis revealed that the index case had two mutations in the GCH1 gene. One allele showed a single base pair deletion in exon 2 and the other allele showed a missense mutation in exon 6, indicating that the index case is a compound heterozygote for GCH gene mutations. The mother, maternal grandmother, and great-grandmother all had only the heterozygous deletion in exon 2 and manifested DRD. The father of the index case showed the missense mutation in exon 6 on one allele; he was clinically asymptomatic but refused neurological examination.

This case is instructive for a variety of reasons. Evaluation of this family led to two new observations about GTPCH deficiency. First, patients with DRD have a systemic BH4 deficiency that is demonstrated as a subclinical defect in phenylalanine hydroxylation. The phenylalanine load test can be useful in the diagnosis of this disorder. Second, patients who are compound heterozygotes for GCH mutations may have a phenotype that is more severe than classic DRD. These patients can present with severe neurological dysfunction in the first year of life without hyperphenylalaninemia; such affected children will not be picked up with newborn screening tests and their plasma amino acid profile may be normal.

From a clinical point of view, this case demonstrates that an excellent long-term outcome is possible with levodopa and BH4 treatment. This patient has been treated with carbidopa/levodopa for 11 years and BH4 for 9 years, and the clinical improvement has been impressive. Wearing-off of levodopa effect and medication-induced dyskinesia can be seen in patients with severe BH4 deficiency. This child had unusual features – oculogyric crises, complete lack of speech development, hyperactive reflexes with apparent extensor plantar responses – all of which resolved or improved with treatment. Finally, this case emphasizes that in children with spasticity and/or dystonia of uncertain etiology, particularly if the brain MRI is normal, a lumbar puncture should be considered for the investigation of defects of dopamine metabolism, and a careful trial of carbidopa/levodopa should be initiated since DRD is a potentially treatable or curable cause of childhood-onset dystonia.

REFERENCES
Legend to video

Case 23  The video clips show the index case at ages 3, 7, and 14. The mother and maternal great-grandmother of the index case, both with autosomal dominant guanosine triphosphate (GTP) cyclohydrolase deficiency (dopa responsive dystonia), are also shown.
Severe truncal flexion in a man with Parkinson’s disease

Michael Samuel and Robert Weeks

CASE PRESENTATION

A 66-year-old man was referred to a movement disorder clinic for diagnosis and management of an abnormal posture which had been present for 2 years. His trunk would flex forward when walking. He could correct this transiently by deliberately straightening up. He could extend his neck so that he could see forward. When lying flat, the trunk flexion resolved.

He was pain-free. Two years ago, a mild bilateral resting hand tremor had been noticed. He had no problems with manual dexterity, gait, or balance. He had no symptoms affecting cognition, vision, speech, swallowing, or sphincter functions. There was a suggestion that he had been generally slowing down over the previous 2 years, and on closer questioning, possibly over the previous 7 years. Two years before referral, a diagnosis of Parkinson’s disease had been made based on facial impassivity and rest tremor. He was started on a small dosage of levodopa three times daily without benefit. Amantadine had also been unhelpful.

There was no history of cranial or spinal injury, neuroleptic use, encephalitis, weight loss, or a family history of neurological disorders. Six years prior to presentation a bout of depression was treated with paroxetine which had been discontinued 12 months ago. He gave no current psychiatric symptoms.

On examination, there was facial impassivity and seborrheic dermatitis. Eye movements and cranial nerve examinations were normal. There was no tremor. He had mild bilateral limb rigidity with similar neck rigidity and mild global bradykinesia. There were no pyramidal or frontal release signs. The reflexes and sensory examination were normal.

While lying on a bed, he could assume a flat position (Figure 24.1), but immediately upon standing, he developed flexion of the trunk of about 40° (Figure 24.2). He had slightly flexed arms, a slow pace, impaired arm swing, and preserved postural reflexes.

Visualization of the whole neuraxis with magnetic resonance imaging (MRI) did not reveal a significant abnormality, although there was a slight degenerative spondylolisthesis at L3/4. A dopamine transporter (DAT) single photon emission computed tomography (SPECT) scan (striatal DAT) showed marked
Figure 24.1  The patient can lie flat and the truncal flexion resolves.

Figure 24.2  On standing, the patient has forward truncal flexion and slightly flexed arms. In this picture, he has mild neck flexion, but he could extend his neck to look straight ahead.
Severe truncal flexion in Parkinson’s disease

bilateral reduced uptake in the putamen and caudate. Electromyography of the lumbar paraspinal muscles and creatine kinase (CK) were normal.

DISCUSSION

A diagnosis of idiopathic Parkinson’s disease associated with camptocormia was made, probably longer than 2 years in duration. He had a history of mild tremor and bradykinesia but these were not symptomatic. His major symptom was trunk flexion present on standing and walking. At presentation to our clinic, he was taking 150 mg of levodopa per day without much benefit. An increase to 600 mg of levodopa per day made him feel significantly better, but the posture was only mildly better in the morning. The addition of cabergoline improved his mobility further but had little effect on his posture.

Camptocormia (Greek – ‘to bend trunk’) has also been termed ‘bent spine syndrome’. It is related to other similar conditions – head drop and head ptosis. Camptocormia was described in World War I as a bent spine syndrome in soldiers, possibly as a hysterical disorder, sometimes responding to psychiatric therapy. Today, neuromuscular causes such as amyotrophic lateral sclerosis and myasthenia gravis need to be considered, especially in the head drop syndrome. Other muscular causes include some familial dystrophies and inclusion body myositis. Local causes should also be considered, for example spinal cord tumors, vertebral infection or hematoma, and spinal stenosis. It has also been described as a paraneoplastic phenomenon. Skeletal causes, such as ankylosing spondylitis, can be distinguished from camptocormia as the latter corrects on assuming a recumbent position (as in Figure 24.1).

A variety of movement disorders are also associated with camptocormia, particularly idiopathic Parkinson’s disease, post-encephalitic parkinsonism, and infarction of the basal ganglia, mostly putamen. In a series of eight patients with idiopathic Parkinson’s disease, three had stooped posture from the beginning of the illness, but the time course of development of the severely bent posture ranged from onset of the disease to 14 years. The truncal flexion ranged from 30 to 90°. Camptocormia was present to a lesser severity while sitting. In some instances, there was also lateral flexion. Some patients could voluntarily overcome the problem, but only temporarily, as in this case.

The response of camptocormia to daytime activity and factors such as fatigue and stress is variable. When part of Parkinson’s disease, its response to medication is variable, occasionally being worse in the ‘off’ state and improving in the ‘on’ state. In some patients, however, there was no correlation to ‘on’ or ‘off’ states, while in others, levodopa caused deterioration in the truncal posture which could be improved if the dose was reduced. Deep brain stimulation of the globus pallidus interna (GPI) may also be beneficial.

It is unclear whether the pathogenesis of camptocormia is related more to dystonia or to a primary disorder of the paraspinal muscles. In patients without extrapyramidal signs, low density changes in the paraspinal muscles on computed tomography (CT) and MRI have been reported, and muscle biopsies may reveal type 2 fiber atrophy, suggesting that some cases may have a myopathic etiology. The association with diurnal variability, worsening with standing (as opposed to sitting), association with putaminal infarction, and occasional
response to dopaminergic medication suggest that in other cases, it behaves more like a truncal dystonia. Other circumstantial evidence, for example the antecollis of multiple system atrophy, may also support this view. Distinguishing these two mechanisms is important as it may influence treatment options, which are currently limited.

This case is instructive because it describes the clinical characteristics and differential diagnosis of the bent spine syndrome (camptocormia), its association with Parkinson’s disease, and its response to treatment.

REFERENCES
CASE PRESENTATION

A 45-year-old woman was referred for evaluation of a 10-year history of slowly progressive deterioration in her gait. She complained of being ‘off balance’. Other complaints included ‘slurred speech’, hand ‘tremors’, and difficulty typing on computer keyboards. Three years earlier, magnetic resonance imaging (MRI) of the brain showed atrophy of the cerebellum and pons.

The patient was being treated with sertraline for mild depression. She was not taking other prescription medication and rarely used over-the-counter drugs. Bilateral tubal ligation was her only surgery. She had had three full-term pregnancies without perinatal difficulties. She had no chronic medical disorders. She quit smoking cigarettes at age 42 years and did not drink alcohol. She was employed as a counselor for disabled adults.

Family neurological history was notable for an undiagnosed progressive gait disorder and dementia manifest in the patient’s father, who was deceased. Her father’s gait disorder began after age 50 and his dementia appeared many years later. This man had fathered eight children (two boys, six girls) with the patient’s biological mother, and five additional children (one boy, four girls) with another woman. The patient’s 12 siblings were 35–46 years of age. One sibling, a 42-year-old half-brother, had a gait abnormality similar to the patient. At the time of her clinic visit, the patient’s three children, ages 24, 28, and 29, were to be reported neurologically normal.

General physical examination was unremarkable. She was alert and conversant. She scored 29/30 on the Mini Mental State Examination, failing to recall one of three objects at 5 minutes. There was no neglect, dyspraxia, or cortical release sign. Pupils were equal and reactive to light. Fundi were normal. There was no nystagmus or square-wave jerks and extraocular movements were full. As shown in the accompanying video (Case 25), saccades were slow and accompanied by blinks and head thrusts. In contrast, smooth pursuit was relatively normal. Facial, trigeminal, spinal accessory, and hypoglossal-innervated muscles showed normal power. Mild ataxic dysarthria was present with prolonged phonemes, irregular articulatory pauses, and imprecise consonants. Mentalis and orbicularis oculi myokymia were seen intermittently. Motor power was normal in the limbs. The patient was mildly hypotonic. There was
no myoclonus, dystonia, or chorea. Action tremors of the arms and legs were apparent during the motor examination (see video). There was no muscle atrophy, hypertrophy, or tenderness. Deep tendon reflexes could not be elicited. Babinski responses were present bilaterally. There was slight distal impairment in sensation to light touch, proprioception, and vibration. There was ataxia on finger-to-nose and heel-to-shin testing. Fine motor control was mildly impaired in the distal upper extremities. Gait was mildly wide-based and ataxic with a staggering quality due to asynergic leg movements.

Neurophysiological studies were obtained to exclude a potentially coexistent demyelinating polyneuropathy. Median, ulnar, and tibial motor conduction velocities and amplitudes were normal. Median and tibial F-wave latencies were normal. H-reflexes were absent bilaterally. Sural, median, and ulnar nerve sensory amplitudes were low, while conduction velocities were normal. These findings were interpreted as compatible with a dorsal root ganglionopathy.

DISCUSSION

The diagnosis of spinocerebellar ataxia type 2 (SCA2) was suggested by the combination of slow saccades, action tremor, areflexia, and ataxia along with a positive family history of gait dysfunction. Genetic testing revealed the presence of a normal SCA2 allele with 22 CAG repeats and a mutant SCA2 allele with 38 CAG repeats. Normal SCA2 alleles contain 14–31 repeats, whereas 34 or more CAG repeats are identified in pathogenic alleles. Individuals with 32 and 33 repeats show reduced penetrance and may present with late-onset disease. SCA2 is due to expansion of an unstable CAG repeat in the gene (SCA2) that encodes ataxin-2.

The prolonged disease course and autosomal dominant family history largely eliminated infectious, toxic, vascular, autoimmune, nutritional, and neoplastic causes of ataxia in this patient. Among the spinocerebellar ataxias, the presence of areflexia made SCA1 relatively unlikely; the absence of pigmentary maculopathy largely excluded SCA7, and the lack of nystagmus was inconsistent with an SCA6 phenotype. The age of onset and inheritance pattern rendered a diagnosis of Friedreich’s ataxia very unlikely.

SCA2 is seen in populations throughout the world, and is a relatively common hereditary ataxia in the United States. The highest prevalence rate is found in the Holguin province of Cuba. Slow saccades are a very characteristic feature of SCA2. On average, saccadic velocities are substantially slower in SCA2 than in SCA1 and SCA3. Besides ataxia, a variety of additional movement disorders including dystonia, chorea, myoclonus, and parkinsonism may be seen in patients with SCA2. In fact, SCA2 parkinsonism may improve with levodopa. Neuropathy is an almost universal early feature of SCA2. Frontal executive deficits become more prevalent as the disease progresses.

As is the case for SCA1, SCA3, SCA7, and several other ‘repeat’ diseases, age of disease onset is inversely correlated with the CAG repeat length in SCA2 and ranges from infancy to more than 80 years. The SCA2 repeat shows meiotic instability with a small paternal bias. Consistent with the broad phenotypic spectrum of SCA2, ataxin-2 is widely expressed in neural tissues.
This case is instructive because it highlights the fact that signature features of specific hereditary ataxias can facilitate narrowly focused confirmatory genetic testing. In this case, the slow saccades with a slowly progressive autosomal dominant ataxia suggested SCA2.

REFERENCES


Legend to video

Case 25  This shows many of the features of SCA2 including slow saccades, often accompanied by a head thrust or blink, myokymia of the mentalis muscle, decreased-to-absent deep tendon reflexes, an irregular postural tremor, dysmetria with finger-to-nose, and gait ataxia.
When both motion and mentation fail

Hasmet A Hanagasi and Murat Emre

CASE PRESENTATION

A 63-year-old man was admitted to the movement disorders clinic because of a history of parkinsonism and cognitive decline. He was a retired bus-driver and had been healthy until age 52 years when he began to notice resting tremor of his right hand. Within 1 year he developed rigidity and bradykinesia, predominantly on the right side, and was diagnosed as having idiopathic Parkinson’s disease (PD). His symptoms improved with levodopa (300 mg/day), and this improvement was sustained during the next 2 years. His symptoms slowly worsened over the next few years, and he started experiencing mild peak-dose dyskinesias and wearing-off phenomenon. Due to the decline of efficacy and motor fluctuations, bromocriptine (15 mg/day) and entacapone (600 mg/day) were added, which resulted in partial improvement.

Nine years after Parkinson’s first became symptomatic, the patient started developing cognitive dysfunction, apathy, and vivid hallucinations. Hallucinations generally consisted of animals or children in the house, they were not frightening, and insight to their unreal nature was generally preserved. He was less motivated, spending most of his time at home and experiencing excessive daytime sleepiness. He became inattentive and forgetful, especially for the details of recent events or conversations. His thought process became increasingly slower; in the later course he had trouble navigating his own home. Upon reduction of dopaminergic medication, hallucinations improved to some extent, but his cognitive dysfunction and motor symptoms worsened. There were no marked fluctuations in his cognitive status although his performance was said to be better on some days, and he was frequently falling asleep during the day.

His medical history was unremarkable except for the presence of typical features consistent with rapid eye movement (REM) sleep behavior disorder, for almost 10 years before the development of motor symptoms. His family history was non-contributory. There were no significant findings on general physical examination.

On neurological examination the patient was cooperative, but intermittently drowsy. His Mini Mental State Examination (MMSE) score was 21/30. He was disoriented to time but not to place, and could remember two out of three words
after distraction; he had particularly poor performance on the construction task and difficulties with serial sevens. He was bradyphasic and his speech was dysarthric. Eye movements and other cranial nerves were normal. His muscle strength, sensory examination in all modalities, and deep tendon reflexes were normal, and plantar responses were flexor. Finger-to-nose movements were slow but accurate and there was no dysmetria. Fine finger movements, foot tapping, and rapid alternating movements revealed marked bradykinesia bilaterally. Axial tone was increased and he had moderate-to-severe cogwheel rigidity in all extremities, more prominent in the right arm. There was a moderate resting tremor in both upper extremities. He had difficulty arising from a chair by himself and his posture was stooped. Gait examination revealed small steps with festination, severe start hesitation, postural instability, and retropulsion. During on-phase the total UPDRS (Unified Parkinson’s Disease Rating Scale) score was 55, motor score (part 3) was 27, and Hoehn–Yahr score was 3.

Neuropsychological testing showed marked impairment in attention/concentration, verbal fluency, visuospatial/visuoconstructional tests, cognitive flexibility, and other tasks of executive functions (Figure 26.1). He was apathetic and had difficulties with abstract thinking, making analogies, and forming or switching concepts. His verbal memory was moderately impaired, and free recall was worse (seven out of 15 words) with better recognition (11 out of 15 words). His visual memory could not be properly tested because he could not copy figures; he was, however, able to recognize correctly most of the test items during delayed recognition. Measure of general intelligence and confrontation naming were within normal limits.

Figure 26.1  Cube and pentagon drawings of the patient, demonstrating prominent visuospatial dysfunction.
Urine analysis and routine blood tests (chemistry, cell count, thyroid, VDRL (Venereal Disease Research Laboratory), vitamin B12, and folate) were all normal. Electroencephalography (EEG) revealed diffuse slowing in background activity at the 6–7-Hz level. Magnetic resonance imaging (MRI) of the brain showed mild generalized atrophy, and hippocampi were largely preserved.

He was diagnosed as having dementia associated with Parkinson’s disease (PDD). Two years after the beginning of cognitive dysfunction, the cholinesterase inhibitor rivastigmine 3 mg/day was initiated, increasing to 12 mg/day after 12 weeks. The patient tolerated rivastigmine well and there were no side-effects. Substantial improvement in cognition and the visual hallucinations were observed, his apathy, bradyphrenia, concentration, and mood improved significantly, and his MMSE score increased to 24/30. This improvement was sustained for approximately 1 year. The patient worsened after discontinuation of treatment because of back surgery, but when rivastigmine was re-started, the patient experienced improvement. His cognitive symptoms, however, slowly progressed over the following one-and-a-half years and he developed increasing impairment in activities of daily living. His last medication scheme was levodopa 800 mg/day, entacapone 800 mg/day, bromocripitine 15 mg/day, and rivastigmine 12 mg/day.

DISCUSSION

Dementia is increasingly recognized as a frequent feature of PD with a prevalence rate of 24–31%. In a prospective study over 8 years, 78% of patients with PD developed dementia, especially at advanced age. This patient first developed motor symptoms which were compatible with a diagnosis of idiopathic PD, including a classic resting tremor, asymmetry, and a beneficial response to dopaminergic treatment. Cognitive and behavioral symptoms emerged slowly and later in the course, approximately 8 years after the onset of motor symptoms. The long delay between the onset of motor and cognitive symptoms differentiates this case from those with a related disorder, dementia with Lewy bodies.

The neuropsychological findings were typical of dementia associated with PD (PDD): he was apathetic with impaired attention, and had severe impairment in executive and visuospatial functions with relatively preserved memory, recognition being better than free recall. The lack of prominent, temporo-limbic type amnesia, and the presence of profound, disproportional deficits in attention, executive, and visuospatial functions are the main differences from Alzheimer’s disease. He had frequent, vivid hallucinations which were well-formed, again typical for PDD. Screening tests did not reveal any other factor which may have caused dementia; his MRI showed generalized atrophy with relatively well-preserved hippocampi. PDD is associated with prominent cholinergic deficits, and a recent large randomized, controlled study demonstrated that the cholinesterase inhibitor rivastigmine provides significant benefits in patients with PDD. This patient also responded well to treatment with rivastigmine: both cognitive and behavioral features improved significantly for at least 1 year, and the subsequent course of the disease was slowly progressive.
This case is instructive because it demonstrates the typical features of dementia associated with PD. When dementia is suspected in a patient with PD, it is imperative to screen and exclude external causes which may cause cognitive and behavioral changes, such as adverse effects of drugs and systemic diseases. Depression is also frequently encountered in PD and should be considered, as some features of depression such as lack of motivation may mimic symptoms of dementia.

REFERENCES

CASE PRESENTATION

A 72-year-old retired stockbroker noted the insidious onset of slow, shuffling gait over several months. Initial medical evaluations were unremarkable and symptoms were attributed to psychological stress and depression. He had suffered from recurrent depression since adolescence, and had been treated with various antidepressants until his mood was stabilized with a combination of bupropion, buspirone, and diazepam. There was no history of psychosis, delusions, neuroleptic exposure, or alcohol or recreational drug use. Family history was significant for multiple first-degree relatives with anxiety and depression.

Two years later, evaluation by a neurologist revealed a rest and action tremor of the right hand. Selegiline was initiated for possible Parkinson’s disease (PD), but this exacerbated his anxiety and was discontinued. Over the next year, sialorrhea, micrographia, and hypophonia developed. Shuffling gait, prominent left leg rigidity, spasticity, and left Babinski sign were noted on examination (see video, Case 27). He described his left leg as ‘non-functional’ and ‘stuck’. Levodopa, pramipexole, and ropinirole were administered without benefit.

At age 75 he developed dramatic worsening of gait, with recurrent falls due to postural instability, freezing, and left leg rigidity resulting in fractured ribs and left arm. Within 1 year, he required a walker for ambulation. Brain magnetic resonance imaging (MRI) at this time showed subtle right insular cortical atrophy (Figure 27.1A). Spine MRI was unremarkable. Electromyography and nerve conduction studies showed a mild chronic left L5 radiculopathy, but no signs of motor neuron disease; activation was poor, indicating upper motor neuron dysfunction. [99mTc] TRODAT single photon emission computed tomography (SPECT) imaging (where TRODAT is a tropane derivative) showed decreased dopamine transporter activity bilaterally, with marked abnormality of the left basal ganglia, affecting the caudate and putamen uniformly. The study was interpreted as consistent with an atypical parkinsonian disorder.

At the age of 80, 8 years after symptom onset, he was wheelchair-bound with severe rigidity and contractures of both legs, left greater than right. Despite his disability, he continued part-time work as a stockbroker. Cognitive assessment
resulted in a score of 29/30 on the Folstein Mini Mental State Examination. Clock drawing, oral trail making, generative naming, and judgment of line orientation were impaired. Testing using the Mattis Dementia Rating Scale revealed relatively isolated and severe impairment in initiation and maintenance of motor and cognitive behaviors. There were mild construction deficits. Memory, attention, and language were relatively preserved. Results were consistent with severe, isolated frontal lobe and mild non-dominant parietal lobe dysfunction. Brain MRI at this time showed progression of atrophy, most prominent in the right frontal, temporal, and parietal regions (Figure 27.1B, C).

DISCUSSION

Several features of this patient’s presentation point to an atypical parkinsonian syndrome. First, symptoms were unresponsive to levodopa and dopamine agonists. Second, the progression to severe motor disability in less than 5 years from initial symptom onset is uncommon in idiopathic PD. Diagnoses to consider include: progressive supranuclear palsy (PSP), multiple system atrophy (MSA), frontotemporal lobar dementia (FTLD), corticobasal degeneration (CBD), and vascular parkinsonism. Had there been a history of neuroleptic exposure, drug-induced parkinsonism would also be a consideration. Early postural instability with falls, although common to all of the atypical parkinsonian syndromes above, is particularly suggestive of PSP or CBD. Lack of autonomic features makes MSA unlikely. The relatively preserved cognition and absence of delusions or hallucinations makes dementia with Lewy bodies less likely.

Prominent asymmetric rigidity and apraxia are highly suggestive of the classical clinical syndrome of CBD. While all parkinsonian syndromes have the potential to evolve asymmetrically, the degree of asymmetry in CBD may be striking. Onset in a single limb is common, followed by progression to the ipsilateral unaffected limb, and finally to contralateral limbs. The limb may develop any combination of rigidity, tremor, bradykinesia, dystonia, or apraxia. When the alien limb phenomenon (or apraxia) is present, patients may describe the affected limb as difficult to control, clumsy, or useless rather than weak. Though 50% of patients with CBD demonstrate alien limb phenomenon,1 this very distinct clinical sign can be found in other neurodegenerative disorders. Strong asymmetry is most suggestive of the diagnosis. In a very rigid and dystonic limb, it may be difficult to assess praxis; therefore, the presence of cortical sensory signs such as agraphesthesia and astereognosis may be useful. Other features of CBD include focal myoclonus (often stimulus sensitive), mirror or overflow movements, hyperreflexia, and extensor plantar signs.

Despite the relentless physical deterioration, cognitive function remained relatively intact in this patient. In the original descriptions of CBD, cognitive dysfunction was thought to be rare, and at one point was considered exclusionary of the diagnosis. However, it has become increasingly recognized that dementia may be the presenting feature of CBD.2 Even when cognition appears intact, psychometric testing may reveal a pattern of frontal executive dysfunction. Language, construction, and visuospatial perception may be affected later in the course.
Increasingly, cases mimicking FTLD and its variants are diagnosed pathologically with CBD.

Antemortem diagnosis of CBD is particularly challenging. The MRI finding of asymmetric frontoparietal atrophy corresponding to the affected side may help to support a clinical diagnosis. Similarly, functional imaging of the dopamine system may show laterализation with uniform uptake between the caudate and putamen.

The diagnosis of definite CBD cannot be made before autopsy. Increasingly, experts refer to the classic clinical syndrome as corticobasal syndrome (CBS), while

**Figure 27.1** (A) Brain MRI from 1999: T1-weighted axial section showing mild asymmetry of the cerebral hemispheres. (B, C) Brain MRI from 2004: T1- and T2-weighted axial sections showing progression with atrophy in the right frontal, temporal, and parietal regions, corresponding to more severe left-sided clinical signs.
reserving corticobasal degeneration (CBD) for the pathological diagnosis. Autopsy series have revealed that clinical CBS may result from multiple pathological disorders including PSP, Alzheimer’s disease (AD), Pick’s disease, and Creutzfeldt–Jakob disease. Nevertheless, the pathology of CBD is quite distinct, consisting of perisylvian cortical atrophy, neuronal loss in focal cortical regions and the substantia nigra, tau positive neocortical plaques, threads, and tangles reminiscent of AD type pathology. In contrast to AD, CBD plaques are derived from astrocytes rather than neurons, typically do not contain amyloid, and are less readily detected by silver staining. Swollen achromatic neurons, similar to Pick cells, are also present in limbic regions.

Progression of CBD is typically more rapid than in PD and other parkinsonian syndromes. Reported median survival is approximately 7 years from initial symptom onset. Therapy is mainly supportive. Modest benefit is seen in a small minority of patients treated with levodopa, and clonazepam may help to reduce myoclonus. Botulinum toxin injections may be effective in relieving painful dystonia, rigidity, or spasticity. Physical and occupational therapy, dysphagia evaluation by a speech–language therapist, and potential gastros-tomy placement are all therapeutic measures to consider as the disease progresses.

This case is instructive because:

1. Unilateral or strongly asymmetric rigidity and apraxia is the hallmark of the corticobasal syndrome (CBS). Alien limb phenomenon, although not specific, is highly suggestive of CBS in the correct clinical setting.
2. Due to clinical and pathological overlap with other disorders, the term corticobasal degeneration (CBD) should be reserved for the pathological disorder, while corticobasal syndrome (CBS) should be used to refer to the clinical syndrome.
3. A multidisciplinary approach to this progressive neurodegenerative disorder is imperative to ensure adequate evaluation and treatment. Botulinum toxin injections should be considered for symptomatic relief of dystonia, rigidity, spasticity, and sialorrhea.

REFERENCES
Legend to video

Case 27  In the first segment, right hand movements to command show mild clumsiness, but normal strength and preserved ability to pantomime and gesture. Mirror movements, dystonic posturing, and wandering athetoid movements are evident in the left hand. Apraxia is evident in the second segment as an inability to pantomime, gesture, or imitate with the limb. The third segment shows that, despite the patient having at least antigravity strength in both legs, there is limited voluntary movement in either leg. In the fourth segment, the left leg can be extended to 160° with difficulty while the right leg can be extended slightly further. Botulinum toxin injections to the hamstring muscles improved rigidity, pain, and cramping. The left extensor indicis was injected for relief of hand dystonia while the parotid glands were injected for sialorrhea.
CASE PRESENTATION

The patient is a 63-year-old woman who carries a diagnosis of idiopathic Parkinson’s disease (PD). She recalls the onset of her illness to be at least 5 years ago when she insidiously developed a resting tremor of the left hand. Subsequently, she noticed her movements were slower and her muscles felt stiff. She also complained of difficulty turning in bed and a softer voice. Her husband recalled that her facial expression decreased and her handwriting became smaller. On examination at that time, cognitive testing was normal. She was found to have a resting tremor of the left hand, bradykinesia, mild rigidity of the left limbs, reduced arm swing, and hypomimia. She was started on carbidopa/levodopa with moderate improvement of her symptoms. For the 2 years prior to presentation, she had been on a stable dose of carbidopa/levodopa 25/100, one-and-a-half tablets, three times daily.

Over the last 6 months, however, her husband had begun to notice significant changes in her cognition. She seemed to be developing loss of episodic memory and reported hallucinations which occurred mainly at night. She reported seeing animals and gargoyle-like appearances to human faces. On a few occasions she reported that a mop or broomstick had the appearance of a human figure. She became preoccupied with checking the locks on doors. She was having difficulties with literacy skills, and her dreams had become more vivid, with episodes of screaming and talking during her sleep, with dream enactment behaviors. On a few occasions over the last month, she had experienced a feeling of light-headedness on standing. She was no longer driving and her husband had taken over balancing their checkbook.

Her past medical history was significant only for the presence of cataracts. She did not smoke or drink alcohol and was only taking carbidopa/levodopa. She mentioned that her father had died with a diagnosis of Alzheimer’s disease.

Recent head magnetic resonance imaging (MRI) revealed only mild generalized atrophy. Blood tests including complete blood count, chemistry panel, and liver, thyroid, and renal function studies were within normal limits.

On examination her supine and standing blood pressure were 110/68 and 92/60, respectively. She was cognitively impaired with a Mini Mental State Examination (MMSE) score of 22/30. She had evidence of mild episodic memory loss and moderate difficulties with spatial and perceptual tasks. She recalled one
of three items, and was unable to visualize one of three fragmented letters. She could not construct a cube, and was unable to perform spatial rotation tasks. The alternating motor task was performed with difficulty. Her face was moderately masked with mild seborrhea. She had a moderate hypokinetic dysarthria. There was a mild resting tremor of her left hand and her alternating motor tasks were performed slowly, particularly on the left side. She had moderate rigidity. Her gait was minimally stooped with reduced left arm swing. The neurologic examination was otherwise normal.

DISCUSSION

At presentation, this patient had features of classic PD. However, four-and-a-half years later, she began to have cognitive decline. She had changes in episodic memory as well as behavioral changes, with some paranoia and psychosis defined as visual hallucinations and illusions. Her activities of daily living were now affected, as she was no longer driving and her husband had taken over the responsibility of balancing the checkbook.

She now seems to have parkinsonism, dementia, psychosis, dream enactment behavior, and mild autonomic dysfunction. Her disease seems to be diffuse, affecting cortical and subcortical regions with prominent parietal and frontal lobe dysfunction but with ‘relative’ preservation of mesial temporal lobe function.

Loss of episodic memory is a key feature to the diagnosis of Alzheimer’s disease (AD). Patients with AD usually complain bitterly of short-term memory loss. In addition, other cognitive spheres are affected either diffusely or multifocally. Language, literacy, frontal dysexecutive, visual spatial, and visual perceptual deficits can all occur. Psychosis can also occur in AD, but happens later in the course and is usually not severe.

This patient’s features, however, seem to be atypical for AD given the prominent psychosis, parkinsonism, dream enactment behavior (limb movements occurring while the patient is in rapid eye movement (REM) sleep), and autonomic dysfunction. Her symptoms and especially the findings of prominent visual perceptual and spatial dysfunction are most suggestive of a diagnosis of PD dementia (PDD). Parkinson’s disease dementia is diagnosed when the onset of the dementia develops at least 1 year after the onset of parkinsonism. This arbitrary timing of the onset of dementia with respect to the onset of parkinsonism distinguishes PDD from dementia with Lewy bodies (DLB), but otherwise they share the same clinical and neuropathological features. A diagnosis of DLB is made when the dementia onset occurs within 1 year of the parkinsonism onset; however, Lewy body disease is the pathological substrate for both PDD and DLB. Hallucinations, fluctuations, and prominent spatial and perceptual deficits are common in PDD, with relatively less dysfunction in episodic memory. Autonomic features and dream enactment behavior are also common.

There are other Parkinson’s-plus disorders that could be included in the differential diagnosis but are much less likely. The presence of dream enactment behavior, also known as REM sleep behavior disorder, is suggestive of a disease with pathological deposition of α-synuclein. Therefore, multiple system atrophy (MSA) would be another possibility. However, prominent cognitive impairment and psychosis argues against MSA.
Appropriate studies for patients such as the one presented here should include laboratory testing for treatable causes of dementia, for example thyroid screen, vitamin B12, and folate as well as brain imaging, to rule out non-degenerative causes of dementia such as hydrocephalus, structural lesion, or stroke. Other potentially treatable causes of dementia to consider include medications, especially anticholinergics, as well as depression causing pseudodementia. The approach to treatment of PDD is difficult and beyond the scope of this chapter. However, management is best determined by considering the different domains that are affected and treating the ones that are the most bothersome for the patient and the family, understanding that the treatment of symptoms in one domain may worsen symptoms in another domain.

This case is instructive because it highlights the fact that dementia occurs in PD. Yet, reversible causes of dementia still need to be ruled out. Treatment of PD with dementia should be individualized, recognizing that antiparkinsonian medications in this setting often cause as much harm as good.

REFERENCES

Bent spine and knees in Parkinson’s disease

MA Hellmann, Ruth Djaldetti, and E Melamed

CASE PRESENTATION

This patient developed a rest tremor of the left hand at age 28 followed by left-sided rigidity. Within 1 year, tremor appeared on the right side also with rigidity. These symptoms, along with bradykinesia, progressed, and a diagnosis of Parkinson’s disease (PD) was made. Two years after the first symptom appeared, carbidopa/levodopa was started. There was a marked response and the patient was almost symptom-free for 3 years, the so-called ‘honeymoon period’. Motor fluctuations then developed, with peak-dose dyskinesias. As the disease progressed the ‘on’ periods shortened, the ‘off’ periods lengthened, and the dyskinesias became violent.

Approximately 6 years after being diagnosed with PD, he developed a gait disturbance with stooped posture, shuffling, and postural instability. The flexed posture worsened gradually to a point that while walking his spine was flexed over 90° (camptocormia). Fifteen years after diagnosis, at age 43, he required a stick to walk, as well as full-time assistance with almost all activities of daily living. The gait disturbance progressed and the camptocormia was accompanied by bent knees and tiptoeing. During ‘on’ periods he was able to stand supported by his caretaker, who dragged him forwards by both arms, with severe camptocormia, bent knees, tiptoeing gait, and intermittent dyskinesias (see video, Case 29, first segment). The camptocormia and bent knees posture only appeared with gait. When recumbent the patient’s back and knees completely straightened without contractures. During ‘off’ periods he was restricted to a wheelchair. He was taking a quarter tablet of carbidopa/levodopa 25/250mg every hour, with a short-lived ‘on’ period accompanied by intermittent dyskinesias.

The camptocormia and bent knees posture did not improve while ‘on’. Treatment with controlled release levodopa and entacapone did not lengthen his ‘on’ periods significantly. His ‘off’ periods were associated with anxiety, treated with clonazepam. Twenty-five years after being diagnosed, he was crippled by PD with an extremely poor quality of life, requiring 24-hour assistance. Despite other signs of progressive PD, there was no dementia. At this point he underwent bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) and the effect was dramatic. For the first time in almost 10 years the patient could stand and walk unaccompanied; the bent spine and knees posture was
significantly reduced; he still walked with slightly bent knees but without tiptoeing (see video, second segment). The dose of levodopa was reduced to one-quarter of the preoperative dose. The symptoms required continuous electrode stimulation. Post-surgery he complained of hypersalivation that did not respond to anticholinergics. At 4 months post-surgery he could eat and dress alone and walk for up to 500 meters unaided, and was riding a horse once a week. He still had a full-time caretaker whose workload had been significantly reduced. His spirits were lifted and his sense of humor returned. There were minor motor fluctuations without significant dyskinesias and the short ‘off’ periods were tolerable.

DISCUSSION

This patient with young-onset PD developed severe camptocormia, bent knees, and tiptoeing as late manifestations of advanced illness, which responded dramatically to surgery. A mildly stooped posture is a hallmark of parkinsonism, yet it is uncommon that flexion of the spine is severe. We described eight patients with idiopathic PD, who had severe forward bending of the thoracolumbar spine during gait that disappeared in the supine position. Electromyography of the paraspinal muscles was normal, excluding comorbidity of myopathy or amyotrophic lateral sclerosis, where isolated cases of camptocormia have been described. In three patients, levodopa therapy aggravated the bent spine, whereas the others improved. We postulated that camptocormia in PD is a type of dystonia. We previously described bent knees and tiptoeing in PD as a clinical manifestation of late illness, and suggested that this phenomenon might represent a form of postural abnormality due to alterations of the automatic postural reflexes, or that it is also a form of dystonia.

In the case described here, levodopa did not improve the posture. However, there was dramatic improvement after bilateral DBS of the STN. Deep brain stimulation has been shown to improve limb akinesia, rigidity, tremor, and gait as well as reduce dyskinesias. There have been no specific reports of the effect of DBS on camptocormia in PD. There is a report describing significant functional improvement in a 39-year-old male with probable neuroleptic-induced camptocormia who underwent DBS of the globus pallidus interna, suggesting that the anatomical site resulting in camptocormia in patients with PD may indeed reside in the basal ganglia.

This case is instructive because it highlights important features of late Parkinson’s disease, including camptocormia, bent knees, and tiptoeing, and the potential for a dramatic response of these uncommon signs to STN DBS.

REFERENCES


**Legend to video**

**Case 29** In the first segment the 52-year-old patient is seen walking, aided by a helper, during the ‘on’ period of his motor fluctuations. He has camptocormia and bent knees, and walks on tiptoes. When recumbent and sitting he is able to straighten his back and knees completely. Dyskinesias occur during gait and while recumbent. In the second segment, the patient is 4 months post-DBS and is able to walk unaided. The bent spine posture has dramatically improved and he now walks with only slightly bent knees without tiptoeing.
A family with progressive atypical parkinsonism, dementia, and neuropsychiatric changes

Yasuhiko Baba and Zbigniew K Wszolek

CASE PRESENTATION

This patient was first evaluated in 1986 at age 35 years. He was healthy, and the neurologic examination performed at that time was normal. He agreed to donate a blood sample for research on the genetics of his family. He was aware that his father’s two sisters, his paternal grandfather, and several distant relatives had a rapidly disabling neurologic condition.

By the time the patient was 41 years old, his handwriting had gradually deteriorated and was smaller. He complained of a mild, intermittent resting tremor in his right hand and difficulty with performing precision movements such as buttoning his shirt, lacing his shoes, and tightening his belt. Shortly afterward, he had impairment of memory and difficulty understanding written material. He was an extremely successful salesman, but in the second year after the onset of symptoms, his job performance declined markedly. He lost his skill for convincing potential customers of the quality of the products he was selling. His superiors became concerned about his work and asked his wife to insist that he see his physician.

The examination demonstrated mild asymmetric bradykinesia and rigidity that affected both right limbs more than the left limbs. He had no resting tremor, postural instability, or eye movement abnormality. Cognition was normal, but he was withdrawn. The results of basic serum and urine laboratory tests, electroencephalography, electromyography, multimodality-evoked potential study, and brain magnetic resonance imaging were normal.

At age 42, about 1 year after the onset of symptoms, he traveled to Vancouver, British Columbia, Canada, for a positron emission tomographic study with $[^{18}\text{F}]$ fluoro-L-dopa and $[^{11}\text{C}]$raclopride tracers. The $[^{18}\text{F}]$fluoro-L-dopa-positron emission tomographic study demonstrated a decreased fluorodopa uptake rate constant throughout the striatum, with the putamen and caudate nucleus affected equally, and $[^{11}\text{C}]$raclopride-positron emission tomography showed increased striatal D2-receptor binding equally in the caudate nucleus and putamen.
sporadic Parkinson's disease, the putamen is affected more than the caudate nucleus).

Neurologic evaluation when the patient was 43 years old indicated that he was fully oriented and cooperative, but formal neuropsychologic testing demonstrated deficits in remote memory and comprehension of written material. Facial expression and voice volume were moderately reduced (see video, Case 30). There was restriction of upward gaze. Axial and appendicular muscle rigidity was present, but still with some asymmetry (right extremities affected more than left). There was generalized bradykinesia, especially of the right limbs. His posture was stooped, and his gait was slow and shuffling, with decreased arm swing on both sides. Treatment with carbidopa/levodopa and a dopamine agonist had only minimal benefit. He was not able to perform his job and had to retire.

The disease was relentlessly progressive, and, at age 46, he required total supervision and considerable assistance in activities of daily living. He was not able to carry on a conversation, although he could still answer simple questions. He scored 23/30 on the Mini Mental State Examination, missing points on orientation, recall, and verbal functions. He had become irritable and easily upset. His face was masked, with reduced blinking. Extraocular movements were moderately impaired in all directions, but upward gaze was absent. Symmetrical eyelid opening and closing apraxia were present. Moderate-to-marked parkinsonism characterized by rigidity and bradykinesia was apparent in all limbs and the trunk. There was a mild, intermittent resting tremor in the right hand. He frequently fell. He was not able to recover on the pull test. Choking was a problem and food had to be pureed. Deep tendon reflexes were brisk, but without ankle clonus or an extensor plantar response. He was incontinent of urine.

At age 48, he was mute but could communicate using a spelling board. He was stubborn and, despite frequent falls that caused multiple injuries, insisted on walking independently. Neurologic examination at this time showed a masked face and almost complete absence of blinking, with bilateral eyelid opening and closing apraxia. There was ophthalmoparesis for all directions of gaze, but oculocephalic reflexes were preserved. He had anterocollis. Muscle rigidity was prominent and, at this time, more so in the axial than appendicular muscles. An extensor plantar response was present bilaterally. T1-weighted magnetic resonance imaging showed moderate-to-severe atrophy of the posterior frontal and temporal lobes and hippocampus bilaterally (Figure 30.1). Positron emission tomography with 2-deoxy-2-fluoro-[18F]d-glucose demonstrated hypometabolism in these same cortical regions. Electroencephalography showed posterior alpha activity of about 9Hz, with occasional theta wave components. An electromyographic multichannel surface recording of the right arm during extension showed myoclonic jerks. Autonomic thermoregulatory sweat testing revealed anhidrosis predominantly in the distal lower and upper extremities, and some milder patchy abnormalities in more proximal sites.

Approximately one-and-a-half years later, at about age 50, the patient was aphagic and a gastrostomy feeding tube was inserted. He became bedridden the following year and developed severe rigidity and joint contractures despite daily physical therapy. He required total care. He died of pneumonia at age 53.
DISCUSSION

The patient is a member of the family with pallidopontonigral degeneration investigated by ZKW since 1987 (VI-53, Figure 30.2). Molecular genetic testing confirmed the presence of the N279K mutation in the \textit{tau} gene on chromosome 17. During the course of the patient’s illness, three of his uncles had become afflicted with the same disease, and clinical genetic testing confirmed their carrier status of the N279K \textit{tau} mutation. The \textit{tau} haplotyping of the patient’s DNA disclosed an H1/H1 genotype.

Gross examination of his brain showed circumscribed cortical atrophy affecting predominantly the superior frontal gyri in the parasagittal and medial regions. The frontal pole and medial temporal lobe had mild atrophy. Coronal sections showed marked atrophy of the hippocampal formation and amygdala. The globus pallidus had a rusty discoloration. Microscopically, severe neuronal loss and gliosis were widespread throughout the brain, including the substantia nigra, pontine tegmentum, and pallidum. Tau deposits were identified in the gray and white matter of the cerebral cortex and basal ganglia.

The family in this report contains 316 members spanning eight generations. In the past, our patient’s relatives had been given the diagnosis of Parkinson’s disease, progressive supranuclear palsy, corticobasal degeneration, post-encephalitic parkinsonism, atypical parkinsonism, parkinsonism-plus syndrome, multiple system atrophy, dementia of unknown type, schizophrenia, and Alzheimer’s disease. Genealogically, the origin of the family has been traced to the Colony of Virginia. To date, 43 afflicted family members have been identified. This family is one of the largest kindred of those belonging to the heterogeneous group of disorders classified as ‘frontotemporal dementia with parkinsonism linked to
Figure 30.2  Pedigree of family with the N279K mutation in the tau gene. The pedigree number of the patient described in this case is VI-53. Squares represent males. Fully darkened squares or circles represent afflicted family members. A diagonal line through a square or circle indicates a deceased person. A caret on the left side of a square or circle indicates that an autopsy was performed. A dot in the center of a square or circle indicates that only historical data are available. The number inside the symbol indicates the age at death.
Progressive atypical parkinsonism, dementia, and neuropsychiatric changes

It is a rare autosomal dominant neurodegenerative disorder with worldwide occurrence. Mutations of the tau gene leading to pathologic tau aggregations are responsible for the development of frontotemporal dementia with parkinsonism linked to chromosome 17. Therefore, it is classified as a ‘tauopathy’. More than 100 families with 33 different mutations in the tau gene have been identified. Afflicted members of families with P301L, +16, and N279K mutations account for more than 65% of cases. Most of the pathologic mutations are localized on exon 10 and the exon 10 splice site (Figure 30.3).

The clinical presentation varies, but a combination of dementia, personality and behavioral changes, and parkinsonism is most common. The onset of symptomatic disease also varies, but in half the families that have been described, the mean age at disease onset is 50 years or older. Disease duration is usually less than 10 years. No curative treatment is available, and the response to symptomatic therapy is usually limited.

The frontotemporal dementia with parkinsonism linked to chromosome 17 phenotype can be divided broadly into two groups: frontotemporal dementia-predominant and parkinsonism-predominant. Persons carrying mutations in exons 9–13 usually have the frontotemporal dementia-predominant phenotype. Parkinsonian features, if present, typically occur late in the course of the illness. The initial symptoms, disease onset, and disease progression are most variable for persons carrying mutations in exon 1, 10, and the exon 10 splice site. The parkinsonism-predominant phenotype is more common in this group.

Comparison of the initial clinical presentation and tau genotype has shown an association between the parkinsonian-predominant phenotype and the H1/H1

Figure 30.3  Schematic representation of pathogenic mutations in the exons and introns of the tau gene localized on chromosome 17q21.
genotype and between the frontotemporal dementia-predominant phenotype and the H1/H2 genotype.\textsuperscript{5}

Language difficulties frequently leading to mutism are common in frontotemporal dementia with parkinsonism linked to chromosome 17. Other clinical features include myoclonus, pyramidal tract signs, amyotrophy, and epilepsy.\textsuperscript{1,2,4}

Macroscopically, frontotemporal dementia with parkinsonism linked to chromosome 17 brains have variable cortical atrophy that ranges from relatively mild to moderately severe, usually affecting mainly the superior, middle, and inferior frontal gyri and temporal gyri bilaterally. Occasionally, cortical atrophy is asymmetrical. Atrophy of the caudate nucleus, putamen, globus pallidus, amygdala, hippocampus, ventral hypothalamus, pontine tegmentum, and substantia nigra is frequent. Microscopically, deposits of tau protein are found in the neurons and glial cells of the cerebral hemispheres, cerebellum, and brainstem. However, the distribution and severity of changes vary, and depend on the specific tau gene mutation.\textsuperscript{1}

The case is instructive because it demonstrates the typical presentation of the parkinsonism-predominant phenotype of frontotemporal dementia with parkinsonism linked to chromosome 17, which should be considered in the differential diagnosis of patients with movement disorder and dementia, especially if there is a family history.

REFERENCES


Legend to video

Case 30  First segment: age 43 years (2 years after symptom onset). Orientation is fully retained. Moderate reduction in facial expression is seen. Note restriction of upward gaze. Gait is slow and shuffling, with reduced arm swing. Second segment: age 48 years (7 years after symptom onset). Blinking is almost absent, with bilateral eyelid opening and closing apraxia. Ocular motor paresis is seen for all directions, but oculocephalic reflexes are preserved. Third segment: age 50 years (9 years after symptom onset). Note akinesia with mute state and prominent drooling. He needs total assistance to walk.
One wrong movement leads to another

Lawrence Elmer, Imran Ali, and Stephen G Reich

CASE PRESENTATION

A 36-year-old gentleman was referred by a neurologist for ‘involuntary muscle twitching.’ This had begun at age 8. He could recall, when running the 40-yard dash, that the initial burst of speed off the line caused ‘spasm’ of the left limbs as well as ‘facial twitching’. The spasms continued without change through adulthood. They occurred exclusively at the initiation of physical activity, even just arising from a chair or rushing to answer a phone. While in the midst of exertion, he did not experience spasms nor did they occur at rest. They involved predominately the left limbs but at other times the right were also affected. The spasms typically lasted 30 seconds. He noticed more recently that the spasms were accompanied by a ‘dysphoric feeling’, and although there was no loss of consciousness, he had an admittedly difficult-to-describe sense during the spells of ‘almost like I’m not here in the moment’. He had noticed that shaking the left lower extremity could precipitate a spasm. In between the spells, he felt well and functioned at a normal level without neurological symptoms. Over the years he had become ‘a master’ at disguising the spasms, and did not seek medical attention until age 30. Initial diagnostic considerations included myotonia congenita and Tourette’s syndrome. Trials of clonazepam, gabapentin, topiramate, and baclofen were ineffective.

As the patient arose from his chair in the waiting room, he immediately developed mild left-hemidystonia lasting about 15 seconds. The neurologic examination was normal. The patient demonstrated on several occasions that shaking the left lower extremity could precipitate a spell (see video, Case 31). Within several seconds of doing so, he developed dystonia of the left upper extremity, facial grimacing, and, on one occasion, cervical dystonia with turning of the head to the left.

The patient was placed on carbamazepine extended release and, on a dosage of 200 mg twice a day, he has been completely free of spells for one-and-a-half years.

DISCUSSION

This patient was diagnosed as having paroxysmal kinesigenic dyskinesia (PKD) based on the historical features of the spells, their precipitation with exertion,
and their phenomenology. Paroxysmal kinesigenic dyskinesia is part of a diverse group of intermittent involuntary movement disorders that may be familial or acquired. Kertesz published the first description of PKD in 1967, labeled then as paroxysmal kinesigenic choreoathetosis. Since then, this rare disorder and variants have generally been classified into three subtypes: paroxysmal kinesigenic dyskinesia (PKD), paroxysmal non-kinesigenic dyskinesia (PNKD, occurring without a precipitating movement), and paroxysmal exercise-induced dyskinesia (PED, associated with prolonged exercise).

PKD is familial in many cases; however, sporadic cases are reported. An association with another genetic syndrome, infantile convulsion and choreoathetosis, has been reported. Three separate loci associated with familial PKD have been identified on chromosome 16. Familial PNKD and PED also have strong genetic associations. PKD is typically provoked by a sudden voluntary movement and frequently preceded by a premonitory sensation, following which occurs the involuntary movement. Over 80% of patients in a recent case series described a premonitory aura such as a feeling of anxiety or numbness and tingling in the affected limb. Immediately after this premonitory symptom most patients would experience the onset of a rapid involuntary movement involving the affected limb lasting 30–60 seconds. The attacks are dystonic in 57%, choreiform in 6%, ballistic in 1%, and non-specific in 3%, and involve a combination of multiple dyskinetic movements in 33% of patients. Attacks may be unilateral, alternating from side to side, bilateral, or a combination of unilateral and bilateral. Most patients respond to anticonvulsant therapy, most commonly carbamazepine and phenytoin. Approximately 50% of individuals with PKD experience spontaneous, complete, or nearly complete resolution of the symptoms as they enter adulthood.

Subjects with both familial and sporadic PKD commonly experience other intermittent neurological disorders, including infantile convulsions, febrile seizures, epilepsy, migraine with aura, migraine without aura, and miscellaneous other movement disorders including writer’s cramp, essential tremor, blepharospasm, and tic disorders. These associated neurological disorders were seen more commonly in familial kindreds than in sporadic cases.

This case is instructive because it demonstrates the typical clinical features of paroxysmal kinesigenic dyskinesia and leads to a discussion of other paroxysmal movement disorders. Furthermore, it emphasizes the importance of recognizing PKD as it may improve dramatically with medication, typically anticonvulsants.

REFERENCES

Legend to video

Case 31 The patient demonstrated on several occasions that shaking the left lower extremity could precipitate a spell. Within several seconds of doing so, he developed dystonia of the left upper extremity, facial grimacing, and on one occasion, cervical dystonia with turning of the head to the left.
A face to remember …

F Geser, KE Egger, and Gregor K Wenning

CASE PRESENTATION

In mid-1999, a 53-year-old woman noticed stiffness and slowness of the right lower limb associated with falls to the front. There was only mild improvement on L-Dopa. Addition of entacapone resulted in no further benefit. There was a pronounced postprandial tiredness at this time. Urinary incontinence developed, and she became constipated, requiring the frequent use of laxatives. When we first saw her at the end of 2002, we observed broken-up smooth pursuit eye movements, gaze-evoked nystagmus at an eye position of more than 45°, slowing of vertical saccadic eye movements, neck and limb rigidity, bradykinesia, and limb ataxia. She pushed herself up with the arms when attempting to arise from a chair. There was postural instability, wide-based stance, mild start hesitation, freezing when turning, and dragging of the right lower limb. At that time, the patient also complained of dysphagia with occasional choking, and features suggestive of a rapid eye movement (REM) sleep behavior disorder (RBD).

T2-weighted magnetic resonance imaging (MRI) scan showed a hyperintense rim lateral to both putamina. On diffusion-weighted imaging (DWI)-MRI, the regional apparent diffusion coefficients (rADCs) were close to the upper limit, suggesting striatal pathology. An \[^{123}\text{I}]\text{iodobenzamide (IBZM) single photon emission computed tomography (SPECT) scan showed a bilateral (more marked on the right) decrease in dopamine (D2) receptor density.}

Six months later, in mid-2003, the patient complained about an increase in orthostatic symptoms, in particular severe dizziness when standing quickly. The patient was markedly bradykinetic and had noticed a symmetric distortion of her lower face and anterior neck. She had stopped taking entacapone with improvement of orofacial dystonia but no aggravation of parkinsonism. At this point the patient was first diagnosed as having MSA of the parkinson type.

At the end of 2003, walking was just possible with the help of a stick. The patient had stopped taking L-Dopa because of the orofacial dystonia that persisted after the withdrawal. At the beginning of 2004, the patient was admitted to our emergency unit owing to a severe increase in parkinsonism with pronounced freezing in fine motor skills, in particular with the right hand. She also complained about start hesitation and problems with turning. Examination demonstrated an akinetic-rigid syndrome (especially on the right side) with an irregular postural and action tremor. The patient was not able to walk and standing was just
possible with assistance. A L-Dopa test was negative with no response as measured by the Unified Parkinson’s Disease Rating Scale.

In mid-2004 five years after the onset of motor symptoms, the patient tried to commit suicide with an overdose of mirtazapine. According to her family, this was the fourth suicide attempt. The patient continues to be disabled by severe motor impairment, dysautonomia and depression.

**DISCUSSION**

This patient demonstrates the risus sardonicus-like, a characteristic of lower facial dystonia, suggestive of MSA.

The clinical diagnosis of MSA is fraught with difficulties, resulting in under-recognition. PD is the most common cause of both false-positive and false-negative diagnosis. However, an accurate diagnosis of MSA is mandatory for several reasons. Existing published diagnostic criteria perform better than clinicians’ diagnosis at the first, but not at the last visit, but specificity and sensitivity are suboptimal. Beside the poor response to L-Dopa, or the presence of pyramidal, cerebellar signs or autonomic features as major diagnostic clues, other warning signs or ‘red flags’ such as sardonicus, raise doubt about a diagnosis of PD and point towards MSA. Based on expert consensus, the European MSA-Study Group (EMSA-SG) defined operational criteria for both motor and non-motor red flags that have previously been proposed, excluding cardinal ‘core’ diagnostic features for use in everyday clinical practice and prospective natural history studies.

Some examples include: rapid progression, early postural instability and falls, disproportionate antecollis, irregular orofacial jerky tremor, severe dysarthria/dysphonia, L-Dopa intolerance, respiratory stridor, RBD, and the ‘cold hand sign’. Many of our MSA patients, particularly, but not exclusively, of the MSA-P subtype, exhibit distinctive spontaneous dystonia of lower facial and platysma musculature. This is reminiscent of the well-known risus sardonicus of cephalic tetanus, which is thought to be mediated by tetanospasmin induced disinhibition of lower motor neurons. We have observed risus sardonicus in L-Dopa naive and treated MSA patients. Dyskinesias emerge in half of MSA patients treated with L-Dopa. In a recent prospective natural history study conducted by the EMSA-SG, orofacial dystonia was observed in 21–22% of patients with no significant difference according to motor subtype.

This case is instructive for many reasons, the major one being risus sardonicus-like orofacial dystonia, a warning sign or red flag of MSA which may occur spontaneously or be a complication of L-Dopa therapy. MSA is a rapidly progressive disorder with shortened life expectancy. Currently, therapeutic options are limited, and lasting improvement of motor disturbance is rarely achieved. Due to the rapidly progressive nature of the illness there is a pressing need for neuroprotective therapies, and
recent initiatives at the European level include establishment of the EMSA-SG (http://www.emsa-sg.org). An accurate diagnosis of MSA will therefore become increasingly important early on when initiation of neuroprotection is still meaningful. Clinical diagnostic criteria might aid in the diagnosis of MSA, and were first proposed by Quinn.\(^3^,\(^5\) However, two retrospective validation studies of these criteria demonstrated suboptimal diagnostic accuracy.\(^4\) Due to several pitfalls associated with the Quinn criteria, an International Consensus Conference developed new operational clinical diagnostic criteria, the Consensus or Gilman criteria. But, although the positive predictive values for both possible and probable MSA are excellent, sensitivity for probable MSA is poor, as shown by a retrospective validation study.\(^4\) Whether the Gilman criteria will improve recognition of MSA patients in early disease stages needs to be established prospectively.

REFERENCES

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**Legend to video**

**Case 32** A patient with probable MSA-P (MSA with predominance of parkinsonian symptoms) showing the risus sardonicus type of orofacial dystonia.
CASE PRESENTATION

A 5-year-4-month-old girl presented with incoordination, drooling, and speech problems (see video, Case 33). She was the product of a normal term pregnancy and had weighed 6 pounds 15 ounces. Developmental milestones were delayed. She sat at 10 months and walked at 20 months. At 24 months, she had increasing falls. She was talking and had been toilet trained by 36 months. At age 4 years, she was noticed to have decreased use of her left arm with a mild left hemiparesis, and was diagnosed with cerebral palsy. Drooling was a long-standing problem which had worsened over the 9 months prior to presentation. A head computed tomography (CT) scan and electroencephalogram (EEG) at age 4 years were normal.

The patient’s mother was healthy and had no family history of seizures, migraine, or neurodegenerative disorders. Her father was described as ‘healthy but a little clumsy’. The paternal grandmother and uncle both had Huntington’s disease (HD) (Figure 33.1). At her initial evaluation, developmental assessment estimated language and problem-solving skills at 22–27 months and gross motor skills at the 36-month level. Laboratory evaluations included normal coagulation studies, thyroid function, creatine kinase, and serum lactate, negative human immunodeficiency virus (HIV) and rapid plasma reagin (RPR), normal serum and urine amino acid levels, and normal serum copper and ceruloplasmin. Her first brain magnetic resonance imaging (MRI) (Figure 33.2A), performed when she was 5 years old, was normal.

When the patient was 7 years old, her father was diagnosed with HD on clinical grounds confirmed by DNA testing showing 47 CAG repeats. DNA testing performed on the patient at the time demonstrated 105 CAG repeats. Brain MRI at 8 years 5 months showed diffuse T2 signal abnormalities as well as decreased volume in the basal ganglia, especially the putamen and caudate (Figure 33.2B). Repeat MRI at 9 years 11 months showed increased T2 signal in the basal ganglia with progressive atrophy. Myelination remained normal (Figure 33.2C).

At age 10 years 1 month she experienced her first generalized seizure, and was started on carbamazepine. Over the previous 2 years, she had had intermittent staring spells lasting 10–15 seconds. An EEG at that time revealed only minimal background irregularities. She was readmitted at age 10 years 2 months
due to increasing falls and dysphagia, as well as painful leg spasms which had not responded to dantrolene, trihexyphenidyl, baclofen, or benzodiazepines.

On examination, she was small-for-age, had sialorrhea, and was wearing a padded helmet. At one point during the evaluation, she fell backwards without warning and did not attempt to right herself. There was no loss of consciousness, staring episodes, or rhythmic movements. On neurologic examination she had dysarthria and impaired fluency, producing two- to three-word sentences. She followed simple commands and could identify her own discomfort, body parts, objects, colors, and family. She had a mild left hemiparesis, generalized increased tone, and dystonic posturing of the left upper extremity, with intermittent hyperextension of the lower extremities. She was bradykinetic. Gait was wide-based with impaired initiation, short steps taken on her toes, en-bloc turns, and frequent retropulsion. Her admission medications included carbamazepine, baclofen, glycopyrrolate, and coenzyme Q.

Admission laboratory studies were normal. She had prolonged video EEG monitoring which revealed intermittent generalized discharges. She was
converted from carbamazepine to valproic acid with improved control of her seizures. She underwent feeding tube placement at her family’s request. Because of the parkinsonian features of rigidity, bradykinesia, and postural instability, as well as the poor efficacy of prior treatment for her dystonia, a trial of levodopa was initiated.

One week after beginning one-half tablet of carbidopa/levodopa 25/100 twice daily, there was improvement in her tone and gait. She had increased fluidity of movement and decreased hyperextension, and could once again transfer from the floor to standing using kneel/half kneel sequence. She continued to improve under observation for several weeks. Re-examination 7 months later revealed less postural instability and bradykinesia with improvement in her lower extremity dystonia. On examination at 11 years 5 months, gait remained improved, although there was increased instability. Four months later, because of increased falls, she required assistance to walk. Hospice care was initiated at age 12, and she died at age 15 after a prolonged period of unresponsiveness.

DISCUSSION

The clinical features of this case are consistent with previous descriptions of juvenile Huntington’s disease. This girl had both delayed development and regression of motor and cognitive skills, with the later development of dystonia, parkinsonism, spasticity, oral-motor dysfunction, postural instability, and generalized seizures. With signs present by 2 years of age, this case is among the earliest documented in Huntington’s disease, and shows a significant expansion of CAG repeats (105) compared to the affected father (47). She presented prior to the diagnosis in her father, and alternative diagnoses were excluded. The neuroimaging studies were also consistent with previously reported findings in juvenile HD.

Juvenile Huntington’s disease is defined as onset before age 20. It is usually of paternal inheritance, associated with a significant expansion in the trinucleotide sequence, and often presents with rigid–dystonic features, a clinical picture known as the Westphal variant. A review of 44 cases of juvenile HD (which included this patient) described the characteristic presentations for both childhood onset (<10 years) and adolescent onset (11–19 years). This patient illustrates the typical features of childhood-onset HD including family history of HD in the father, and two or more of the following: declining school performance, seizures, oral-motor dysfunction, rigidity, and gait disorder. In an earlier review of 28 childhood-onset cases, with 25% occurring before age 5 years, cognitive decline was the most frequent finding, in 78%, with 68% showing rigidity and 46% a movement disorder. Seizures occurred in 46% and cerebellar signs developed in 18%, which was not seen in this case. In contrast to our patient, early milestones (language and mobility) may be normal; regression of previously achieved milestones is an important diagnostic clue. Nevertheless, as in this case, childhood-onset HD may be misdiagnosed as cerebral palsy, particularly if the patient presents prior to onset in the affected parent or early in the course before progressive changes are appreciated.
This case is instructive for several reasons. First, it illustrates that the pronounced expansion in CAG repeats which can occur with paternal transmission of Huntington’s disease sometimes leads to presentation in the affected child before symptoms in a parent. An unusual feature of this case was the improvement in bradykinesia, rigidity, dystonia, and gait disorder with levodopa. Prior reports have described use of antiparkinsonian medications in adult-onset HD presenting with an akinetic–rigid syndrome. Our patient improved quickly on levodopa without behavioral or dyskinetic side-effects, suggesting that levodopa administration can improve parkinsonian features and dystonia in juvenile-onset Huntington’s disease, despite atrophy and abnormal T2 signal in the striatum.

Second, it demonstrates the typical features of childhood-onset HD including dystonia, parkinsonism, delay and regression of developmental milestones, and seizures. Third, it demonstrates that childhood-onset HD can be mistaken for cerebral palsy. And finally, it reminds us that even though Huntington’s disease is a devastating disorder, palliation of symptoms remains an important and realistic goal and, along with supportive care and genetic counseling, can improve the quality of life for patients and families.

REFERENCES
Legend to video

Case 33  First segment: age 5 years 8 months. The patient was recorded climbing stairs, walking, and turning. During these activities, there was mild unsteadiness and postural instability. While stacking blocks, she used her right hand primarily but not exclusively and tended to maintain her left arm flexed. Second segment: age 9 years 11 months. Before levodopa/carbidopa the patient was recorded sitting, crawling, attempting to stand, and walking up and down stairs. There was increased abnormal left arm posturing. Her gait was unsteady with toe walking. Stair climbing was slow and stiff with frequent retropulsion and she had an episode of freezing at the top of the stairs. Block stacking was also slow and she has greater difficulty using the left hand. Third segment: age 10 years 9 months. On carbidopa/levodopa, the patient was recorded walking and stacking blocks. Her walking and bending were more fluid and she easily performed one-step turns. Although she had some postural instability, this also was much improved. Her gait and upper extremity movement were less bradykinetic with more spontaneous use of the left hand.
CASE PRESENTATION

Six months prior to presentation, this 32-year-old man fell 10 feet from a ladder, striking his head, with loss of consciousness for several minutes. Two days later, he noticed difficulty speaking and walking. Within 2 weeks of the fall, he was fired from his construction job. Over the next several weeks, his mother noticed that he had slurred speech. He then developed dysphagia for solids, liquids, and saliva with a 50-pound weight loss, generalized weakness, and left-sided sensory loss. He was evaluated several times in a tertiary care medical center emergency room and was given outpatient neurology and otolaryngology appointments. No information on diagnostic studies was available.

His medical, childhood, and psychiatric history were negative. After completing high school, he worked in construction. He denied use of alcohol, tobacco, or illicit drugs and recalled no exposure to toxins. He had no allergies and took no medications. Family history included cardiac disease and lung cancer. Five siblings were well, and one brother reportedly had multiple sclerosis. The patient reported loose stools for the past 4 days with epigastric tenderness. There was no history of melena, hematochezia, nausea, vomiting, jaundice, cough, fever, chills, urinary symptoms, rheumatologic complaints, or hematologic or endocrine disorders.

On examination, he was afebrile with a pulse of 108, blood pressure of 125/81, and respiratory rate of 18. There were brown crescent-shaped lines at the superior and inferior edges of the irises (Figure 34.1A). He had mild epigastric tenderness with deep palpation, but no masses or hepatosplenomegaly.

Neurologically, he was alert and oriented. Language, concentration, recall, and fund of knowledge were all normal. Pupils were reactive and optic disc margins were sharp with good venous pulsations. Gaze was full and conjugate and his visual acuity was normal. He had decreased pinprick, light touch, and temperature sensation on the left side of his face. There was lower facial dystonia with restricted jaw opening and a fixed smile. He had facial weakness and could not create a seal with his lips. Speech was severely dysarthric and he had visible difficulty in swallowing. His palate elevated symmetrically when eliciting a gag reflex. He had difficulty protruding his tongue. He had rigidity in all extremities and mild wasting of the hypothenar eminence bilaterally. Limb strength was normal. There was diffuse hyperreflexia with extensor plantar responses.
Pinprick, light touch, and temperature sensation were decreased throughout his left arm and leg. Vibration sense was intact and Romberg testing was negative. Coordination was slow but accurate with a subtle action tremor. His gait was wide-based and slow with decreased arm swing and dystonic posturing of the arms. He had mild unsteadiness on tandem gait but a stable turn (see video, Case 34).

Routine laboratory evaluation was normal, including liver function studies with a high-normal creatine of 1.3 mg/dl (0.7–1.3). Serum ceruloplasmin was 2.8 mg/dl (normal 25–63) and serum copper was 271 µg/l (normal 590–1180). Urinary excretion of copper was increased at 223.5 µg/l over 24 hours (normal 2–30). Magnetic resonance imaging (MRI) of the brain (Figure 34.1B) showed abnormal T2 hyperintensity in the midbrain and central pons, hypodensity in the putamen, globus pallidus, red nucleus, and substantia nigra, and diffuse central and cortical atrophy. He required placement of a feeding tube for severe dysphagia with weight loss. After consultation with hepatology, he was offered participation in a clinical trial of ammonium tetrathiomolybdate.

**DISCUSSION**

This case demonstrates that delays in the diagnosis of Wilson’s disease remain a serious problem. In one series, two-thirds of patients presenting with neurologic features were initially not recognized, and the diagnosis was delayed for an average of 13 months. This patient presented with a characteristic clinical picture of progressive dysarthria, dysphagia, and gait disturbance. On examination, there were Kayser-Fleischer (KF) rings as well as severe dysarthria,
dystonia including facial dystonia (risus sardonicus), diffuse hyperreflexia, Babinski signs, rigidity, and an abnormal gait. Despite several evaluations in the emergency department the diagnosis was not considered. Although the history of a head injury and the atypical sensory features may have confounded an early diagnosis, the progressive symptoms as well as the MRI findings, characteristic of Wilson’s disease, were important clues. Furthermore, the presence of a neurologic illness in a sibling was a further clue about the possibility of a genetic condition. The diagnosis of Wilson’s disease was confirmed on laboratory evaluation with low ceruloplasmin and elevated urinary copper, and did not require extensive ancillary testing.

Wilson’s disease most often presents with either hepatic or neurologic symptoms. Neurologic features are more common in patients presenting in adulthood. The most frequent findings in patients with Wilson’s disease presenting with neurologic involvement include tremor, dysarthria, dysphagia, and dystonia. Although Wilson’s disease is often considered in young individuals presenting with an unexplained hyperkinetic movement disorder, tremor and dystonia may be subtle and many patients present with rigidity and bradykinesia, as in this case. Dysarthria and dysphagia are characteristic features and should prompt consideration of Wilson’s disease in a young adult, even if there is not a movement disorder.

Wilson’s disease is autosomal recessive and results from mutations of the ATP7B gene on chromosome 13, which encodes a P-type adenosine triphosphatase (ATPase) involved in copper transport, resulting in reduced hepatic excretion of copper into bile. In addition, copper is not incorporated into ceruloplasmin, which is secreted as the apoprotein and rapidly degraded. Accumulation of copper leads to liver damage and eventual release of copper into the bloodstream with deposition in other organs, particularly brain and kidney, as well as episodes of hemolytic anemia. Because of the large number of mutations identified to date, laboratory diagnosis is still based on biochemical rather than genetic testing, particularly low serum ceruloplasmin and elevated urinary copper excretion. Ceruloplasmin may be normal in up to 10% of affected individuals or low in asymptomatic carriers, so that both tests are needed for screening; liver biopsy to measure hepatic copper content may be necessary. While other conditions may cause copper deposition in the cornea, the combination of characteristic neurological features in an individual with Kayser-Fleischer rings, low ceruloplasmin (<5 mg/dl), and elevated urinary copper excretion (>100 μg/24 hours) is virtually diagnostic of Wilson’s disease. Although a KF ring may be visible at the bedside, slit-lamp examination should be performed in all suspected cases. Once a patient has been diagnosed, all first-degree relatives should be screened, even if asymptomatic.

The importance of diagnosing Wilson’s disease early is underscored by the fact that effective treatment is available. Treatment is most effective when signs are mild, and may not reverse advanced features. The copper chelating agent penicillamine is generally recommended as initial treatment in symptomatic patients, although neurologic symptoms may worsen during initial therapy and there is a high incidence of side-effects. Trientine is an alternative oral agent, and tetrathiomolybdate is under investigation as another potential initial therapy in patients with neurologic symptoms. Zinc may be used as adjunctive
therapy to reduce copper absorption, along with a low copper diet. Liver transplantation is generally reserved for those patients with fulminate or refractory hepatic failure.6

This case is instructive because it emphasizes the need to keep Wilson’s disease in mind. Although the initial neurologic features are usually a movement disorder (tremor, dystonia, parkinsonism), they may be absent or subtle and, instead, the presenting symptoms may be dysarthria and dysphagia. Identification of the mutation causing Wilson’s disease has led to substantial progress in understanding of the disorder. However, clinical suspicion remains essential to the diagnosis, which rests on demonstration of the characteristic biochemical abnormalities of low ceruloplasmin and elevated urinary copper excretion, as well as identification of a KF ring, and typical MRI changes.

REFERENCES

Legend to video
Case 34 On cranial nerve examination, eye movements are slowed but full range. The patient demonstrates a fixed dystonic smile or risus sardonicus throughout this portion of the examination. He has limited range of jaw opening; tongue protrudes in the midline but lateral movements are slowed. He has hypophonic speech with dysarthria for all speech components and speech is interrupted by an episode of dysphagia when he attempts to say his name. He has visible difficulty in swallowing and intermittent drooling. On point-to-point testing he has a terminal tremor without dystonia. Pronation-supination is slowed, more so on the left. He has bradykinesia with slowed finger and heel tapping. Dystonic posturing is evident in the right foot. Plantar responses are extensor bilaterally. Gait is slow with shortened stride length but a normal base and he demonstrates dystonic posturing of the hands while walking. He is unsteady during tandem walk, and when walking on his toes and heels, with increased dystonic posturing.
A case of hand tremor where deep brain stimulation failed

Zoltan Mari, Masao Matsuhashi, Noriaki Hattori, Hiroshi Shibasaki, and Mark Hallett

CASE PRESENTATION

A 67-year-old woman suffered a respiratory arrest due to anaphylactic shock during allergy desensitization. After resuscitation she remained comatose for several days. Upon regaining consciousness, she was found to have poor vision, rigidity, gait imbalance, and tremor. Most of her symptoms improved gradually, but she was left disabled due to hand tremor.

She was evaluated by multiple physicians and thought to have parkinsonism. Several antiparkinsonian medications had no effect on the hand tremor. She then underwent left subthalamic deep brain stimulation (DBS) which provided no benefit and was turned off. The patient was first seen in our clinic 4 years after the arrest.

Her general examination and vital signs were unremarkable. Her mentation and language were normal and her speech was fluent, but mildly dysarthric with occasional stuttering. The cranial nerves were significant for low visual acuity, bilateral paracentral scotomas, diplopia on upgaze, and hypometric saccades. She was mildly bradykinetic. Her muscle tone was increased. Muscle strength was normal. Her tremor was seen in the right hand and composed mainly of wrist flexion–extension, but occasionally involved the metacarpophalangeal joints, the left hand, and the right foot. The tremor could be seen at rest (see video, Case 35), while at other times the tremor could be triggered by tactile stimuli and passive or active hand movements, but this was not consistently reproducible. The rate of tremor was about 5 Hz. The tremor was slightly irregular and had a jerky quality. There were occasional larger amplitude jerks in phase with the tremor. She had mild finger incoordination and minimal limb ataxia. Other than the wrist tremor, there were no other abnormal movements. The sensory examination was significant for distal impairment of proprioception and vibration. Her gait was slow and minimally ataxic. Magnetic resonance imaging (MRI) of the brain showed hyperintense signal on T2 images in the basal ganglia and deep white matter in all lobes, consistent with hypoxic injury.

Electrophysiological assessment included somatosensory-evoked potentials and magnetic fields (SEPs/SEFs), jerk-locked back-averaging (JLA), and task-related corticomuscular coherence analysis using multichannel electroencephalographic (EEG), magnetoencephalographic (MEG), and simultaneous
surface electromyographic (EMG) polygraphy recordings. SEPs/SEFs were unremarkable. Polygraphy confirmed that the ‘tremor’ was generated by rhythmic myoclonic jerks in wrist flexors and extensors (more prominently in extensors) and intrinsic hand muscles. The jerking was irregular with a variable rate between 2 and 5 Hz. There were periods of unilateral right-handed, unilateral left-handed jerking, bilateral silence, and bilateral jerking (Figure 35.1). There was no consistent temporal relationship between the two sides during bilateral jerking. The individual EMG discharges were short (<50 ms) and sharp. Jerk-locked averaging showed a consistent cortical correlate beginning at about −20 to −25 ms (with respect to jerk EMG onset), maximal at central electrodes contralateral to the myoclonus (Figure 35.2). Source localization confirmed the pre-jerk cortical correlate in the primary sensorimotor areas, but accurate localization was difficult due to an artifact from the DBS coupler (in the left occipitotemporal region, data not shown). Single-trial analysis demonstrated high consistency across trials in the EMG and EEG waveforms, and thus the presence and timing of the cortical correlate.

The conclusion of the electrophysiological testing was: cortical tremor due to post-hypoxic myoclonus. The patient has had a minimal-to-moderate response to antmyoclonic medications, including clonazepam, levetiracetam, piracetam, and valproic acid, limited by side-effects.

**DISCUSSION**

Tremor is a common movement disorder, with many possible etiologies.\(^1\)\(^2\) Rhythmic myoclonus, as the present case demonstrates, may clinically appear to

![Figure 35.1](image)

**Figure 35.1** Electromyographic (EMG) polygraph showing four different 1-second segments: (A) bilateral discharges; (B) exclusively left sided discharges; (C) exclusively right sided discharges; (D) no jerks. FCU, flexor carpi ulnaris; FDI, first dorsalis interosseus.
be a tremor. The literature on tremor etiology often fails to list this possibility,\(^1\),\(^2\) despite accurate descriptions of cortical tremor.\(^3\),\(^4\) In cortical myoclonic tremor, palpation of muscle contraction is helpful for detecting the shock-like nature of each individual movement. However, electrophysiological testing is very useful for confirming the diagnosis.\(^5\),\(^6\) The present data demonstrated that the apparently tremulous movements were in fact due to repetitive myoclonic jerks. Despite the basal ganglia and cerebellar signs, the myoclonus in this patient likely had a cortical generator. Myoclonus is often seen after respiratory arrest, when perfusion is maintained.\(^7\) Our data are consistent with previous electrophysiological observations of cortical myoclonus.\(^8\)

**Figure 35.2** Jerk-locked averaging (JLA) showing a cortical correlate preceding the jerk onset in EEG. (A) Spatial distribution of the pre-jerk potentials on scalp contour maps at −20 ms (20 ms pre-jerk onset) when right first dorsal interosseous (RFDI) and left first dorsal interosseous (LFDI) muscles were used as triggers, respectively. (B) The temporal evolution of the cortical potential (C4 electrode; LFDI jerk onset as trigger; right ear reference). Time axis shows −0.2 to +0.2 second interval around the EMG onset. The three separate traces show two partial averages and the grand average (number of averaged trials in brackets).
ACKNOWLEDGMENTS

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This case is instructive because it demonstrates that myoclonus can mimic a tremor. Quasi-rhythmic myoclonic jerks can deceive even the careful observer, and the correct diagnosis in this patient was reached only by a proper physiological study to characterize the nature of abnormal movements.

REFERENCES


Legend to video

Case 35 The first segment shows bilateral hand jerking. Note that some jerks appear synchronous between hands, while others are apparently independent. Although we have no video (only electrophysiological) record of exclusively left hand jerking, the second segment shows primarily left hand jerking. The following segments show, respectively, exclusively right hand jerking, jerk-free period, and finger-to-nose testing, followed by transition from jerk-free to exclusively right hand jerking.
CASE PRESENTATION
A 33-year-old man was referred by his psychiatrist for complaints of being forgetful, fidgety, and clumsy. He had first sought psychiatric evaluation 4 years earlier and was diagnosed with adult attention deficit disorder (ADD). He had tried a variety of medications including methylphenidate, bupropion, pemoline, and sertraline without benefit. During this time period, his family reported several episodes of acute confusion and disorientation. One episode, during which he was lost for several hours, resulted in an emergency evaluation which included magnetic resonance imaging (MRI) and electroencephalography (EEG), both normal. A subsequent psychiatrist changed his diagnosis to atypical bipolar disorder and placed him on lithium and amphetamine.

He had had several automobile accidents over the previous few years, including two with possible loss of consciousness. Around this same time, elevated liver enzymes found on routine testing led to a liver biopsy, which was normal. The year before neurological evaluation, he was hospitalized for ‘major memory loss’ attributed to his medications. After hospitalization, he was unable to return to his job as a medical technician due to anxiety, irritability, an inability to sit still, and disorientation. He had a ravenous appetite and gained 30 pounds. He was tried on various combinations of medications including divalproex sodium, clonazepam, lorazepam, desipramine, diazepam, imipramine, olanzapine, paroxetine, and carbamazepine. His mother described him as a clumsy child who was always bumping into things. He had always had slightly slurred speech. He completed high school but did not attend college. There was no history of recreational drug or alcohol use. His neurological family history included a first cousin with the onset of seizures at age 35 and a maternal grandmother with dementia.

On physical examination, he was alert and oriented with good memory. His speech was slightly slurred (see video, Case 36). There was no apraxia or left-right confusion. Cranial nerve examination was normal. He had a slight decrease in vibratory sense in both feet, but otherwise normal sensation. Muscle tone was normal. Minimal weakness was noted in the left arm and leg. Deep tendon reflexes were diminished at the knees and ankles. Babinski responses were absent. Coordination and gait were normal. Throughout the examination, he moved almost constantly, shifting position in the chair and touching objects.
Movement Disorders

around him. Superimposed on these large movements were rapid shoulder
shrugs and jerks of an arm or leg. There were frequent facial grimaces and noises
including sniffing, throat clearing, coughing, and humming. He was aware of the
movements, which did not disturb him. He did not feel restless or an urge to
move. He was able to partly suppress the movements.

A second MRI of the brain was again normal. Laboratory testing showed a
slight elevation in hepatic transaminases, triglycerides, and cholesterol. Heavy
metal screen, VDRL (Venereal Disease Research Laboratory) testing, genetic test-
ing for Huntington’s disease, Lyme serology, human immunodeficiency virus
(HIV) testing, 24-hour urinary copper excretion, serum copper level, ceruloplas-
min, vitamin E, vitamin B12, and folate were all negative or normal. He achieved
a full scale intelligence quotient (IQ) of 91, with particularly low scores on the
memory and learning scales on neuropsychological testing. Electromyography
(EMG) and nerve conduction studies revealed a generalized axonal sensorimotor
neuropathy. All medications were tapered and discontinued. He had a grand
mal seizure 2 weeks after stopping the carbamazepine he had been on for mood
stabilization. It was restarted. Red blood cell morphology, performed twice on a
fixed smear, was normal. Only after direct discussion with a hematologist was
subsequent examination performed on a fresh, saline-diluted wet preparation. It
showed 11% acanthocytes (normal < 6%) and a diagnosis of neuroacanthocytosis
(NA) was made. There was gradual worsening in most symptoms over the next
several years. A third MRI, 1 year after diagnosis, showed increased signal on
FLAIR (fluid attenuated inversion recovery) sequences in both mesiotemporal
lobes. Increased chorea, poor concentration, disorganization, insomnia, and agi-
tation partially responded to risperidone and sertraline. Eating difficulties and
tongue biting due to the orofacial dyskinesia became prominent. His behavioral
problems seemed exacerbated by carbamazepine, so he was switched to pheny-
toin. Over time his seizures became difficult to control. By age 40 he was having
seizures every 3–6 months despite a combination of phenytoin, gabapentin, and
lamotrigine. He is currently able to perform activities of daily living, but cannot
work, drive, or live independently.

DISCUSSION

This patient presented with behavioral symptoms initially diagnosed as adult
ADD. The chorea was not appreciated as a movement disorder, but, rather, was
dismissed as agitation and anxiety in a patient who had always been ‘fidgety’.
The differential diagnosis of cognitive decline and chorea includes Huntington’s
disease, which, in this patient, was ruled out by the absence of family history
and negative genetic testing. Wilson’s disease was especially important to con-
sider in light of his elevated liver enzymes, but was also eliminated by copper
and ceruloplasmin measurements and the earlier liver biopsy. Although the
patient had motor and vocal tics, the degenerative nature of his illness and the
late age of onset were not consistent with Tourette’s syndrome. Other neuro-
logical disorders associated with acanthocytes include abetalipoproteinemia
(formerly Bassen–Kornzweig disease), pantothenate kinase-associated neuro-
degeneration (PKAN; formerly Hallervorden–Spatz syndrome), and McLeod’s
syndrome, an X-linked disorder associated with abnormal expression of Kell
blood group antigens that presents with acanthocytes and neurologic symptoms similar to NA.\(^1\) NA has recently been linked to the VPS13A locus on chromosome 9q21 which encodes chorein, a protein possibly involved in membrane stability or protein–protein interactions. The inheritance is autosomal recessive. The mutations tend to be scattered throughout this large gene and unique to the individual or family, so genetic testing is not currently feasible.\(^2\) While there is no treatment for the underlying neurodegeneration, seizures can be controlled with anticonvulsants. In addition, medications such as antidepressants, neuroleptics, and anxiolytics may provide at least partial symptomatic relief. Although associated with a shortened lifespan, the progression of disease may be very slow, with survival into the sixth or seventh decade.

This case is instructive because it highlights the key symptoms and evolution of neuroacanthocytosis.\(^3,4\) The onset of symptoms in early adulthood is typical, as are the progressive cognitive and behavioral changes characterized by disorganization and poor concentration (found in approximately 70% of NA patients), tics and orofacial dyskinesia (90%), dysarthria (88%), chorea (85%), axonal peripheral neuropathy (85%), vocalizations (62%), and seizures (42%). This diagnosis should be considered in patients presenting with chorea, especially with orofacial dyskinesia or vocal tics, and cognitive decline or psychiatric symptomatology. The case also demonstrates a laboratory pitfall in making the diagnosis. Acanthocytes are not readily found on the dry smear done during routine hematologic testing; they need to be specifically sought on a fresh preparation.\(^5\)

REFERENCES


Legend to video

Case 36 First segment: patient observed during conversation. Involuntary movements of trunk, limbs, shoulders, and face are present. Second segment: involuntary movements of outstretched hands, partially suppressible. Third segment: normal finger-to-nose testing bilaterally. Fourth segment: while walking, arm swing is decreased on the right; leg chorea interferes, especially with tandem gait.
Too much of a good thing

Kevin R Cannard

CASE PRESENTATION

In 1985, at age 34, a man with a history of alcohol abuse began to experience tremor and loss of dexterity in his right hand and dragging of the right foot. He came to medical attention at age 37 and was diagnosed as having Parkinson’s disease (PD). He was placed on levodopa/carbidopa, which produced a dramatic reduction in his symptoms and signs. Bromocriptine and selegiline were soon added. Within the first year of treatment he developed intermittent mild dystonic posturing or choreiform dyskinesias of the right arm and foot. Over the following year his dose of levodopa was incrementally increased from 400 to 900 mg per day, but often by the patient without consulting his physician. He also began to deviate from the prescribed dosing schedule, preferring to take the medication whenever he felt it was needed.

By age 47, the patient developed end-of-dose wearing-off and admitted to taking as much as 1600–2000 mg per day of levodopa. Despite pronounced dyskinesias and few parkinsonian signs on examination (near constant peak-dose state; see video, Case 37), the patient resisted attempts to lower and regulate his dose. He acknowledged that he was dosing in excess of what was needed from a movement standpoint. To explain his irregular and often impulsive pattern of levodopa use, he described baseline anxiety that rapidly increased as he sensed the effects of levodopa wearing off. Less frequently, he would experience a rapid plunge into a deep depressive state. While the patient did describe the rapid transition into a motor ‘off’ state, it was the sense of intense dysphoria that he identified as the impetus for his irregular dosing. He admitted to some vague mood elevation from levodopa but denied a euphoric response.

Entacapone was added in an effort to minimize drug level fluctuations but this had little effect on his use of levodopa. He began to dose in an anticipatory manner to avoid rapid mood swings. He would binge on several tablets if dysphoria or anxiety occurred, often chewing the tablets for a quicker effect. Sertraline was added and psychiatry consulted to help control his anxiety and worsening depression. At age 49, in order to gain control of his dyskinesias and parkinsonism on lower doses of levodopa, deep brain stimulation surgery (DBS) was performed on the left subthalamic nucleus (STN). There was a clear benefit, with his Unified Parkinson’s Disease Rating Scale 3 (UPDRS-3) score dropping from 39 (out of 108) preoperatively to 20 following surgery with the stimulator.
on. However, after a brief period of adhering to a schedule of diminished levodopa use, he returned to a pattern of irregular and excessive use. He discontinued selegiline and took bromocriptine inconsistently. The patient developed insomnia and a rapid eye movement (REM) sleep behavior disorder. Nightly clonazepam was added to control these symptoms along with escalating anxiety and panic attacks. Despite this, he became more irritable and had periods of hypomania and paranoia. This caused marital, family, and financial problems. Low-dose quetiapine was added with some benefit. Still, he continued to dose levodopa at briefer intervals and in larger doses.

At age 52, preceding planned DBS to the right STN, a urine drug screen revealed cocaine. He confessed to smoking crack cocaine intermittently, but persistently, over the preceding year. The patient completed a residential drug rehabilitation program but relapsed, placing surgery on indefinite hold. The severe, abrupt ‘off’ states worsened and he increased his levodopa intake to as much as 700 mg at a time to ‘overpower’ them. While the resulting dyskinesias bothered others, appeared to impair his gait, and seemed to heighten his progressive social isolation, he denied that they were a problem. He also discovered that cocaine could yield motor improvement if taken at the onset of an abrupt ‘off’ state. The patient was hospitalized to re-establish a rational dosing regimen. He was placed on levodopa 150 mg with entacapone every two-and-a-half hours while awake (maximum of eight doses) supplemented by a trial of apomorphine injections as a rescue medication for abrupt ‘off’ periods. However, the patient declined further drug rehabilitation, felt apomorphine was ‘not strong enough’, and discontinued the medications recommended by psychiatry. After discharge he returned to the same pattern of levodopa overuse, taking as much as 1500 mg over a period of 10 minutes. To date at age 55, the only real control over his regimen has come by prescribing a fixed amount each month with a recommended dosage schedule that he must then manage. He denies obtaining medication from other sources, but this is questionable.

**DISCUSSION**

This patient suffers from the dopamine replacement therapy (DRT) overuse/abuse syndrome of hedonistic homeostatic dysregulation (HHD) (Tables 37.1 and 37.2). Also known as dopamine dysregulation syndrome,1 the hallmark of this disorder is excessive and compulsive use of DRT beyond that needed for optimal motor control of parkinsonism. While uncommon, it is not rare.2,3 It is most frequently seen in men with young-onset, levodopa responsive PD, often with a history of alcoholism.1,2,4 These patients have an irrational, self-directed dose escalation and preoccupation with levodopa or, less commonly, other DRT.5 Despite increasingly intense dyskinesias and adequate relief of the motor features of PD, patients may further facilitate increases via drug hoarding and drug seeking behavior akin to that seen in other addiction syndromes.5 Rapid dose increases in large increments or binges are common.2 Daily intakes of 1–4 of levodopa are typical.1 A withdrawal state emerges if DRT is reduced or eliminated. Withdrawal is often rapid in onset and characterized by intense dysphoria, anxiety, depression, or irritability, all of which may occur before any motor ‘off’ symptoms. Rapid mood swings tracking apparent drug levels are
seen, resulting in the appearance of a rapid-cycling (cyclothymic) affective syndrome. Hypomania, at times progressing to mania and frank psychosis, may occur during high intake periods. Social and occupational dysfunction, even aggression, is common. Patients are frequently demanding and may exaggerate their motor impairment in hopes of receiving increased doses of DRT. Other observed behaviors have included: pathological gambling or spending, hypersexuality or paraphilias, punding (prolonged, complex stereotypies), walkabouts (purposeless long walks), and disordered eating patterns. Patients report that they only feel ‘on’ when they are notably dyskinetic, and resist all efforts to reduce total DRT or establish a dosing schedule. Total avoidance of ‘off’ periods appears to be their primary motivation. The shorter the half-life of the DRT is, the more likely it appears to trigger HHD, and apomorphine rescue injections may be particularly likely to trigger or escalate HHD.\(^1,6\)

In most current theories of addiction and dependence, the nucleus accumbens is thought to play a key role, perhaps as the major ‘reward center’. This nucleus is the target of dopaminergic neurons arising in the ventral tegmental area of the mesencephalon, projecting via the mesolimbic pathway. Degeneration and dysfunction of these neurons, while less pronounced than those of the substantia nigra, is also seen in PD. Levodopa and other DRT are not selective of the

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<tr>
<th>Table 37.1</th>
<th>Diagnostic criteria for hedonistic homeostatic dysregulation (HHD)</th>
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<tr>
<td>• Levodopa responsive PD</td>
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<tr>
<td>• A compulsive need to increase dopamine replacement therapy (DRT) in excess of that needed to control parkinsonian motor symptoms and signs</td>
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<tr>
<td>• A pattern of pathological DRT use: DRT intake despite peak-dose dyskinesia and behavioral disturbances (irritability, hypomania/mania, psychosis), drug preoccupation, drug seeking, drug hoarding, surreptitious acquisition</td>
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<tr>
<td>• Impairment of social or occupational functioning</td>
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<tr>
<td>• Development of a withdrawal state characterized by severe dysphoria, anxiety, or depression upon reduction of DRT intake</td>
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<th>Table 37.2</th>
<th>Clinical features associated with HHD</th>
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<td>• Men with early-onset PD</td>
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<td>• Previous medical history of alcohol or drug abuse</td>
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<tr>
<td>• Rapid, self-directed increases or binges of DRT</td>
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<tr>
<td>• Affective disorders: rapid mood swings, anxiety, panic attacks, depression</td>
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<tr>
<td>• Pathological gambling or shopping</td>
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<tr>
<td>• Punding</td>
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<td>• Walkabout</td>
<td></td>
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<td>• Alterations of appetite</td>
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<td>• Hypersexuality or paraphilias</td>
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nigrostriatal pathway but also stimulate mesolimbic neurons.\textsuperscript{4} Many of the psychotic adverse effects of DRT in PD patients and the addictive effects of DRT in HHD patients are thought to arise from stimulation of the nucleus accumbens. This is supported by the features that HHD shares with cocaine and amphetamine addiction, both of which involve enhanced dopaminergic stimulation of the nucleus accumbens.\textsuperscript{3,6,7} The fact that only a minority of patients with PD develop HHD points to a predisposing factor, perhaps genetic in nature. The abuse of cocaine in this patient is an exception to most cases of HHD but is intriguing.

The management of HHD is extremely challenging and the prognosis poor. Because patients need DRT to relieve their parkinsonism and withdrawal can even be dangerous, elimination of the \textquote{abused} DRT is not an option. During periods of hypomania/mania, psychosis, or rapid dose escalation, hospitalization is often required. Baseline cognitive status can usually be restored in 12–72 hours merely by limiting or temporarily stopping DRT intake.\textsuperscript{2} The establishment of a rational and scheduled regimen is often easy to initiate only to be quickly abandoned soon after discharge. Daily rationing of DRT doses by a family member is perhaps the most effective intervention but often damages that relationship.\textsuperscript{1} Some patients have no family support and very limited means of transportation, making rationing periods of less than a month impractical. While a switch to longer-acting dopamine agonists seems to be an obvious intervention, left to themselves, patients invariably return to levodopa. Apomorphine rescue injections should be strictly avoided. Low doses of atypical antipsychotics, particularly quetiapine, may not only reduce psychotic features but also enhance mood stabilization and suppress REM sleep behavior disorder symptoms without undermining the motor effects of DRT.\textsuperscript{1,2} While DBS often leads to a reduction in DRT in idiopathic iPD patients, this may not be the case in patients with HHD. Rare cases of worsening of HHD or escalation of stimulation parameters have been reported.\textsuperscript{3} Despite numerous and varied attempts at intervention, relapse to excessive use of DRT is the rule rather than the exception.

ACKNOWLEDGMENTS

The views expressed in this chapter are those of the author and do not reflect the official policy of the Department of Army, Department of Defense, or US Government.

This case is instructive because it presents a typical case of Parkinson’s disease complicated by an uncommon disorder of dopamine regulation, hedonistic homeostatic dysregulation, which is characterized by the compulsive excessive use of DRT beyond that needed to yield optimal motor control.
REFERENCES


Legend to video

Case 37  ‘Peak-dose’ choreic dyskinesias, often more prominent than shown, are typical of this patient’s motor state while awake.
Parkinsonism with dysautonomia: MSA or PD?

Susan Criswell and Brad A Racette

CASE PRESENTATION

A 53-year-old man presented with episodic lightheadedness for 2 years. The episodes occurred whenever he was exposed to temperatures > 85°F and were exacerbated by exercising or golf. With the lightheadedness he also experienced nausea, frequent urination, erectile dysfunction, shallow breathing, and palpitations. The episodes lasted a day. One year after the episodes started he developed urinary frequency, nocturia, and incontinence, and 6 months later he developed a shuffling gait and hypophonia followed by micrographia. He had a history of gout but no other medical problems. There was no family history of similar illness. He worked as a supervisory engineer but had no relevant environmental exposure.

His supine blood pressure was 150/96 and pulse was 72. His standing blood pressure was 84/60 and pulse was 76. Eye movements were normal. He had mild, symmetric rigidity, minimal left sided bradykinesia, and moderate axial akinesia. There was no tremor, dystonia, chorea, or myoclonus. He had a stooped posture and reduced arm swing. He took no steps with a pull test. Reflexes were symmetric and plantar reflexes were flexor. The initial Unified Parkinson’s Disease Rating Scale – motor subsection (UPDRS-3) score was 15.5.

Nerve conduction studies were normal. The sympathetic skin response showed no evidence of sudomotor dysfunction. There was mild increased RR interval variation on deep breathing suggesting mild parasympathetic dysfunction. Electromyography of the anal sphincter showed no evidence of denervation. Basal plasma norepinephrine levels were normal.

He was diagnosed as having multiple system atrophy (MSA) and the initial management consisted of treatment of his orthostatic hypotension with hydration, increased salt intake, caffeine, fludrocortisone (0.3 mg/day), and midodrine (12.5 mg every 3 hours). With treatment of his orthostatic hypotension, he was able to continue working. Parkinsonism progressed and he eventually required treatment with levodopa. Prior to starting levodopa, his UPDRS-3 score was 44. Gradual titration of carbidopa/levodopa to 75 mg/150 mg three times per day improved the UPDRS-3 score to 22. Higher doses were not tolerated due to worsening of orthostatic hypotension. During the course of his illness, his mean
‘on’ UPDRS-3 score was 29 (range 22–34.5). Orthostatic hypotension resulted in a fall with a fatal cervical fracture 6 years after the initial onset of symptoms. Autopsy revealed a decreased number of pigmented neurons and scattered Lewy bodies in the substantia nigra and locus coeruleus consistent with idiopathic Parkinson’s disease (PD) (Figures 38.1 and 38.2). There were no abnormalities in the ventral pons or cerebellum and no glial cytoplasmic inclusions.

**DISCUSSION**

This case demonstrates that prominent early autonomic dysfunction can occur in idiopathic Parkinson’s disease and is not exclusive to the diagnosis of MSA. The autonomic features of idiopathic PD are variable and can include cardiovascular, gastrointestinal, urogenital, respiratory, sudomotor, and thermoregulatory dysfunction, pupillary abnormalities, and sleep disorders. Up to 70% of patients with clinically diagnosed PD report symptomatic postural hypotension during the course of disease. Clinical features associated with MSA include greater severity of motor dysfunction, autonomic dysfunction occurring at a
younger age (54.4 vs 60.6 years) and earlier in the course of their illness, symmetric signs, and lack of sustained response to levodopa. Nevertheless, pathologic series demonstrate that severe autonomic dysfunction can occur in idiopathic PD. In retrospect, the clear objective response to levodopa and asymmetric onset were clues that this patient had PD and not MSA, although we felt that the asymmetry was modest, as has been reported in large MSA series previously.

Autopsy series of patients with parkinsonism suggest that patients presenting to a specialist with Parkinson’s disease are only correctly identified in 76% of cases. In that series, 12% of those with PD had atypical features including severe autonomic dysfunction. It is likely that longitudinal follow-up including response to levodopa improves diagnostic accuracy.

This case is instructive because it demonstrates that it can be difficult, if not impossible, to distinguish MSA from Parkinson’s disease with dysautonomia. As such, it is important to remain open to both diagnoses in patients with prominent autonomic dysfunction and parkinsonism and appreciate that the autopsy is the final arbiter.
REFERENCES


Levodopa responsive parkinsonism: is it Parkinson’s disease?

David Riley

CASE PRESENTATION

A 59-year-old right-handed woman developed progressive generalized pain, stiffness, and slowness of movement, attributed to arthritis and fibrositis. Various anti-inflammatory and antidepressant medications provided no benefit. Two-and-a-half years into her illness, she fell and broke her left hip. She returned to walking, but experienced persistent disequilibrium. Three years after onset, a rheumatologist thought she showed evidence of parkinsonism, and referred her for neurologic evaluation.

Her history revealed that her right side felt more affected than the left, and that her handwriting had become progressively smaller. She reported a tendency to walk on her toes, and had had freezing of the right foot for 6 months. She required occasional help getting dressed or cutting food, and had difficulty turning over in bed. She still had severe generalized pain. Relatives had noticed low voice volume, a stooped posture, and impaired mobility. There was no history of tremor. Examination demonstrated hypophonia and hypomimia, a mild action tremor of the upper limbs, slightly greater on the left, and symmetric mild rigidity and moderate akinesia, worse in the lower limbs and slightly more pronounced on the left. She leaned to the left while sitting. She stood and walked very slowly, and there was no arm swing bilaterally (see video, Case 39, first segment). She tended to lose her balance spontaneously. There was no rest tremor and no orthostatic hypotension. The rest of the examination was normal.

She began taking carbidopa/levodopa 25/100, one half-tablet three times a day, and noticed improvement the very first day. When reassessed 1 month later (on 300 mg levodopa per day), her pain had disappeared, and her mobility and posture had improved considerably. However, she continued to have postural instability and no arm swing. Interestingly, she had slight dyskinesias of the left foot and head (see video, second segment).

Subsequently, her dyskinesias became generalized. She developed levodopa dose-related motor fluctuations, morning foot dystonia, and restless legs syndrome less than a year after starting levodopa. She fell and broke her right patella. Fifteen months after initiating treatment, she was taking levodopa every
4 hours around the clock, each dose providing benefit for two-and-a-half hours. Her dyskinesias occurred primarily at the beginning and end of her periods of benefit. A trial of pergolide, up to 0.75 mg three times a day, almost abolished her fluctuations, but resulted in an ‘uncontrollable’, unacceptable increase in libido. Her daughter-in-law noticed that she had begun ‘screaming in her sleep’. A reduction of pergolide led to marked stiffness again. This was followed by numerous medication adjustments, none particularly satisfactory but all demonstrating responsiveness correlated with doses of levodopa and pergolide.

Five-and-a-half years after onset, she began a progressive downhill course. When assessed 1 year later, she was taking carbidopa/levodopa 10/100 every 2 hours, with only 45–60 minutes of benefit and many ineffective doses. When ‘off’ she had dysarthria, dysphagia with drooling, neck flexion, dystonic left foot inversion, depression, and pain ‘like a fresh sunburn’. She was unable to arise without assistance, and occasionally unable to walk. Her examination showed a scoliosis to the left, her arms dystonically extended backward, and she had no righting reaction on the pull test, causing her to fall. Medication adjustments produced no major improvements. She entered an assisted-living facility. She fell and broke her right shoulder, and then her right hip. Afterward, she remained largely wheelchair-bound.

When seen eight-and-a-half years after onset, she reported progressively less benefit from medication. During ‘off’ periods she had severe distal limb pain and blepharospasm. She had had multiple urinary tract infections due to retention. She reported occasional dizziness on standing and profuse night sweats. On examination, there was severe akinesia of all limb movements, severe tenderness of leg muscles, and moaning on exhalation. Her diagnosis was changed to multiple system atrophy (MSA). Autonomic laboratory testing provided evidence of severe, diffuse autonomic failure. Tilt table testing at 72° from horizontal showed a drop in blood pressure from 139/106 to 90/62 at 3 minutes and 70/51 at 6 minutes.

Her subsequent course was marked by progressive motor deterioration, syncope, urinary tract infection, and institutionalization. Ten years after onset there were moderate dyskinesias, most pronounced in the lower limbs, and antecollis. When attempting to walk she made erratic movements of her feet in a modified goose-step fashion, and she could not walk without support (see video, third segment). She died at the age of 72, 13 years after onset. Her autopsy confirmed multiple system atrophy.

**DISCUSSION**

This woman came to me in 1988, shortly after I first established my practice. I mention this because her correct diagnosis was gradually revealed to me contemporaneously with Dr Niall Quinn’s publication of ‘Multiple system atrophy – the nature of the beast’.

This landmark article described the clinical picture of MSA far better than had been done before, and served as a blueprint for establishing the correct diagnosis in this case. It truly deserves the overworked term ‘classic’, and I recommend it to all neurologists. It is fair to say that I learned much of what I know about MSA from this patient and this reference almost simultaneously.
Although she presented with features of atypical parkinsonism (no rest tremor, minimal asymmetry, early freezing and postural instability, severe pain), I decided that these were trumped by her dramatic response to levodopa. When she reported the initial benefit and I saw the results, I thought she had Parkinson’s disease (PD), and I told her so. As her clinical course evolved, it became apparent within a few years that she demonstrated many of the ‘red flags’ warning that she did not have PD \(^2\) (Table 39.1) When she developed early motor fluctuations and dyskinesias, I initially explained these away as consequences of a delayed diagnosis, and clung to my original conclusion. It was only later when she developed overt dysautonomia that I realized the correct diagnosis, but, in retrospect, the atypical motor features earlier in the course could have set me on the correct path.

Parkinson’s disease is the disorder for which MSA is most often mistaken.\(^2\) These disorders share not only many motor features, but also non-motor complications such as dysautonomia and rapid eye movement (REM) sleep behavior disorder. Up to 30% of MSA patients experience a good response to levodopa,\(^3\) and many will develop dose-related motor fluctuations and dyskinesias,\(^4\) as did the patient presented here. However, the rapid deterioration in the quality of her response was typical of MSA, as was her accelerated rate of decline. In defense of the original diagnosis of PD in this case, early on, she technically did not qualify for a diagnosis of MSA according to consensus criteria.\(^5\) These criteria stipulate that dysautonomia (orthostatic hypotension or urinary incontinence) must be present, along with either parkinsonism or cerebellar deficits, to establish the diagnosis of MSA.\(^5\) Thus, in order to identify patients with MSA promptly, the finding of features of atypical parkinsonism should prompt a diligent search for evidence of autonomic dysfunction, if it is not obvious on routine clinical assessment.

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<tr>
<th>Table 39.1</th>
<th>‘Red flags’ suggesting a diagnosis of MSA rather than Parkinson’s disease(^2)</th>
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<td>Rapid progression</td>
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<td>Early disequilibrium and falls</td>
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<td>Action myoclonus</td>
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<td>Urinary incontinence or retention</td>
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<td>Cold, violaceous hands and feet</td>
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<td>Raynaud’s phenomenon</td>
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<td>Respiratory stridor</td>
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<td>High-pitched dysphonia</td>
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<td>Dysphagia</td>
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<td>Antecollis</td>
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<td>Contractures</td>
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<tr>
<td>Cerebellar signs (dysarthria, dysmetria, ataxia)</td>
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<td>Corticospinal tract signs</td>
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This case is instructive for several reasons. First, it emphasizes that one should always maintain a margin of diagnostic latitude with parkinsonian patients no matter how robust their initial response to levodopa. The syndrome of MSA may only become apparent as a patient diagnosed with PD is followed over time. These clinical diagnoses always warrant periodic scrutiny. Second, it illustrates the importance of appreciating and actively looking for the ‘red flags’ that cast doubt on the diagnosis of PD. Last, it demonstrates that MSA may respond to levodopa, at times even dramatically, with dyskinesias and fluctuations usually considered characteristic of PD.

REFERENCES


Legend to video

Case 39 First segment: three years after onset and prior to treatment, the patient demonstrates moderate akinesia without rest tremor. Second segment: one month after initiating levodopa therapy, her mobility and gait were noticeably improved; dyskinesias of the head and left foot had already appeared. Third segment: ten years after onset, she exhibited a complete loss of equilibrium, requiring support to stand and walk.
A woman with recurrent ataxia and facial myoclonus

Timothy Kleinig and Philip Thompson

CASE PRESENTATION

A 50-year-old woman presented with the third episode of acute unsteadiness, confusion, agitation, restlessness, vomiting, and eventually obtundation. The two previous episodes had occurred 14 and 24 months earlier. On each occasion, examination revealed ataxia, and exaggerated tendon reflexes with extensor plantar responses. Computed tomography of the brain was normal and a diagnosis of brainstem stroke was made on both occasions. The signs and symptoms resolved spontaneously over 2 weeks. Aspirin then aspirin/dipyridamole were prescribed. There was no family history of a similar disorder. There was a past history of depression treated with fluoxetine.

On this occasion she began to improve as in the past. She was given two doses of metoclopramide for persistent nausea. Following this she became less responsive and developed extensor rigidity. Tonic seizures were suspected and she was referred for further investigation.

On arrival she was diaphoretic and flushed with a tachycardia. Her eyes were open with a staring facial expression and she made no attempt to interact or communicate spontaneously with her surrounds. She responded intermittently to questioning in a soft whisper with palilalia and echolalia. She followed simple instructions but would perseverate. She was distractible and would stop what she was doing and divert her attention and gaze elsewhere. The pupils were dilated. Spontaneous and action facial myoclonus was present (see video, Case 40). Muscle tone was increased in all limbs. Tendon reflexes were brisk with clonus at the knees and ankles. There were bilateral grasp reflexes. Forced groping and waxy flexibility with sustained abnormal posturing of the arms was also present. She was unable to stand or walk and was incontinent. Creatine kinase (CK) (429 U/l) and liver transaminases were elevated. A range of other investigations including cerebrospinal fluid examination, thyroid autoantibodies, urinary amino acid screen, and further brain imaging were normal.

DISCUSSION

A clinical diagnosis of the serotonin syndrome was made. No specific treatment was given. Fluoxetine was withheld. Over the following 2 weeks she gradually
improved in all spheres. Eventually it emerged that before each of the previous episodes she had taken an excessive amount of fluoxetine in addition to a long-term daily dose of 60 mg. This was again the case. On this occasion she had also taken St John’s wort and Demazin® (chlorpheniramine/pseudoephedrine).

The differential diagnosis of recurrent stereotyped neurological events, with normal imaging studies and spontaneous complete recovery over a period of days, encompasses migrainous, epileptic, metabolic, drug-related or toxic, vascular, and other paroxysmal processes. The duration of the recovery phase in this patient suggested a toxic, metabolic, or drug-related etiology. Facial myoclonus, a frontal syndrome, and hyperreflexia along with a flushed appearance, pupillary dilatation, and tachycardia raised the possibility of the serotonin syndrome, though at presentation there was no history of drug overdose. However, she was known to be taking fluoxetine, a recognized precipitant of the serotonin syndrome. Her condition resolved with cessation of fluoxetine. Direct questioning later confirmed the diagnosis.

The diagnosis of serotonin syndrome is suggested by a typical constellation of signs in the context of an overdose or change in dosage of an implicated agent. Sternbach’s original diagnostic criteria require at least three of the following: agitation, mental state changes, myoclonus, shivering, tremor, hyperreflexia, ataxia, diarrhea, and fever. Laboratory investigations are relatively non-specific, but may show increased CK, elevated transaminases, and leukocytosis. Simplified diagnostic criteria, with a higher sensitivity and specificity, have recently been proposed.

Current recommendations for the management of serotonin syndrome focus on withdrawal of the offending drugs and basic supportive care of vital functions. In the majority of cases the condition is self-limiting and resolves within 24 hours. In some, agitation, hyperthermia, and autonomic instability may require specific management. The benefits of serotonin 2A (5HT2A) antagonists have not been firmly established. Benzodiazepines, cyproheptadine, and atypical antipsychotic drugs with 5HT2A antagonist activity may be considered in severe cases.

The causes of myoclonus are extensive and have been reviewed recently. A number of drugs are implicated in precipitating myoclonus including most antidepressants, lithium, narcotics, quinolone antibiotics, anticonvulsants, calcium channel blockers, and antiarrhythmics. Myoclonus is particularly prominent in the serotonin syndrome and characteristically, though not exclusively, affects the face. Polytherapy with concurrent administration of several drugs may precipitate the serotonin syndrome as in the present case.

This case is instructive because it: (1) illustrates that the careful observation of subtle neurological signs, in this case facial myoclonus, is still vital for reaching a correct diagnosis even in this era of technological investigations; (2) demonstrates the clinical features of the serotonin syndrome; and (3) emphasizes the necessity of taking a careful drug history including the use of non-prescription medications, not all of which are benign.
REFERENCES


Legend to video
Case 40  Small amplitude myoclonic movements of the mouth.
Parkinson’s disease: after the honeymoon

Lars Timmermann and Alfons Schnitzler

CASE PRESENTATION

A 71-year-old man with a 19-year history of Parkinson’s disease was referred to the emergency department of the University Hospital. On admission there were severe dyskinesias of the head, trunk, arms, and legs, which impaired walking and other voluntary movements. He was disoriented in time and claimed that he saw dwarfs in his bedroom that were frightening. He was cachectic and dehydrated. His speech was hypophonic and dysarthric. The dyskinesias were more pronounced in the right limbs where there was also mild bradykinesia. There was no rigidity or tremor. His postural reflexes were good.

His wife reported that he was extremely afraid of getting into an ‘off state’. During these states he was totally immobile. During periods of good mobility (‘on state’), after taking levodopa, he felt much better, with resolution of the anxiety and depression he experienced when ‘off’. In the days preceding admission, during his ‘on state’ he became increasingly agitated and reported seeing people and dwarfs in the flat who were frightening him. His wife had recognized slight deterioration in his memory and concentration within last few years.

Parkinson’s disease (PD) had begun 19 years previously with hypokinesia of the right limbs. He had an excellent initial response to dopaminergic medication. After 4 years the patient developed worsening of symptoms before the next dose of medication (‘end-of-dose wearing-off’) that was well-managed for several years with increasing single doses of levodopa, decreasing the interval between doses, adding a COMT (catechol-O-methyltransferase) inhibitor (initially tolcapone, later entacapone), as well as the long-lasting dopaminergic agonist, cabergoline. In the ‘off state’ the patient was totally disabled, unable to walk, and wheelchair-bound. This akinetic state was associated with severe anxiety and depression. In the ‘on state’ he was dyskinetic but demonstrated good mobility (see video, Case 41).

Three years prior to this admission the patient underwent bilateral deep brain stimulation (DBS) of the subthalamic nucleus (STN) to treat severe motor fluctuations which could not be managed with medical treatment options. The patient initially had an excellent response to DBS; dyskinesias were almost completely abolished and medication could be reduced by about 50%. In the
following years – even though the overall clinical situation of the patient slowly deteriorated – the relative improvement of mobility by STN DBS remained.

One year after DBS the patient developed slight deficits in short-term memory and concentration, and 2 years later the Mini Mental State Examination (MMSE) score was 23/30. Neuropsychological testing revealed deficits in attention and memory, visual-constructive, and executive functions. Therapy with donepezil 5 mg was initiated and increased to 10 mg with improvement in the MMSE, and the patient and his wife recognized improvement in memory functions, orientation, and functioning in everyday activities.

The visual hallucinations that led to the emergency admission were satisfactorily controlled by a small reduction in levodopa, withdrawal of the dopamine agonist, and a low dose of the antipsychotic quetiapine (25 mg in the morning and 50 mg in the evening). This regimen not only abolished the hallucinations but also improved sleeping at night. Because of the difficulty in caring for the patient, the couple moved to a facility for the care of elderly people.

DISCUSSION

This case demonstrates many of the complications in the long-term management of Parkinson’s disease. In the initial years the patient had an excellent response to levodopa. He subsequently developed typical levodopa-associated motor fluctuations with dyskinesias when ‘on’, akinesia when ‘off’, end-of-dose wearing-off, sudden ‘offs’, and a fear of the ‘off states’, which were complicated by depression and anxiety. The primary goal of treatment in the setting of such fluctuations is to accomplish continuous dopaminergic stimulation by using long-acting dopamine agonists, administering smaller but more frequent doses of levodopa, inhibiting the catabolism of dopamine with COMT and MAO inhibitors, and applying the glutamate antagonist amantadine for both PD as well as dyskinesias. If pharmacologic treatment fails to treat motor fluctuations, as in our patient, STN deep brain stimulation should be considered.

In addition to the motor complications of advancing Parkinson’s disease, many patients also develop psychological complications. Hallucinations and delusions, when bothersome, can usually be managed successfully by replacing dopamine agonists and amantadine by levodopa, and if that is not successful, administration of low doses of an atypical neuroleptic medication. In addition to hallucinations, this patient also developed cognitive deficits which emerge in the long-term course of the disease in up to 80% of patients, and dementia in approximately 30%. The development of dementia is increasingly recognized, since the control of motor symptoms has been dramatically improved by dopaminergic treatment and DBS. Cholinesterase inhibitors have been shown to slightly but significantly ameliorate cognitive deficits associated with PD.
REFERENCES


Legend to video

Case 41 This video illustrates the motor complications of this 71-year-old gentleman with Parkinson’s disease during standardized Unified Parkinson’s Disease Rating Scale (UPDRS) testing by Dr Lars Wojtecki (Department of Neurology, University Hospital Düsseldorf). Initially, the patient is shown without medication and STN DBS is switched off. During this period he has almost no tremor, but a low voice, akinesia, and impaired gait and posture, as well as postural stability in the pull test. In the second part of the video the patient is tested with medication and STN DBS switched on. He speaks louder and more clearly and shows an improvement in movement but he is also dyskinetic. Although he can now easily arise from a chair and walk he is still suffering from impaired postural stability.
An unusual hazard of treating depression

Vandana Dhawan and K Ray Chaudhuri

CASE PRESENTATION

A 58-year-old accounts manager presented to his general practitioner for memory problems which were thought to be due to stress and depression. Paroxetine 20 mg was prescribed. He had no significant medical history and a normal birth history, and did not drink alcohol. There was no family history of any neurological disorder. He was married with four children.

After 2 weeks on paroxetine, he noticed involuntary bilateral blinking, pain in the neck, and ‘spasms’ of his facial, neck, and shoulder muscles. He also had difficulty breathing which lasted for approximately 6 hours. The next day paroxetine was discontinued, and his symptoms were relieved immediately and completely resolved over the next 2 days. However, 3 months later the symptoms reappeared in a similar fashion affecting the craniocervical musculature. At this time he had spasmodic antecollis with sustained spasm of the platysma (see video, Case 42, first segment). There was no palatal tremor and no evidence of dystonia or parkinsonism elsewhere in the body.

The following tests were normal or negative: magnetic resonance imaging (MRI) of the brain, awake electroencephalography (EEG), neuropsychometry, copper studies, acanthocyte screen, autoantibody screen, anti-gliadin and anti-endomysial antibodies, thyroid function test, vitamin B12 and folate levels, antistreptolysin O (ASO) titers, and creatine phosphokinase (CPK). Lumbar puncture showed negative oligoclonal bands and a borderline elevated cerebrospinal fluid (CSF) protein. Nerve conduction studies revealed mild bilateral slowing of ulnar nerve velocity at the elbow. Genetic screening for Huntington’s disease and dentatorubropallidoluysian atrophy was negative. A repeat MRI brain scan performed 3 years after the first scan was normal.

A presumptive diagnosis of recurrent paroxetine-induced craniocervical dystonia was made. A trial of benzhexol, starting at 2 mg, and subsequently baclofen 40 mg per day, failed to produce any significant benefit. Injections of botulinum toxin type A to the platysma and sternocleidomastoid muscles were of limited benefit. A trial of levodopa, however, produced a dramatic initial response (see video, second segment), with complete cessation of the dystonic spasms. He was thereafter maintained on levodopa 300 mg/day with sustained benefit to date.
DISCUSSION

Selective serotonin reuptake inhibitors (SSRIs) have been reported to rarely cause movement disorders ranging from hypokinetic syndromes such as parkinsonism to hyperkinetic problems such as dystonic reactions.\(^1\),\(^2\) Most reports of dystonic reactions from SSRIs have occurred when patients were also taking a dopamine blocking drug, and isolated SSRI-induced dystonia is extremely rare. There is only one case recorded where a patient with a brainstem stroke developed a dystonic reaction within a few days following use of paroxetine.\(^3\) Our patient developed a severe craniocervical dystonic reaction after being prescribed paroxetine for depression. The dystonia resolved almost completely on cessation of paroxetine, but resurfaced 3 months later and has continued to be evident, suppressible only with levodopa.

An enquiry with the manufacturer of paroxetine at the time of presentation revealed a few unpublished cases of paroxetine-induced dystonic reactions involving facial but not neck muscles.\(^4\) There was a single case report of left-sided limb dystonia after exposure to paroxetine in a patient with left hemiparesis due to stroke.\(^5\) We believe that our case is the first of probable paroxetine-induced craniocervical dystonia, which at onset resembled Meige syndrome. An interesting link between dopa responsive dystonia (DRD) and paroxetine was described by Mathen et al who reported reversal of levodopa-induced benefit in two cases of DRD when SSRIs were prescribed.\(^5\) Although we did not test for the DRD genetic mutation, the phenotype of our patient, and the absence of any family history, did not suggest DRD; thus, the response to levodopa is interesting, although some apparently idiopathic craniocervical dystonias do respond to levodopa.

Dystonia is a rare side-effect of SSRIs such as paroxetine, and may present as craniocervical dystonia, after a variable period of exposure. Withdrawal of the SSRI typically resolves the dystonia, although, like drug-induced parkinsonism, the symptoms may re-appear, and in such cases a trial of levodopa is worthwhile.

This case is instructive because:

1. It demonstrates that SSRIs such as paroxetine can rarely cause dystonia affecting the face and neck. The dystonia may resolve completely after discontinuation of paroxetine.
2. Our patient illustrates that dystonia occurring during treatment with paroxetine may resolve when the drug is discontinued, but recur after a variable interval without further exposure to paroxetine.
3. This patient had a dramatic and sustained improvement in dystonia with levodopa without any phenotypic evidence of typical dopa responsive dystonia (DRD), emphasizing that a trial of levodopa is warranted in most patients with dystonia, even when drug-induced.
REFERENCES


Legend to video

Case 42 The first segment shows the patient with repetitive dystonic spasms affecting facial muscles and platysma spreading to the anterior chest. There is also antecollis. The second segment shows recovery after treatment with levodopa.
Parkinson’s gait: when falls become pitfalls

Samay Jain and Stanley Fahn

CASE PRESENTATION

A 58-year-old right-handed man began dragging his right foot while walking (see video, Case 43). A few months later, he had difficulty using his right hand. Four years later, he began having problems using his left side and difficulty turning, with poor balance. Two years later, he had tremor in both hands, more on the right side. There was urinary urgency and frequency. Recently, he began having ‘locking up’ episodes when attempting to turn. His symptoms continued to progress despite trials of pergolide and bromocriptine.

On examination, he had a masked face, cogwheeling on the right, and bilateral bradykinesia. His posture was slightly stooped with a festinating gait and poor arm swing. He had en-bloc turning. The remainder of his examination was normal. He was diagnosed with Parkinson’s disease 13 years after his initial symptoms, with an activities of daily living (ADL) score (Schwab and England scale) of 65%. Carbidopa/levodopa was added to his regimen, which included pergolide.

The patient improved with carbidopa/levodopa and pergolide. He then developed back pain which improved with bed rest. Four years after his initial visit, he developed motor fluctuations with delayed on-time and dyskinesias. Extended-release carbidopa/levodopa was added. His walking worsened, with shorter steps, and more fatigue. Entacapone was added and he had increased falls, so he stopped taking it. Because of tingling and numbness in his fingers, an electromyogram (EMG) was performed, which showed chronic bilateral denervation in the C6–7 and L5–S1 myotomes with axonal loss. It also demonstrated bilateral median nerve compression at the carpal tunnel and bilateral ulnar nerve compression at the elbow. When he called his doctor complaining of difficulties walking and more off-time, pergolide was increased.

During a follow-up appointment 1 month later, he was unable to walk while ‘on’ and ‘off’. Within 1 month, he had gone from using a quad-cane to using a walker and then a wheelchair. His ADL score had decreased to 20%. On examination, his gait was spastic and he was weak with 4/5 strength in bilateral elbow extension and flexion as well as hip and knee extension and flexion, more on the left. Deep tendon reflexes were hyperactive with bilateral Babinski signs. These findings suggested a cervical myelopathy. Emergency magnetic resonance imaging (MRI) demonstrated severe spinal stenosis with moderate spinal cord
compression, cord atrophy, and probable myelomalacia at C2/3 extending to C4/5. The patient underwent emergent decompression. The strength returned in his legs and he was able to walk without a walker during on-time but with some difficulty due to dyskinesias. His ADL score improved to 80%, and continues to be at this level during on-time with medication adjustment 4 years later.

DISCUSSION

This case illustrates potential pitfalls in managing Parkinson’s disease (PD). Patients often report worsening motor function, including difficulty walking, and this is commonly assumed to be due to evolution of the disease itself or motor fluctuations prompting an adjustment of antiparkinsonian medications. However, one must be careful not to overlook the possibility that another process may occur in the context of PD.

Disturbances of gait are common, estimated to occur in 63% of all neurological inpatients, regardless of diagnosis.1 Risk factors for having a gait disorder include advanced age, dementia, alcohol abuse, and treatment with antiepileptics, neuroleptics, benzodiazepines, and chemotherapy. A decline of cognitive function is associated with a reduction of walking speed. Thus, deterioration of gait is often multifactorial. Among inpatients with PD, 93% have a disturbance of gait.1

In this case, clues that the subacute deterioration of gait was not due to PD included observation that: (1) the gait disorder did not fluctuate with on/off time, but was constant and progressive; (2) the gait had features of spasticity; (3) there was muscular weakness which is not encountered in PD; (4) the tendon reflexes were hyperactive with Babinski; and especially (5) the rapid progression was not in keeping with the natural slow progression of PD. Furthermore, the gait continued to worsen despite adjustments in dopaminergic therapy; however, this alone would not be unexpected in PD. For example, improved mobility in PD, in the presence of poor balance, weakness, freezing, or dyskinesias (especially if they involve the legs) can paradoxically result in an increase in falls. In this case, the patient was getting weaker due to cervical myelopathy despite increasing dopaminergic medication.

Falls or predominantly lower body parkinsonism early in the course of ‘Parkinson’s disease’ should make one consider the possibility of other parkinsonian syndromes. This includes progressive supranuclear palsy, vascular parkinsonism, and normal pressure hydrocephalus. If gait ataxia is present, multiple system atrophy and other causes of cerebellar degeneration should be considered. Careful examination of gait can distinguish PD from other disorders.2,3

This case is instructive because it demonstrates that other treatable neurologic problems, such as cervical spondylitic myelopathy, may be overlooked in the context of Parkinson’s disease. It underscores the importance of conducting a thorough neurologic history and examination if a patient with PD reports an abrupt change, especially if gait disturbance is refractory to dopaminergic therapy. In this patient, the recent change in gait along with signs not expected in PD, including weakness, hyperreflexia, and upgoing toes, were clues that something other than PD was at fault.
REFERENCES


Legend to video

Case 43 The first segment (initial visit) shows a 58-year-old man with right arm tremor and bradykinesia. He is able to walk without assistance with decreased arm swing, shuffling gait, en-bloc turning, and recovery on the pull test. He was diagnosed with Parkinson’s disease. The second segment is 4 years later when the patient cannot walk due to weakness. It is effortful for him to lift arms or legs against gravity. Note that he is in a wheelchair. The third segment is 3 months after cervical cord decompression. Strength is restored to his limbs, and he is able to lift his arms and legs with ease. He can walk with a walker. The gait shows evidence of spasticity with scissoring, in addition to parkinsonian features. The fourth segment is 18 months after cervical cord decompression and physical therapy. He can walk independently.
A 70-year-old man with tremor, ataxia, and bright middle cerebellar peduncles

Amrit K Grewal and Stanley Fahn

CASE PRESENTATION

A 70-year-old man presented with a 10-year history of bilateral hand tremor. He noticed the tremor mainly when drinking from a cup or holding heavy objects, but not at rest. He also developed gait instability about 5 years prior to presentation, worsening to the point where he had 8–10 falls in 1 year. He reported extreme fatigue and weakness in his lower extremities after walking, and he described ‘jerks’ of his right hand that occurred infrequently and had been present for a long time.

The patient’s medical history included hypertension, hypercholesterolemia, renal calculi, appendectomy, inguinal hernia repair, and cataract surgery. There was no exposure to dopamine receptor blocking agents. He had a 12.5 pack-year history of tobacco smoking. He denied heavy alcohol use, but had a history of drinking two glasses of wine every day. There was a family history of mental retardation in his paternal first cousin.

On examination, he was normotensive and did not have orthostatic hypotension. He was alert and completely oriented. Speech and language were normal. The cranial nerves were notable only for saccadic smooth pursuit. There was normal power and bulk in the upper extremities. He had bilateral, mild hip flexor weakness, but the remainder of the muscles in the lower extremities had normal power. Deep tendon reflexes were absent in the upper extremities, and 1+ at the knees and ankles. Toe responses were extensor bilaterally. There was decreased sensation to pinprick and temperature in his toes bilaterally. He had absent vibration sense in his toes and diminished at the ankles and knees bilaterally. Vibration sense was normal in the upper extremities. He had normal proprioception throughout. There was a mild postural tremor. He did well drawing a spiral and had normal handwriting. He had a very mild intermittent rest tremor of the right hand, especially the first two fingers. Tone was normal. There was no bradykinesia. There was subtle dysmetria in the upper limbs. Heel–knee–shin testing was normal. He was able to get up from a chair without using his arms. He had a waddling gait and some difficulty tandem walking. He had slightly decreased arm swing on the right. Pull test was normal.
We reviewed a magnetic resonance imaging (MRI) scan of his brain obtained recently (see video, Case 44). It revealed cerebral and cerebellar atrophy. In addition, he had several punctate areas of increased signal intensity on T2-weighted images in the white matter bilaterally. Although not described in the written report, we noticed increased signal intensity in the middle cerebellar peduncles (MCP) and cerebellar hemispheres. This abnormality suggested the possibility of fragile X-associated tremor/ataxia syndrome. After we mentioned this to the patient and his family, they provided additional family history of premature ovarian failure in two of his daughters, one of whom was found to have fragile X premutation. His mother had also developed premature ovarian failure.

Given the patient’s family history of fragile X premutation, and clinical findings of mild postural and intention tremor, ataxia, lower extremity weakness, evidence of peripheral neuropathy, and aforementioned MRI findings, he was tested for the fragile X premutation. It revealed an expanded \textit{FMR1} (fragile X mental retardation 1) allele with 63 CGG trinucleotide repeats, indicating that the patient was a carrier of fragile X premutation.

**DISCUSSION**

The fragile X-associated tremor–ataxia syndrome (FXTAS) is a recently described cause of adult-onset sporadic tremor and ataxia, with a reported frequency of about 4.2% in cases with onset of ataxia after age 50 years.\textsuperscript{1} It has been described in men who are carriers of the \textit{FMR1} premutation.\textsuperscript{2} Twenty per cent of women with \textit{FMR1} premutation can present with premature ovarian failure. So far, there have been only five women described with FXTAS, suggesting that they may be relatively protected from this disorder.\textsuperscript{3} A CGG repeat size between 55 and 200 is considered a premutation, whereas the full mutation occurs in repeats >200 and is manifested as fragile X syndrome which is the most common inherited form of mental retardation.

FXTAS usually develops after the sixth decade, and is characterized by gait ataxia and intention tremor. These signs may be associated with progressive cognitive and behavioral difficulties such as memory loss, executive function deficits, anxiety, and reclusive behavior; parkinsonism; peripheral neuropathy; lower limb proximal muscle weakness; and autonomic dysfunction.\textsuperscript{2} The symptoms are usually progressive and treatment is supportive. In a study of 26 patients with FXTAS, cerebellar signs were present in 78–93%, tremor in 80% (intentional in 70%, intentional and mild resting in 30%, resting alone in 10%), neuropathy in 61%, parkinsonism in 57%, proximal lower limb muscle weakness in 30%, and extensor toe responses in 23%.\textsuperscript{2}

The MRI scan in FXTAS shows a typical pattern of increased signal on T2-weighted images in the MCP and white matter of the cerebellar hemispheres sparing the dentate nuclei.\textsuperscript{3} In addition there may be mild to moderate cerebellar and cerebral atrophy. Areas of increased T2 signal intensity may also be seen in the subependymal and deep white matter, especially in the frontal and parietal lobes.\textsuperscript{2} Signal abnormalities in the middle cerebellar peduncles have been suggested as one of the inclusion criteria for the diagnosis of FXTAS, in addition to the presence of tremor or ataxia,\textsuperscript{2} but this MRI finding may also be seen in other
conditions such as multiple system atrophy and autosomal dominant cerebellar ataxias. The neuropathological features of FXTAS include eosinophilic, intranuclear inclusions positive for ubiquitin but negative for tau, synuclein and polyglutamine in neurons, and astroglia throughout the cortex and cerebellum but not in Purkinje cells.

This case is instructive because it demonstrates the typical clinical and radiographic features of the fragile X tremor–ataxia syndrome. It also emphasizes the importance of taking a careful family history, inquiring about mental retardation and premature ovarian failure. Finally, it illustrates the utility of having new patients bring their scans with them and not simply accepting the report of a radiologist. There was no mention of the increased signal in the MCP in the report, but we noticed it, and it immediately suggested the diagnosis of FXTAS.

REFERENCES


Legend to video

Case 44  Findings demonstrated on examination include a subtle tremor when touching the finger on finger-to-nose testing, past-pointing, a slight postural tremor, mild gait ataxia, decreased distal vibratory sense in the lower extremities, and upgoing toes. MRI demonstrates increased T2 signal in the middle cerebellar peduncles and subcortical white matter.
Tremor after quarrel and minor head trauma: organic cause or psychologic trigger?

Jan Raethjen and Günther Deuschl

CASE PRESENTATION

A 38-year-old man presented with tremor, slight paresis, and markedly increased muscle tone of his right arm. These symptoms began suddenly, 6 months prior to presentation to us, just after a heated argument with his father-in-law, resulting in a fight during which he was slapped on the head several times. A computed tomography (CT) scan and an electroencephalogram (EEG) performed 2 hours after this incident were both normal. A magnetic resonance imaging (MRI) scan performed 1 month later did not show any abnormalities. The patient’s medical history was unremarkable. Until the onset of the symptoms the patient had worked as an accountant for a building maintenance company. He is currently on sick leave; neither application for a pension nor litigation is pending.

On examination we found a high amplitude, medium frequency, right hand and arm tremor accompanied by increased muscle tone and slight paresis (MRC (Medical Research Council) grade 4) in the whole arm (see video, Case 45). The tremor was regular and seemed to be mainly postural but, due to the constantly increased tone and paresis, a full postural, action, or resting condition could not be examined. During inpatient treatment in our institution, all symptoms showed great variability over time, with a marked decrease when the patient felt unobserved. Demanding mental or contralateral motor tasks led to some reduction in tremor amplitude, indicating distractibility. In the clinical entrainment test the patient was asked to tap his contralateral hand rhythmically at a lower frequency; doing so led to a decrease in tremor amplitude, an increase in the variability of tremor frequency (distraction), and intermittent reduction of the right hand tremor frequency. There was also obvious synchronization with the left hand voluntary rhythm (entrainment).

The remaining neurological examination was normal. A psychiatric evaluation revealed symptoms indicating depression.
ELECTROPHYSIOLOGICAL TESTS

Spectral analysis of hand accelerometry and electromyography (EMG) recordings from forearm extensors revealed a right sided EMG-driven tremor (Figure 45.1A) at 5 Hz. The frequency remained stable when a 1000-g weight was put on the hand. The electrophysiologic ‘coherence entrainment test’ was performed analogous to the clinical entrainment test. The patient was gently tapping his non-affected left hand at 3 Hz on the armrest of the chair during the 30-s recording. The tremor amplitude was clearly decreased (Figure 45.1B) compared to the spontaneous tremor (Figure 45.1A), and the tremor frequency became more variable, as seen in the raw accelerometry and EMG data and confirmed by the much wider power spectral peaks now ranging from the original tremor frequency (Figure 45.1A) to the lower contralateral tapping frequency (Figure 45.1B). Only this lower frequency activity was coupled (coherent) between both arms (Figure 45.1C). The main peak frequency of the tremor was only slightly reduced, and did not completely change (entrain) to the lower tapping frequency, displayed in the bottom row of (Figure 45.1B). The accelerometry trace in (Figure 45.1B) seems to indicate a superposition of two different rhythms, both of which fall within the frequency range covered by the broadened peak of the accelerometer spectrum.

DISCUSSION

This patient’s clinical and electrophysiological findings are indicative of a psychogenic tremor. Such tremors can be difficult to diagnose, as the clinical presentation alone with an ongoing rhythmic hand tremor between 4 and 7 Hz often does not allow a distinction from organic tremors. Being mainly postural and action tremors they often remain at rest, especially when the patient cannot relax completely. The history and specific clinical tests offer some clues that a tremor is psychogenic. While organic tremors typically develop gradually over time, the vast majority of patients with psychogenic tremor report a sudden onset, often in connection with minor trauma. Previous or other somatizations and psychogenic symptoms, such as the accompanying paresis in the present case, can be another hint but may be misleading. One typical clinical sign of a psychogenic tremor is distractibility: demanding mental or motor tasks will reduce the tremor and make it more variable.

Another well-established clinical characteristic of a psychogenic tremor is the ‘coactivation sign’ designating a constant isometric activation of antagonistic muscles. This continuous increase in motor neuron excitability may lead to an enhancement of physiological oscillatory mechanisms (e.g. clonus). It can be assessed clinically, similar to testing for rigidity, and was extremely strong in the present patient (see second segment of video, Case 45). While organic tremors typically occur independently (non-coherently) in different limbs, voluntary rhythmic movements are usually synchronized or coupled (coherent) between different extremities. Provided that the psychogenic tremor relies on similar mechanisms to voluntary movements this interlimb coherence could be one way to distinguish it from an organic tremor. Indeed, when looking at the relation between the tremor in different limbs or between a voluntarily maintained
rhythm of the one hand with the tremor in the other hand (entrainment test), they were often found to be coupled.\textsuperscript{1,5} However, in about one-half of patients with psychogenic tremors the rhythm in both limbs was independent, as in organic tremors.\textsuperscript{5} In those cases the suggested mechanism of enhanced non-voluntary but physiological oscillatory mechanisms (e.g. clonus) seems to be more important.

In the present patient, two different oscillations seem to be superimposed during the entrainment test in the affected arm: one is coherently entrained to the frequency of the voluntary contralateral movement; the other seems to remain independent around the original tremor frequency. Thus, mechanisms similar to voluntary rhythmic movements represented by the entrainable component and non-voluntary physiological oscillations reflected by the non-entrained tremor component both seem to contribute to psychogenic tremor within the same patient. In practice, the ‘coherence entrainment’ test is useful, as the detection of an entrainable tremor component is an indication of psychogenesis. A negative entrainment test does not exclude a psychogenic origin, however.

**Figure 45.1** Raw data, spectral analysis, and coherence analysis of spontaneous psychogenic tremor and psychogenic tremor in the coherence entrainment test. (A) The raw acclerometry (Acc, top trace) and extensor EMG data (Ext) and the respective power spectra on the right show a regular 5-Hz tremor that is driven by the rhythmic EMG burst activity at the same frequency. (B) During contralateral rhythmic tapping at 3 Hz (entrainment test) as displayed in the EMG recording from the contralateral forearm extensor and its power spectrum (bottom), the tremor amplitude decreases (upper and middle trace) and its frequency becomes more variable, as also indicated by the much broader spectral peaks (right).
This case is instructive because it shows several typical clinical features of psychogenic tremor, including abrupt onset following trauma, variability, distractibility, and entrainment. It also demonstrates that electrophysiological tremor analysis is useful to distinguish organic from psychogenic tremors, and, in this patient, illustrates that different pathophysiological mechanisms are concurring in psychogenic tremor.

REFERENCES

Legend to video
Case 45 First segment: spontaneous regular tremor of the right arm is seen. Note that all the arm muscles are visibly activated compared to the relaxed left side. No pure resting condition could be examined because of the continuous muscle activation, and no pure postural condition could be examined due to the accompanying psychogenic paresis of this arm. Second segment: the ‘coactivation sign’ becomes most evident during passive movements of the affected arm. It was not possible to relax the muscles in any arm position. Third segment: entrainment test. When the patient taps with his left hand at a lower frequency the right hand tremor becomes visibly more irregular and intermittently synchronizes with the tapping frequency. Fourth segment: the same phenomenon can be seen with contralateral foot tapping.
An 82-year-old man with flailing movements of his right side after a stroke

Julie Leegwater-Kim and Steven J Frucht

CASE PRESENTATION

An 82-year-old man with a history of hypertension, renal insufficiency, and polycystic kidney disease was admitted to hospital for acute onset of right hemiparesis and right facial paresis. His vital signs were significant for a blood pressure of 244/110. Head computed tomography (CT) demonstrated a hemorrhagic stroke involving the left thalamus and left cerebral peduncle. His blood pressure was lowered; he was monitored and treated with supportive care for several days before being discharged to a rehabilitation center. The hemiparesis improved slowly. Approximately 1 month later he began having involuntary flailing movements of the right arm and leg, which worsened with effort and decreased at rest. They did not occur while asleep. Successive trials of clonazepam, gabapentin, and haloperidol (maximum dose: 12 mg per day) were unsuccessful. The movements significantly impaired his functioning, making all activities of daily living difficult.

He was admitted to hospital for further evaluation and treatment of the movements. On examination he was alert and oriented to person, place, and time with intact language, praxis, and memory. Cranial nerves were normal. There were frequent ballistic movements of the right side, more severe in the arm than in the leg (see video, Case 46). Tone was increased on the right side. Finger-to-nose and heel-knee-shin testing were impaired due to right hemiballismus. His gait was normal-based but impaired by frequent ballistic movements of the right side. Brain magnetic resonance imaging (MRI) revealed multiple areas of chronic hemorrhage including the left cerebral peduncle, the left inferior thalamus, the right thalamus, and right anterior basal ganglia. Fluid attenuated inversion recovery (FLAIR) sequence demonstrated multiple white matter chronic infarctions in the bilateral frontal, temporal, parietal, and subinsular regions (Figure 46.1).

Tetrabenazine (TBZ) was started at a dose of 25 mg at bedtime and increased over 1 week to a total of 125 mg per day. The haloperidol was simultaneously tapered off. At 75 mg per day of TBZ the hemiballismus began to improve
Six weeks after TBZ therapy was initiated he was seen in the clinic. Examination at that time revealed minimal hyperkinetic movements at rest. With activation, there were mild choreiform movements of the right arm but no violent ballism (see video). On the last visit to the office, TBZ was decreased to 75 mg per day due to depression and anxiety.

**DISCUSSION**

This 82-year-old man experienced the subacute onset of hemiballismus 1 month after a hemorrhagic stroke of the left midbrain and left inferior thalamus. Hemiballismus is an uncommon movement disorder characterized by vigorous, flailing, poorly patterned movements involving one side of the body. The arm and leg are usually involved, with variable involvement of the face. Movements are triggered by action, diminish with rest, and disappear during sleep. Onset is typically acute or subacute and most cases are self-limited and resolve over time. Hemiballismus and hemichorea often coexist in the same patient, and are distinguished by the severity of movements and the tendency for hemiballismus to involve proximal muscles.

Traditionally, hemiballismus was thought to be due to lesions of the contralateral subthalamic nucleus, but recent studies suggest that hemiballismus is more often caused by lesions in other structures, i.e. putamen, caudate, thalamus, and frontal and parietal cortex. Virtually any focal lesion involving the basal ganglia and, less commonly, cortical structures can cause hemiballismus.
A variety of lesions have been reported, including: stroke, arteriovenous malformation, infection (i.e. cryptococcoma), and neoplasms. In addition, metabolic derangements including hypocalcemia secondary to hypoparathyroidism and non-ketotic hyperglycemia may also lead to hemiballism–hemichorea.

The first-line treatment for hemiballismus is typical and atypical antipsychotics. There have also been reports of successful treatment with a number of antiepileptic medications (i.e. valproic acid, topiramate) and benzodiazepines. In addition, tetrabenazine (TBZ), a benzoquinolizine compound which inhibits presynaptic dopamine release and blocks postsynaptic dopamine receptors, has been shown to be effective. Unlike typical and many atypical antipsychotics, TBZ has little if any risk of tardive dyskinesia. Side-effects of TBZ include parkinsonism and depression. If resolution of hemiballismus occurs with TBZ then patients should be maintained on the minimal effective dose for several months; it can be tapered thereafter or sooner if problematic side-effects develop. In cases which are medication-refractory, persistent, and disabling, functional neurosurgery can be considered.

This case is instructive because it demonstrates the phenomenology of hemiballismus. It also considers its anatomy, differential diagnosis, and treatment options, including tetrabenazine.

REFERENCES


Legend to video

Case 46  Prior to initiation of tetrabenazine (TBZ) therapy, the patient demonstrates frequent ballistic movements of the right side, at rest and with action. On TBZ 75 mg/day the right hemiballismus has improved and he exhibits greater control of the right arm when performing tasks such as finger-to-nose. On TBZ 125 mg/day he has minimal spontaneous movements at rest and very mild choreiform movements of the right arm with action.
An 11-year-old boy with jerky movements and impaired gait

Julie Leegwater-Kim and Steven J Frucht

CASE PRESENTATION

An 11-year-old boy presented to our neurological clinic for evaluation of jerking movements of his body. Problems were first noticed at age two-and-a-half years when he began tripping over his right foot while walking in an airport. His foot involuntarily assumed a plantar-flexed position when walking. By age four-and-a-half he had developed intermittent jerking of his arms. The jerks mainly involved the right arm, and therefore he favored his left hand for most tasks such as typing or playing piano. At age 7 he developed truncal jerks which were often so violent that they would cause him to fall backwards or collapse to his knees. The jerks were most prominent when he was sitting unsupported and disappeared when lying flat in bed. At age 14 he noticed slurred speech and underwent a lingual frenectomy, with mild improvement.

There was no weakness, sensory disturbance, imbalance, visual change, hearing loss, tremor, or cognitive change. There was no history of encephalitis, hypoxic injury, traumatic head injury, seizures, fever, rash, or joint pain. Gestational and birth histories were unremarkable except for mild hypoglycemia at birth, which was treated with intravenous glucose. The family history was negative for dystonia, myoclonus, or neurological symptoms. It was unknown on initial evaluation whether the movements were responsive to alcohol.

On examination, he was alert, bright, and interactive. The non-neurological examination was unremarkable. There were no Kayser–Fleischer rings and his thyroid was not enlarged. He had prominent intermittent myoclonic jerks of the proximal limbs and trunk, particularly the right arm. The truncal jerks were of large amplitude and lightning-like, while the jerks involving the lower trunk and left arm were less severe (see video, Case 47). There were occasional fine myoclonic jerks of the fingers. When lying down, the jerking resolved. The jerks were not stimulus-sensitive and did not occur with startle. When performing finger-to-nose, his right hand assumed a dystonic flexed posture. When walking, his right leg was extended and stiff. Postural stability was normal.

Laboratory work-up included normal ceruloplasmin, liver function tests, creatine kinase, and sedimentation rate. Electrocardiogram (ECG), brain magnetic resonance imaging (MRI), and electroencephalogram (EEG) were
normal, and there were no epileptiform correlates for the jerking movements. Somatosensory-evoked potentials (SSEPs) and brain auditory-evoked responses (BAERs) were normal as well.

DISCUSSION

Based on the history and examination, a diagnosis of myoclonus–dystonia (essential myoclonus) was reached. Specialized electrophysiologic testing to further evaluate the nature of the myoclonus and a trial of alcohol to determine alcohol-responsiveness were recommended. Testing of the ε-sarcoglycan gene revealed a pathogenic mutation associated with myoclonus–dystonia. Trihexyphenidyl was started, and when he reached 15 mg per day, he experienced drowsiness, decreased concentration, and nausea, without benefit. It was tapered off and he underwent successive trials of piracetam (maximum: 7.2 mg per day), clonazepam (maximum: 3 mg per day), valproic acid (maximum: 1500 mg per day), levetiracetam (maximum: 2000 mg per day), and baclofen (maximum: 30 mg per day). Only clonazepam conferred a very mild benefit. In his late teens, he noticed temporary improvement in his symptoms with consumption of alcohol. At age 17 he developed symptoms of obsessive–compulsive disorder that were successfully treated with paroxetine. At age 20 he was enrolled in an open-label trial of sodium oxybate (Xyrem®). At 4 g per day he experienced modest improvement in his symptoms (see video). At a dose of 7 g per day, he experienced a 45% improvement in the severity of myoclonus and remains on this medication.

Inherited myoclonus–dystonia (MD) is an autosomal dominant disease linked to mutations in the ε-sarcoglycan gene and also to an as yet unidentified gene on chromosome 18. MD is characterized by myoclonus or dystonia alone or in combination, with no other neurological symptoms. In the majority of cases, the predominant, presenting sign is myoclonus, which tends to affect the axial muscles and upper limbs more than the lower limbs. Dystonia develops in approximately two-thirds of patients and is seen mainly with action. In a minority of patients, dystonia can occur alone. MD usually begins in the second decade and progresses for several years into adolescence and young adulthood but then plateaus. In most cases, both myoclonus and dystonia are exquisitely responsive to alcohol. 1

The diagnosis of MD is made clinically, and can be confirmed in some cases by mutation screening of the ε-sarcoglycan gene (SGCE). 2 ε-Sarcoglycan is ubiquitously expressed and its function is unknown. In muscle, ε-sarcoglycan is a component of the dystrophin–glycoprotein complex, a group of membrane-associated proteins which play a critical role linking the intracellular cytoskeleton with the extracellular matrix. Whether ε-sarcoglycan has a similar association with this complex in central nervous system (CNS) neurons is not known. At least 15 different mutations of SGCE have been discovered, with most leading to truncation of the protein. Though the inheritance pattern of MD is autosomal dominant, there is significant variation in penetrance, which is dependent on the parental source of the affected allele: paternal transmission results in 90% penetrance while maternal transmission leads to 5–10% penetrance.

Treatment of MD is symptomatic. Dystonic symptoms can be treated with anticholinergic medications such as trihexyphenidyl and benztropine. Myoclonus
has been reported to improve with clonazepam, valproic acid, levetiracetam, anticholinergic medications, and piracetam. Although myoclonus is alcohol-responsive in many cases, the medicinal use of alcohol is discouraged given its short duration of action and potential for abuse.

Recently, sodium oxybate has emerged as a promising treatment for alcohol-responsive movement disorders. In a recent open-label trial in alcohol-responsive movement disorders, sodium oxybate was effective in reducing myoclonus in three subjects with MD. Future studies are needed to determine the long-term efficacy and tolerability of this medication. Finally, case reports of deep brain stimulation of the globus pallidus in patients with medication-refractory myoclonus–dystonia have suggested that surgery may be an option in patients with disabling disease.

This case is instructive because it reviews the clinical presentation and genetic etiology of myoclonus–dystonia and demonstrates the potential use of a novel agent, sodium oxybate, to treat alcohol-responsive myoclonus.

REFERENCES

Legend to video
Case 47  At baseline, the patient has myoclonic jerks of the right leg triggered by walking and frequent violent myoclonic jerks of the trunk and arms brought out with writing and pouring. After ingestion of 4 g sodium oxybate, he exhibits modest improvement in his walking and writing.
A 32-year-old woman with lymphadenopathy, arthritis, and chorea

Julie Leegwater-Kim and Steven J Frucht

CASE PRESENTATION

A 32-year-old woman with a history of developmental delay was admitted to hospital for subacute adenopathy, arthritis, fever, and tongue ulcerations. Shortly after admission, she developed severe chorea of the extremities, head, and trunk. She had no prior history of a movement disorder, recent bacterial infection, or exposure to dopamine-receptor blocking agents. There was no history of tobacco, alcohol, or illicit drug use and she was not taking any medications. Family history was significant for a maternal aunt with systemic lupus erythematosus.

A chest X-ray revealed bilateral pleural effusions, and chest computed tomography (CT) also demonstrated a pericardial effusion. She was found to have mild renal insufficiency and proteinuria. Serological testing revealed a positive antinuclear antibody (ANA) test (1:640) and the presence of anti-Ro and anti-La antibodies. Brain magnetic resonance imaging (MRI) with gadolinium was normal. Systemic lupus erythematosus was diagnosed and she was started on high-dose intravenous steroids and cyclophosphamide. Her choreiform movements improved on the immunosuppressant regimen but her movements re-emerged upon taper of the steroids. Steroids were restarted but the movements continued and became more severe and ballistic. She was started on haloperidol (maximum dose: 2.5mg three times a day) and benzodiazepines with no benefit, and was subsequently transferred to our hospital.

On arrival, the examination demonstrated near-continuous choreiform and ballistic movements of the head, neck, trunk, and extremities (see video, Case 48). She was alert and opened her eyes spontaneously, intermittently tracking the examiner. She could not vocalize secondary to severe dyskinetic movements of the tongue and lips. Tone was increased in all extremities. She withdrew to touch in all four extremities. Toes were downgoing.

Tetrabenazine (TBZ) was started at 25mg per day and increased to three times per day over several days. She was given another course of high-dose steroids (starting 1 day after initiation of TBZ) as well as cyclophosphamide (starting 1 week after initiation of TBZ). Within 48 hours of starting TBZ the movements
Movement Disorders
decreased in amplitude and force. After 1 week of TBZ therapy the chorea had decreased sufficiently that she was able to perform purposeful movements (see video). She had frequent dystonic movements of the extremities, the arms more affected than the legs. As the orobuccolingual movements decreased, she was able to speak in monosyllables, though she had moderate dysarthria. She remained on TBZ 25 mg three times per day, and 1 week later was discharged to a rehabilitation facility.

Two months later she was seen in the clinic (see video). The examination revealed no evidence of chorea. There were mild overflow movements when she voluntarily used her arms and legs. She was alert and interactive. Speech was fluent and clear. Tone was mildly increased in the arms. TBZ taper was initiated and she is currently taking 12.5 mg per day with no recurrence of chorea. She is now able to perform all activities of daily living without assistance and is functioning at her pre-hospitalization baseline.

DISCUSSION
We present a case of an adult who developed acute, generalized, disabling chorea during the initial presentation of systemic lupus erythematosus. The differential diagnosis of chorea includes: (1) heredodegenerative diseases such as Huntington’s disease, Huntington’s disease-like diseases (e.g. HDL2), and neuroacanthocytosis; (2) autoimmune diseases such as systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome, and Sydenham’s chorea; (3) drug-induced chorea (e.g. levodopa, oral contraceptives); (4) vascular disease; (5) hyperthyroidism; and (6) infectious diseases such as acquired immune deficiency syndrome (AIDS). The lack of family history, absence of antecedent or concurrent infection, and lack of exposure to chorea-inducing drugs argued against inherited, post-infectious, infectious, or drug-induced causes of chorea. The acute presentation of chorea in association with prototypical serological abnormalities and other signs of SLE (i.e. arthritis, renal insufficiency, and pleural and pericardial effusions) supported a diagnosis of chorea caused by SLE.

The prevalence of neuropsychiatric syndromes in SLE is 50–70%, and chorea is the most common movement disorder, occurring in about 2% of cases. Chorea can appear at any time during the disease course, but usually manifests early and can last from days to years. The pathophysiologic mechanism underlying chorea in SLE is poorly understood, but is thought to reflect lesions in the basal ganglia. Both vascular and autoimmune mechanisms have been postulated, the latter supported by the association between chorea and the presence of antiphospholipid antibodies.

Treatment of SLE-associated chorea has traditionally involved corticosteroids and neuroleptic drugs. However, some cases, such as ours, do not respond to either. Moreover, treatment of chorea with typical as well as atypical neuroleptic drugs can introduce the risk of subsequent development of tardive dyskinesia and other tardive syndromes. Therefore, alternative treatments for chorea should be considered.

Tetrabenazine is a benzoquinolinizine compound that inhibits presynaptic dopamine release and blocks postsynaptic dopamine receptors. Although TBZ
was initially used in the treatment of psychosis, it has subsequently been discovered to be an effective treatment for hyperkinetic movement disorders, particularly chorea and facial dyskinesias.\textsuperscript{4,5} The main side-effects of TBZ include depression and parkinsonian symptoms, i.e. bradykinesia, tremor, and cogwheel rigidity.

This case is instructive because: (1) it illustrates that chorea can be caused by lupus, (2) it reviews the differential diagnosis of chorea, and (3) it demonstrates the potential use of tetrabenazine as an effective treatment for steroid-refractory chorea associated with SLE.

REFERENCES

Legend to video
Case 48  Before initiation of tetrabenazine (TBZ), the patient demonstrates near-continuous chorea involving the head, neck, extremities, and trunk. She is unable to follow commands. On TBZ 37.5 mg per day the chorea is less severe and she is able to follow some simple commands. After 2 months on TBZ 75 mg per day, she has no chorea and has mild overflow movements when voluntarily using her arms and legs. She is alert and interactive.
A tremor in multiple sclerosis
Kelvin L Chou and Joseph H Friedman

CASE PRESENTATION
This 40-year-old woman with a long history of multiple sclerosis was referred for evaluation of hand tremor (see video, Case 49, first segment). Two years prior to our evaluation, she saw a neurologist who noticed an action tremor of both hands without a resting component. Propranolol (60 mg daily) was ineffective in controlling the tremor, but clonazepam (12 mg daily) resulted in mild improvement. A few months before presenting to us, another neurologist noticed the presence of a new rest tremor and diagnosed a rubral tremor. This did not respond to gabapentin (dose unknown). A 2-day trial of carbidopa/levodopa 25/100 three times daily was undertaken but stopped without explanation.

At the time of our evaluation, the patient was unable to supply any information verbally as she had a tracheostomy tube and had trouble gesturing due to the tremor. She had recently had a long hospitalization for aspiration pneumonia. She was taking clonazepam 12 mg daily and an unknown dose of lorazepam. Her family history was remarkable only for a son with Apert’s syndrome.

On examination, she was alert but not attentive. Cranial nerves were normal except for absence of movement of the uvula. She had a severe rest tremor of both hands and a tremor of the jaw. With maintenance of posture there was a severe, coarse tremor of the upper limbs of slower frequency than the resting tremor. She also had severe dysmetria on finger-to-nose testing bilaterally. Strength was normal in the arms and 3/5 in the legs. Tone was increased in the arms and reduced in the legs. Tendon reflexes were normal except at the ankles, where they were absent. Plantar responses were flexor.

She was placed on carbidopa/levodopa and titrated to 25/250 mg four times a day, with increasing benefit as the dose was increased. Six weeks after our initial evaluation (see video, second segment) the tremor had improved significantly. She became able to partly feed herself and remained relatively stable neurologically for the next 2 years, after which she moved out of state.

DISCUSSION
This patient has a rubral tremor, also known as Holmes’ tremor or midbrain tremor. It is characterized by the combination of rest, postural, and intention
tremor involving proximal and distal muscles.\textsuperscript{1} It has a slow frequency (2–5 Hz) and is more irregular than other tremors.\textsuperscript{2} It is not unusual for a rubral tremor to appear weeks to months after a central nervous system insult.\textsuperscript{3,4} Despite its name, a rubral tremor is generally not caused by lesions confined to the red nucleus. Instead, evidence suggests that damage to the cerebellothalamic or nigrostriatal fibers must also be present.\textsuperscript{5} Because more cases of rubral tremor are being described with lesions outside the red nucleus, the term ‘Holmes’ tremor’, named for Gordon Holmes, is being used increasingly.\textsuperscript{2}

Rubral tremor is often difficult to treat. Multiple medications have been used, including benzodiazepines, propranolol, anticholinergics, bromocriptine, and levodopa, with varying degrees of success.\textsuperscript{6} Some cases respond to surgical procedures such as thalamic deep brain stimulation.\textsuperscript{7} It has been observed that a rubral tremor is composed of two ‘separate’ tremors: a cerebellar (intention) component and a parkinsonian (rest) component.\textsuperscript{4} The theory behind the use of levodopa for rubral tremor is that therapy should focus on the parkinsonian component since there is no effective treatment for the cerebellar component. We believe that the first carbidopa/levodopa trial in our patient was inadequate. Symptomatic therapies should be pushed to toxicity, when necessary, for disorders that are otherwise untreatable. Furthermore, the patient with a mixed tremor syndrome often experiences a synergistic relationship so that one tremor ‘drives’ the other. Although treating one does not actually ‘treat’ the other, it may ameliorate it indirectly, as seen in our patient. This synergistic effect of tremors was demonstrated in a case report of a patient with a static ataxia who was given a neuroleptic and developed a severe rubral tremor.\textsuperscript{5} In that particular case, the rest component of the tremor resolved with a dopamine agonist, while the sustention and action components improved dramatically.

This case is instructive because it demonstrates the clinical features of a rubral tremor and emphasizes the potential benefit of treatment with levodopa.

REFERENCES

Legend to video

**Case 49** First segment: severe bilateral hand tremor with rest, postural, and intention components characteristic of rubral tremor. She has a coarse tremor of the jaw as well. Second segment: same patient after treatment with carbidopa/levodopa. Her rest tremor has resolved and her action tremor has improved.
CASE PRESENTATION

A 35-year-old veterinarian was aware even in high school of tight shoulders, and by her mid-20s she had noticed an abnormal posture of her feet and a lurching gait. The discomfort in her feet and tightness in her legs were worse later in the day. Family history was negative for neurological disease. On examination she had dystonia in both her legs with posturing of her hands. Her balance was modestly impaired. In all other respects the examination was normal. Wilson’s disease was suspected and one ceruloplasmin level was slightly low, but follow-up was normal. Three slit lamp examinations were normal, and a 24-hour collection of urine for copper was also normal. Other laboratory examinations that were normal or negative included antinuclear antibodies (ANA), acanthocytes, paraneoplastic screen, polymerase chain reaction (PCR) for Whipple’s disease, acetylcholine (ACh) receptors, calcitriol level, spinal fluid, striated muscle antibodies, routine hematological evaluation, and sedimentation rate. DNA assessment for levodopa responsive dystonia was not obtained. A trial of levodopa produced remarkable and immediate amelioration of the dystonia.

Despite the relief of the dystonia a new symptom appeared. She developed a series of spontaneous fractures in her ribs, femur, and pelvis. On one occasion a spillover of amino acids into the urine was noted, but extensive evaluation by nephrologists and endocrinologists and at centers for osteoporosis revealed no clear explanation for the fractures and the resultant bone pain. Nor did a bone biopsy and numerous X-rays reveal much except osteopenia. Magnetic resonance imaging (MRI) of the neck and brain were normal. Endocrinologists labeled her condition as vitamin D-resistant rickets.

During pregnancy, and she now has five daughters, the dystonia fluctuated and may have improved slightly, but worsened following the deliveries. She continued on low doses of levodopa even while pregnant. Mild but persistent dyskinesias have appeared and she requires as much as 600 mg of levodopa daily to control the dystonia. Without levodopa the dystonia is incapacitating; with it she has continued to work and usually appears normal. Depression has been a problem for this busy woman, but bupropion has helped.
This case of dopa responsive dystonia is instructive for several reasons:

1. Although there are animal studies indicating that levodopa can be mutagenic in large doses, most clinical reports do not suggest that levodopa must be discontinued during pregnancy. Movement disorders may vary, and when a patient is pregnant may even improve.

2. Dopa responsive dystonia (DRD) is one of the most important considerations in a young person with dystonia. Patients with DRD may respond for years to low doses of levodopa. Dyskinesia correlates with the use of larger doses and may lessen when levodopa is reduced. A patient’s requirement for levodopa may decrease with time, and if this is not appreciated, continuing the same dose may lead to dyskinesia.

3. Both genetic correlates and penetration vary from case to case, but DRD can be dominantly inherited with deficiency in the cyclohydrolase I GTP gene, GCHI, in about 50% of cases. Multiple genes may be involved in the pathogenesis of this condition, the diagnosis can be difficult, and DNA assessment is not always helpful.

4. Any possible linkage between the patient’s fractures and the dystonia remains a mystery, but she seems stable now taking levodopa, calcitriol, and vitamin D.

REFERENCES


An infrequent form of focal dystonia

Gabriel F Mizraji and Oscar S Gershanik

CASE PRESENTATION

A 35-year-old man presented with abnormal involuntary movements of the tongue for the last 6 months. Aside from a history of cocaine abuse since age 20, his medical history was unremarkable. There was no exposure to neuroleptics and no history of facial trauma or viral infections. There was no relevant family history.

The abnormal movement started acutely and was characterized by spontaneous, involuntary tongue protrusion, which was partially relieved by mastication. More recently though, tongue protrusion not only appeared at rest but was also triggered by chewing food or speaking, causing significant interference with both activities (see video, Case 51).

A routine blood work-up including a search for acanthocytes was non-contributory. Non-contrast enhanced brain magnetic resonance imaging (MRI) was normal. Baclofen was titrated up to 10 mg three times a day, with improvement allowing him to speak and eat with minor discomfort.

DISCUSSION

This patient was diagnosed as having lingual dystonia, an infrequently observed form of focal dystonia. It is characterized by increased tone of the lingual muscles causing involuntary forced protrusion of the tongue, interfering with speech and feeding.\textsuperscript{1,2}

It has been associated with neuroleptic exposure as part of a more generalized oromandibular syndrome,\textsuperscript{3} trauma,\textsuperscript{4} electric shock,\textsuperscript{5,6} and viral infections.\textsuperscript{7} Lingual dystonia may also be idiopathic (primary) or on a psychogenic basis. Only a very few familial cases have been observed (Lees, personal communication).

In the majority of reported cases, dystonic protrusion of the tongue appears either spontaneously at rest or is triggered by different stimuli, such as speaking, opening the mouth, or chewing. It may be attenuated by sensory tricks such as teeth clenching or chewing gum.\textsuperscript{1,8,9} As with other primary focal dystonias, central mechanisms attributed to a genetic predisposition, either alone or in combination with peripheral triggering factors, may be responsible for lingual dystonia. In our case the possible influence of cocaine cannot be ruled out.
Treatment of lingual dystonia is often challenging. Our patient responded to baclofen. Trihexyphenidyl and botulinum toxin have also been reported to be of benefit.\(^1,^3\)

This case is instructive because it demonstrates an uncommon focal dystonia affecting exclusively the tongue.

**REFERENCES**


**Legend to video**

**Case 51** Video segment illustrates the presence of abnormal involuntary tongue protrusion triggered by mouth opening, drinking, or eating as seen on first consultation and after treatment with baclofen.
A 43-year-old woman with severe involuntary movements

Stacy Horn

CASE PRESENTATION

A 43-year-old woman diagnosed with Tourette’s syndrome (TS) 10 years ago presented for consideration of surgical treatment due to lack of benefit from medications. The patient and her family were unsure when the involuntary movements began, but she was described by her family as ‘nervous all of her life’. Over the years, the movements slowly worsened. They were not preceded by an urge and could not be suppressed. She never had vocalizations. She started falling 3 years before presentation and also developed slurred speech and dysphagia, with significant weight loss. She became depressed and developed compulsions such as spending money and eating. She was unable to pay bills due to cognitive impairment. She had tried multiple neuroleptic medications without relief of her involuntary movements and other symptoms.

Her medical history was significant only for hypothyroidism. Medications at presentation included clonazepam, haloperidol, hydrocodone, and levothyroxine. She had never abused tobacco, alcohol, or drugs. She was living alone and had no children. The family history was reportedly negative for involuntary movements or neurological illness. Her mother died at age 62 of hypertensive cardiomyopathy and her father died at age 70 of lung cancer. She is the youngest of five siblings (four females and one male). There was no family history of depression, anxiety, institutionalization, or suicide; her brother had drug addiction. All siblings were present at the visit with the exception of the brother with addiction, and they denied psychiatric problems and none had an obvious movement disorder.

The neurological examination was notable for slurred speech with normal content and language. There was poor concentration and recall. She had slow saccades and saccadic pursuit eye movements. She had moderate chorea of her upper and lower face, trunk, and extremities, with mild bradykinesia in all extremities and diffusely increased tone. She could not perform the Luria test. She had a wide-based gait and could not tandem; there was mild retropulsion with the pull test.
DISCUSSION

This patient’s constellation of symptoms and signs was suggestive of a degenerative neurological disorder. Despite the negative family history, Huntington’s disease was suspected on the basis of the psychiatric manifestations, cognitive impairment, abnormal eye movements, and extrapyramidal signs including chorea, rigidity, and bradykinesia. Although some of the signs could have been attributable to neuroleptic exposure, the presence of abnormal eye movements made the diagnosis of a pure drug-induced movement disorder unlikely. After discussion with the patient and family it was decided to test for Huntington’s disease, which revealed CAG repeat lengths of 46 and 18 (normal <35), confirming the diagnosis.

This case is interesting for several reasons. First is the long diagnosis of TS. Tourette’s syndrome is a constellation of symptoms and signs that begin in childhood with both motor and vocal tics that last longer than 1 year and fluctuate in character and severity.\(^1\) It is often accompanied by depression, attentional problems, and obsessive-compulsive disorder. The diagnosis of TS in this patient is problematic for several reasons. First is the lack of vocal tics. Second is the chronic decline with falls, dysarthria, dysphagia, and dysphonia. Third is the lack of fluctuation of her involuntary movements. Last, although the psychiatric manifestations seen in this patient, including depression and obsessive-compulsive disorder, may be seen in Tourette’s syndrome, cognitive loss is not a feature of TS. The second interesting portion of this case is the lack of an apparent family history suggesting Huntington’s disease (HD), such as neurologic illnesses, addiction, suicide, or depression. Her parents died at older ages without any apparent abnormal movements or psychiatric problems, suggesting that they did not suffer from Huntington’s disease or that it was so mild as to go largely unnoticed.

Huntington’s disease is an autosomal dominant disorder with the gene located on chromosome 4, and results from expansion of the trinucleotide CAG.\(^2\) Individuals possessing repeat lengths greater than 40 develop symptoms and signs of HD. The incidence of Huntington’s disease is 2–10 per 10 000 individuals.\(^3\) Repeat length can be unstable, especially in males, and often increases during spermatogenesis, termed anticipation, causing the disease to become symptomatic earlier in successive generations.\(^4\) This is thought to account for ‘sporadic cases’ of HD. Such cases tend to have shorter repeat lengths (40–46) and develop symptoms later in life.

This case is instructive because it illustrates the need to consider Huntington’s disease in any patient presenting with chorea regardless of family history and age of onset. Genetic testing is widely available, and before it is done, the ramifications of testing must be reviewed carefully with both symptomatic and especially at-risk, asymptomatic individuals. It also emphasizes the need to critically evaluate the diagnosis in all new patients and not simply accept a prior diagnosis as correct, especially in the field of movement disorders, as many diagnoses are purely clinical, such as TS, without objective confirmation, and are therefore subject to error.
REFERENCES


Is it PD, PSP, CBD, DLB, or MSA?

Bhaskar Rao and Irene Litvan

CASE PRESENTATION

A 75-year-old man whose medical history was significant only for diabetes mellitus presented with progressive slowness, intermittent right hand tremor at rest, and double vision, for the last 5 years. He also complained of imbalance and difficulty looking down, as well as difficulty speaking and swallowing for the last 2 years. He was a skilled writer who had become withdrawn and less spontaneous over the past few years. There was little if any improvement with carbidopa/levodopa, methylphenidate, and amitriptyline. His brother had reportedly died from Parkinson’s disease (PD) years ago, but no autopsy was performed.

On examination (see video, Case 53), he was alert and oriented to time, place, and person. He had a normal score on the Mini Mental State Examination (MMSE) (30/30). There were frontal signs including bilateral grasping, decreased verbal fluency, and difficulty sequencing, but no apraxia, sensory neglect, or aphasia. The cranial nerves were notable for slow vertical saccades, absent vertical optokinetic nystagmus, and mild limitation of vertical gaze (particularly upward) and pursuit. The horizontal eye movements were full, but saccades were also slow with preserved pursuit. There was decreased convergence and blink rate.

There was normal strength in all extremities. Tone was more increased axially than distally. There was mild, symmetrical bradykinesia. There was a mild right hand rest tremor (not pill-rolling), and dyskinesia was observed occasionally in the left lower extremity. The deep tendon reflexes were normal and symmetric, with downgoing toes. There were no cerebellar signs. The sensory examination was normal except for decreased distal vibration in the lower extremities attributed to a mild diabetic neuropathy. The gait was wide-based and unstable, and he tended to fall into the chair. He fell on the pull test.

DISCUSSION

This patient presents with parkinsonism including bradykinesia, rigidity, tremor, and postural instability. Parkinsonism results from involvement of the nigrostriatal pathway. However, the lack of response to dopaminergic therapy
observed in our patient suggests that he has lesions affecting additional basal ganglia nuclei, including the putamen, internal and external segments of the globus pallidus, and/or substantia nigra reticulata.  

There are additional features which are also atypical for Parkinson’s disease, such as the relatively rapid progression with early postural instability. He also has a supranuclear vertical gaze palsy manifested by the limitation in vertical voluntary and pursuit gaze with preservation of the oculocephalic reflex and absence of the quick phases of vertical optokinetic nystagmus. The preservation of the oculocephalic reflex (shown with the doll’s head maneuver) indicates that the lesion is supranuclear. Since this patient also has decreased convergence, the lesion may involve the periaqueductal gray and superior colliculi. Marked slowing of horizontal saccades indicates involvement of supranuclear pathways for horizontal gaze. The speech and swallowing difficulties without signs of direct involvement of cranial nerves IX and X is a sign of a supranuclear bulbar palsy (pseudobulbar palsy). Our patient’s history of progressively decreasing spontaneity, along with impaired verbal fluency, difficulty sequencing, and a grasp reflex, indicates that he has frontal lobe disturbances, but his normal performance on the MMSE and lack of other cognitive features indicate that he does not have dementia. 

The presence of a parkinsonism that affects axial more than limb muscles and which does not respond to dopaminergic therapy, in the presence of early postural instability, supranuclear gaze palsy affecting vertical more than horizontal gaze, pseudobulbar palsy, and frontal lobe dysfunction, suggests that this patient has progressive supranuclear palsy (PSP). The left lower extremity dyskinesia is an atypical feature in PSP, and reported in only a few autopsy-confirmed cases. 

PSP typically occurs in the seventh decade, and rarely before the age of 40. Most patients present with postural instability and falls during the first year of symptom onset, followed by speech, gait, and oculomotor disturbances. The vertical supranuclear gaze palsy, which is the diagnostic hallmark of PSP, usually takes about 3 years to manifest; however, it is preceded by marked slowing of vertical saccades, which may allow an earlier diagnosis. Staring, absence of blinking, and sitting ‘en-bloc’ are also features typically observed in PSP. Patients can also present with altered feeding behaviors, with oversized mouthfuls or overstuffing of the mouth when eating as well as florid frontal lobe symptoms, as is the case in our patient. 

This patient does not have features suggestive of other atypical parkinsonian disorders. He does not have lateralized parkinsonism, limb ideomotor or limb kinetic apraxia, dystonia, myoclonus, aphasia, alien limb syndrome, or sensory or visual neglect, as observed in corticobasal syndrome, which in two-thirds of patients corresponds to an underlying pathologically-confirmed corticobasal degeneration. Neither does he have early autonomic failure (i.e. orthostatic hypotension, urinary disturbances, skin changes), or cerebellar or pyramidal signs to suggest multiple system atrophy; nor does he have hallucinations and delusions with dementia, as observed in dementia with Lewy bodies. The relatively gradual progression of the patient’s symptoms also rules out transmissible spongiform encephalopathies such as Creutzfeldt-Jakob disease. Another disorder which
may have features of PSP is Whipple’s disease caused by *Tropheryma whippelii*, but this patient does not exhibit the pathognomonic oculomasticatory myorhythmia characterized by slow, smooth convergent–divergent pendular nystagmus associated with synchronous contractions of the jaw.

Genetic and environmental factors have been implicated in the pathogenesis of PSP. Interestingly, patients with PSP are found to be homozygous for and overexpress a tau haplotype, H1, also observed in 60% of the general population. The contributory role of bioenergetic defects possibly caused by environmental exposure and mitochondrial DNA aberrations causing electron transport chain pathology and oxidative stress has also been suggested. In PSP, four-repeat tau accumulates in the cytoplasm of neurons and glia. At electron microscopy, the accumulation is shown as straight neurofilaments. Astrocytic tufts are nowadays considered the morphological marker of PSP. Tau protein accumulates in oligodendrocytes as ‘coiled bodies’ and in their processes as ‘threads.’

Paraclinical studies such as magnetic resonance imaging may support the diagnosis of PSP, rule out related diseases (i.e. vascular parkinsonism), and help provide better management. The use of a modified barium swallow test with videofluoroscopy helps the selection of proper dietary strategies (i.e. thickeners, percutaneous endoscopic gastrostomy) and the prevention of complications. There is currently no effective treatment for PSP, but palliative treatment improves patients’ quality of life. The effect of dopaminergic therapy is usually temporary and limited, but is useful to support the diagnosis. Weighted walkers and physical therapy are frequently beneficial. Prisms may help to improve visual difficulties, while artificial tears may prevent corneal lesions. Further research is needed to search for biological markers and appropriate biological therapies.

This case is instructive because it: (1) necessitates consideration of the differential diagnosis of parkinsonism; (2) points out many of the clinical symptoms and signs (‘red flags’) casting doubt on the diagnosis of Parkinson’s disease as the cause of parkinsonism; and (3) illustrates typical features of PSP.

REFERENCES

Legend to video

Case 53  Many of the features of progressive supranuclear palsy (PSP) are demonstrated, beginning with vertical ophthalmoparesis. Although the horizontal saccades are slow, the vertical saccades are even slower. That the ophthalmoparesis is supranuclear is confirmed by the greater vertical excursion of the eyes with the oculocephalic (doll’s eyes) reflex. Rapid repetitive movement of the lower extremities are performed well, emphasizing the axial> appendicular bradykinesia and rigidity in PSP. The gait in PSP is often wide-based in contrast to the narrow base of PD. There is significant impairment of postural righting reflexes going along with early falls in PSP. Finally, the axial bradykinesia and rigidity are illustrated by the en-bloc seating in which the patients ‘plops’ onto the sofa.
Valvular heart disease in a man with Parkinson’s disease

Daniel G Baseman, Sharon C Reimold, and Richard B Dewey Jr

CASE PRESENTATION

A 62-year-old man was diagnosed with Parkinson’s disease in 1993 and treated with amantadine, benztropine, and carbidopa/levodopa. Three years later, due to adverse effects and inadequate efficacy, amantadine and benztropine were eliminated and pergolide was begun. Within 9 months, the dose of pergolide was adjusted to 1 mg three times daily and he was able to reduce the dose of controlled/release carbidopa-levodopa 50/200 from one to one-half tablet three times a day. Following the addition of pergolide, his left hand resting tremor and rigidity resolved and his left hand bradykinesia improved.

In 1999, he developed an asymptomatic heart murmur and underwent echocardiography which showed mild mitral regurgitation, mild tricuspid regurgitation, and mild-to-moderate aortic regurgitation with a normal ejection fraction. Two years later repeat echocardiography revealed that the aortic and mitral regurgitation had worsened to moderate severity, with no change in the mild tricuspid regurgitation. No specific treatment was initiated, and he remained asymptomatic from a cardiac standpoint.

Echocardiography was repeated in 2003, showing progression of aortic regurgitation to the severe range by color Doppler imaging in the parasternal long-axis view (Figure 54.1). There was no substantial change in the mitral regurgitation and slight improvement in tricuspid insufficiency. By that time, the first paper calling attention to the possibility of a pergolide-associated valvulopathy had appeared in the literature, and the patient chose to switch from pergolide to pramipexole with no deterioration of his parkinsonism. A repeat echocardiogram performed 7 months after the switch showed an improvement in aortic regurgitation (reduction in color jet width on the parasternal long-axis view, Figure 54.1) and mitral regurgitation to mild with complete resolution of tricuspid regurgitation. Another echocardiogram done in February 2004 showed no further change in valve function.

DISCUSSION

Pergolide is a widely used drug, having been given to an estimated 500 000 patients since 1989. Isolated cases of retroperitoneal, pericardial, or pleural fibrosis have been reported in the literature, but it was not until recently that
valvular regurgitation was linked to pergolide as well as cabergoline, another ergot dopamine agonist.\textsuperscript{4,5} In the initial report of this complication, Pritchett et al described the pathology with pergolide as being similar to carcinoid valvulopathy, an abnormality that was widely seen in patients ingesting fenfluramine–phentermine preparations.\textsuperscript{1} The carcinoid-like change linked to these drugs is believed to be due to stimulation of serotonin 2B (5HT\textsubscript{2B}) receptors, and it is noteworthy that pergolide has been reported to interact with serotonin as well as dopamine receptors.\textsuperscript{6}

In deciding whether or not to use pergolide in patients with Parkinson’s disease (PD), it is important to know both the frequency of this valvular complication and its natural history following drug discontinuation. Van Camp et al compared echocardiograms obtained in 78 PD patients treated with pergolide with echocardiograms in 18 control PD patients not treated with ergot-derived dopamine agonists.\textsuperscript{7} According to their criteria, 33% of pergolide treated patients had some form of restrictive valve disease compared to none in the control group, and ‘important disease’ was present in 19% of the pergolide treated patients. They also found a positive correlation between mitral valve abnormalities and the cumulative dose of pergolide.

Basemen et al performed standard transthoracic echocardiography in 46 patients taking pergolide (all but three for PD) and showed that potentially serious valvular regurgitation was seen in >44% of this group.\textsuperscript{8} Compared to a control population matched for age and sex (but not disease or agonist use), this cohort of pergolide treated patients had a 2–3-fold increased risk of valvular regurgitation overall and a 14-fold increased risk of important tricuspid regurgitation. The composite valve score (higher numbers indicating more regurgitation) was positively correlated with the lifetime dose of pergolide ingested. No adequate studies have yet determined whether stopping pergolide results in regression of the regurgitant valvular abnormalities, though the literature on fenfluramine–phentermine suggests that improvement in valve function may occur after discontinuation of the offending agent.

**Figure 54.1** Video frame captures from echocardiographic parasternal long-axis views showing severe aortic regurgitation (A) in January of 2003 with improvement in color jet width by August 2003 (B), consistent with a decrease in regurgitant severity.
This case is instructive because it suggests that patients treated with pergolide for PD may be at risk for developing a regurgitant valvulopathy. We suggest that all patients taking pergolide should receive periodic echocardiograms looking for this possible complication. As in this case, the valvulopathy may improve following drug discontinuation, but how much improvement is seen, and how long is required for such improvement to occur, are questions which remain to be answered by future studies.

REFERENCES

Ataxia and parkinsonism

Neng Huang and James Tetrud

CASE PRESENTATION

A 54-year-old man of Mexican ancestry, the brother of a patient with Parkinson’s disease (PD), was brought in by his family for evaluation of possible PD. He had developed a gradually progressive unsteady gait over 4 years with frequent falls, slurred speech, and short-term memory loss. He had become withdrawn and emotional, and would cry spontaneously. There was no history of tremor, sphincter disturbance, or orthostatic symptoms. The family history revealed that his father, paternal grandmother, two brothers, and three sisters also suffered from a gait disorder. His younger brother exhibited typical PD with asymmetric onset resting tremor, bradykinesia, rigidity, shuffling gait, and responsiveness to levodopa.

On examination, there was short-term memory loss, emotional lability, dysarthria, and gaze-evoked nystagmus. His muscle tone was normal, and there was no resting tremor, bradykinesia, or muscular weakness. The reflexes were brisk, but with downgoing toes. There was dysmetria and dysdiadokinesis and his gait was broad-based and ataxic such that he required a walker (see video, Case 55). The sensory examination was normal.

Magnetic resonance imaging (MRI) of the brain and routine blood tests were normal. A few months after the initial visit, the patient suffered an unprovoked seizure. A diagnostic test was performed.

DISCUSSION

Based on the description from the patient and his brother, the affected relatives appeared to have gait ataxia. Although the proband and his first-degree relatives appeared to be suffering from a hereditary ataxia syndrome, one family member exhibited typical PD. The distinction is important, since both ataxia and parkinsonism can be familial. Parkinsonism and ataxia may coexist in certain diseases, such as multiple system atrophy and some forms of spinocerebellar ataxia (SCA).

In this family, the gait disorder affected multiple siblings and spanned several generations, suggesting an autosomal dominant inheritance. Another useful clinical point is the age of onset. Generally, young-onset hereditary ataxias (<20 years) tend to be autosomal recessive whereas late-onset ataxias tend to be autosomal dominant. X-linked hereditary ataxias are rare. Considerations in this
patient include the dominant SCAs, including dentatorubropallidoluysian atrophy (DRPLA), since this patient appears to have a seizure disorder as well as ataxia. Some acquired forms of ataxia that are potentially treatable include those due to vitamin E deficiency, paraneoplastic degeneration, celiac disease, and alcoholism.

There are at least 26 types of SCA, and additional subtypes are frequently added to the list. Pinpointing a specific SCA on clinical grounds is challenging, since symptoms and signs overlap. A common scheme is to group them into three classes, based on the original classification of autosomal dominant cerebellar ataxia (ADCA) proposed by Harding. ADCA type I is characterized by progressive cerebellar ataxia associated with one or more extracerebellar neurological signs including ophthalmoplegia, optic atrophy, peripheral neuropathy, dementia, and pyramidal and extrapyramidal manifestations. The major distinguishing feature of ADCA II is the presence of pigmentary macular dystrophy. ADCA III is a relatively pure cerebellar syndrome with few or no extracerebellar abnormalities.

Currently, molecular genetic assays are commercially available for SCA1, SCA2, SCA3, SCA6, SCA7, SCA8, SCA10, SCA12, SCA14, SCA17, and DRPLA. The genetic assay in our case was positive for the SCA10 mutation, with 2223 ATTCT pentanucleotide repeats. Interestingly, his brother, with what appeared to be typical PD but no ataxia, also tested positive, with 1968 ATTCT repeats (Figure 55.1).

The genotype of SCA10 is an expanded repeat of ATTCT pentanucleotide located on chromosome 22q13. The function of the SCA10 gene remains unknown. Normal alleles have 10–29 ATTCT pentanucleotide repeats. Expanded repeats leading to ataxia generally range from 800 to 4500. The major clinical feature of SCA10 is typically ‘pure’ cerebellar ataxia associated with progressive dysmetria, dysarthria, and nystagmus. Seizures can occur in up to 50% of cases. In fact, the combination of pure cerebellar ataxia and a seizure disorder is considered phenotypically unique to SCA10. Other clinical features include mild cognitive dysfunction, behavioral disturbances, pyramidal tract signs, and peripheral neuropathy. Parkinsonism has been reported in SCA10. Thus far,
SCA10 has been reported only in individuals of Mexican or Brazilian ancestry.\textsuperscript{6,7} Anticipation has been reported in some families.\textsuperscript{8} At present, there is no effective treatment for SCA10; however, the seizure disorder usually responds to conventional anticonvulsants.

This case is instructive because it demonstrates the clinical features of SCA10 and considers the differential diagnosis of adult-onset ataxia. It also teaches that 'typical Parkinson’s disease' may not be so typical when there is a strong family history, since parkinsonism can be a manifestation of several of the autosomal dominant spinocerebellar ataxias.

REFERENCES

Legend to video
Case 55 This 54-year-old man has dysmetria with finger-to-nose and an ataxic gait with a broadened base and incoordination, especially when turning, necessitating a walker.
What looks like corticobasal degeneration but is not corticobasal degeneration?

Michaela Stampfer-Kountchev, Sylvia Bösch, and Werner Poewe

CASE PRESENTATION

A 64-year-old woman presented in September 2005 with a progressive gait disorder. She had first developed difficulty walking in 1994, initially affecting only the right leg, with unsteadiness and occasional falls. About 1 year later she noticed difficulty with coordination of her right hand and involuntary cramping involving distal muscles of her right arm. At about the same time she started to experience urinary urge incontinence. Symptoms were progressive, with stiffness and incoordination involving her left leg as well. By 2000, she needed a walker frame, and by 2004 she had become wheelchair-bound because of increasing instability and falls. By that time she had also developed cognitive slowing and dysarthria with slurred speech. Her family history was notable for one sister out of six siblings reportedly being similarly affected. This sister had died at age 67 with a diagnosis of Alzheimer’s disease.

Neurological examination at the time of presentation (see video, Case 56) revealed markedly asymmetric parkinsonism with bradykinesia and rigidity. In addition to slowing and incoordination of hand movements there was also apraxia of her right hand. The patient was unable to copy simple gestures or imitate the use of simple objects. There was hypomimia and a hypophonic, dysarthric voice, with marked difficulty understanding the patient. Saccadic eye movements were slow and hypometric but there was no vertical gaze palsy. Tendon reflexes were brisk and there was a Babinski sign bilaterally. She was unable to stand or walk unassisted. Frontal release signs including snout and grasp reflexes were present bilaterally and there was cognitive slowing. Neuropsychological testing revealed severe executive dysfunction including profound impairment of set shifting, planning, problem solving, and working memory.

A computed tomography (CT) scan (Figure 56.1) revealed extensive calcification in the periventricular region, basal ganglia, thalamus, and the cerebellar dentate nuclei.
DISCUSSION

This patient was diagnosed as having striopallidodentate calcinosis (‘Fahr’s disease’). Although bilateral striopallidodentate calcinosis is commonly referred to as ‘Fahr’s disease’, it is a misnomer, as Fahr described a case with calcification in the white matter with only little calcification of the basal ganglia. However, the term ‘Fahr’s disease’ has gained widespread acceptance and refers to familial or sporadic idiopathic calcification of the basal ganglia, thalamus, dentate nucleus, and centrum semiovale. The autosomal dominant form has linkage to the long arm of chromosome 14, with significant clinical heterogeneity. Secondary forms of striopallidodentate calcinosis can be due to hypoparathyroidism, pseudohypoparathyroidism, primary hyperparathyroidism, lupus, intoxication, infections (human immunodeficiency virus (HIV), Epstein–Barr),...
carbon monoxide poisoning, and radiation therapy. A fair proportion of cases remain enigmatic as to the cause of calcification. In this case, laboratory work-up revealed elevated serum parathormone, decreased 1,25-di hydroxycholecalciferol, and serum Ca⁺⁺ in the normal range, corresponding to secondary hyperparathyroidism. However, in contrast to primary hyperparathyroidism, this endocrine abnormality is not regarded as a cause of solid organ calcification, so a genetic cause may be more likely here (see family history above).

The clinical features of bilateral striopallidodentate calcinosis include movement disorders (55%), mainly parkinsonism (57%) and chorea (19%), cognitive impairment (39%), dysarthria (36%), cerebellar ataxia (36%), psychiatric symptoms (31%), pyramidal signs (22%), and gait disorder (18%). Neuropsychological deficits include a dysexecutive syndrome, anterograde amnesia, and attentional impairment.⁴

This case is instructive because of its presentation with markedly asymmetric bradykinetic parkinsonism combined with cortical sign of asymmetric apraxia plus a frontal dysexecutive syndrome, initially raising the diagnosis of corticobasal degeneration (CBD). Instead, this patient is an example of bilateral striopallidodentate calcinosis producing a CBD look-alike.⁵ This case also leads to consideration of the differential diagnosis of striopallidodentate calcinosis.

REFERENCES

Legend to video
Case 56 The video shows a 64-year-old woman with markedly asymmetric parkinsonism with severe bradykinesia and rigidity. Slowing and incoordination of hand movements, as well as apraxia of the right hand, can be seen. The patient is unable to copy simple gestures. There is marked hypomimia and a hypophonic, dysarthric voice which is difficult to understand. Saccadic eye movements are slow and hypometric but there is no vertical gaze palsy. She is unable to stand or walk unassisted.
Rapidly progressing parkinsonism

Lisa M Shulman

CASE PRESENTATION

A 69-year-old man with a 9-year history of parkinsonism presented with marked worsening of tremor, rigidity, gait, and balance over the last 18 months. He had been diagnosed with Parkinson’s disease 7 years ago following gradual progression of the initial symptoms of resting tremor affecting the right arm and generalized slowing. He responded to treatment with a dopamine receptor agonist, selegiline, and amantadine. Levodopa had been introduced 2 years ago with marked improvement. Over the last year-and-a-half, his condition had deteriorated dramatically, with the emergence of frequent freezing, falling, and the inability to walk or perform most activities of daily living without assistance. Multiple visits for medical evaluations during this period of decline resulted in several increases of levodopa from the initial dose of 300 mg to the current dose of 1250 mg per day with no apparent benefit.

Severe depression had begun in the last 6 months and there was a suicide attempt by drug overdose 2 months prior to this visit. An episode of hallucinosis resolved with discontinuation of the dopamine agonist. He reported urinary urgency, symptomatic orthostasis, severe sialorrhea, and mild dysphagia.

His medical history included type 2 diabetes, chronic dysthymia, and chronic gastrointestinal distress described as stomach heaviness and bloating. Current medications included: carbidopa/levodopa 25/250, five times daily, venlafaxine XR 150 mg daily, ditropan XL 10 mg daily, glimepiride 2 mg daily, tamsulosin 0.4 mg daily, and metoclopramide 10 mg four times a day.

The Mini Mental State Examination (MMSE) score was 24/30, with errors on spelling ‘world’ backwards, following a three-step command, recall, and writing a sentence. Speech was hypophonic and dysarthric, but intelligible. He appeared depressed, and endorsed depression but not suicidal ideation or hallucinosis. There was severe, facial masking. There was a moderate resting tremor of the right arm, a mild tremor on the left, and a perioral tremor. Cogwheel rigidity was severe, involving all limbs, trunk, and neck. Dexterity in all limbs was severely impaired. He was unable to rise from a chair without assistance (see video, Case 57) and lost balance spontaneously. Gait was characterized by a flexed posture and markedly shortened stride length with freezing. The cranial nerves were intact without vertical ophthalmoplegia. There was no apraxia, weakness, ataxia, sensory impairment, or reflex abnormality.
DISCUSSION

Every new office visit for Parkinson’s disease (PD) begins with a re-evaluation of the diagnosis. The typical findings in this patient include onset at 60 years of age, initial symptom of resting tremor of the right hand, gradual progression over 7 years, persistent asymmetry of signs, and robust response to levodopa. However, a number of ‘red flags’ were present, most important the precipitous decline over the last 18 months resulting in severe disability less than 10 years since the initial presentation. The rapid elevation of levodopa dosage with no apparent response was another red flag in light of the earlier history. Other concerns included cognitive dysfunction, depression, hallucinosis, and autonomic dysfunction. All of these features are seen in the setting of advanced PD; however, the possibilities of atypical syndromes such as dementia with Lewy bodies or multiple system atrophy (MSA) were raised.

What caused the precipitous decline and sudden need for a fourfold increase in levodopa dose? The medication history holds the key to this case. Metoclopramide was started 1 month prior to the sudden worsening of motor function. Review of the medical record revealed that previous physicians did not record this history. However, even if the patient neglected to give his medication history, the possibility of exposure to a dopamine-blocking agent was raised by the rapid deterioration to a severely parkinsonian state with loss of previous levodopa response. Although the accuracy of the diagnosis of idiopathic PD was not clear, the first step was to discontinue the metoclopramide.

The patient was seen 1 month following discontinuation of metoclopramide. Severe parkinsonism continued; however the Unified Parkinson’s Disease Rating Scale (UPDRS) motor examination score had declined from 82 to 68, with improvements mostly in repetitive movements and resolution of orthostasis. A new problem of paranoid ideation emerged with calls to the police and concerns about spousal infidelity. Quetiapine 25 mg at bedtime was introduced with good response. Venlafaxine was increased from 150 to 300 mg per day with partial improvement of depression. Over the following 7 months he returned to walking without assistance while his levodopa dose declined from 1250 to 1000 mg per day. He is now reporting motor fluctuations, whereas he previously had no ‘on time’ at all. The exacerbation of parkinsonism by metoclopramide is supported by the gradual improvement with concomitant reduction of levodopa.

When patients are evaluated for parkinsonism, a complete drug history is mandatory. Although drug-induced parkinsonism (DIP) may be clinically indistinguishable from PD, the signs of DIP tend be symmetric and occur more acutely.¹ There is remarkable variation in susceptibility to the extrapyramidal effects of dopamine-blocking drugs; however, risk factors include pre-existing extrapyramidal signs, age, female sex, drug potency, and increased drug dose.² After discontinuation of a dopamine-blocking agent, parkinsonian signs often resolve over a period of weeks, although the effects may last longer, even months to years,¹³⁵ emphasizing the need to ask all patients presenting with parkinsonism about exposure to dopamine-blocking agents within the past year and not just their current medications.
This case is instructive because it highlights the ‘red flags’ of rapid progression and steep escalation of levodopa dosage that should prompt questioning the diagnosis of PD. Rapid progression is not in keeping with the natural history of PD, and suggests either an alternative diagnosis, such as a parkinsonian syndrome (MSA, progressive supranuclear palsy), or a superimposed condition such as depression, a new medical problem, or, as in this case, the addition of metoclopramide. Many physicians are unaware of the antidopaminergic effect of metoclopramide and therefore fail to recognize drug-induced parkinsonism or tardive syndromes.\textsuperscript{5,6}

\section*{REFERENCES}


\section*{Legend to video}

\textbf{Case 57} The first segment is from the initial visit, demonstrating severe parkinsonism with hypophonia, bradykinesia, inability to arise from a chair independently, and a significant gait disorder. One month later, off metoclopramide, there is still moderately severe parkinsonism but there is already evidence of improvement in his gait.
Clumsy gait and leg pain

N Robb Whaley and Ryan J Uitti

CASE PRESENTATION

A 41-year-old woman of Portuguese descent developed incoordination with frequent tripping by age 18. Her mother reported that she was a ‘clumsy’ child and that she suffered from severe separation anxiety that interfered with her education and social life. The patient endorsed symptoms of depression since childhood that contributed to her use of ethanol and cocaine while a teenager.

Her gait problems progressed, and at age 26 she began having difficulty swallowing. Soon afterward, she was diagnosed with restless legs syndrome. She subsequently noticed an intermittent resting left-hand tremor. Concomitantly, she began having double vision that was not improved with strabismus surgery. Her depression worsened in her early 30s, and she attempted suicide by drug overdose and at another time with a gun. Depression was successfully treated with venlafaxine. At age 33, she became unable to work as a paramedic secondary to her gait problems and has not been employed since.

At age 34, she developed ‘severe deep, achy bone pain’ (not relieved by gabapentin or opioids) in her legs associated with increased tone and involuntary leg extension and plantar flexion. She also reported an inability to perceive the position of her legs covered by a blanket while in bed. Bilateral facial numbness (‘novocain type sensation’), ‘freezing’ of her legs and arms with inability to move them at times unless she touched them, and short-term memory loss began at 38. She subsequently developed urinary urgency and urinary incontinence. By age 41, she required a wheelchair and suffered from chronic insomnia, diplopia and worsening dysphagia (both liquids and solids). Her chief complaint was severe pain in her legs that took on a persistently stiff posture.

There was no history of liver disease or other systemic illness. The patient’s father, paternal grandmother, and great grandmother all had clumsy gaits and numbness with inability to walk later in life.

On examination, she appeared to have a depressed mood. For example, she cried when discussing her history of depression. Her speech was dysarthric with hypokinetic and ataxic components. There was nystagmus with right and left lateral gaze and subjective decreased hearing on the right to finger rub. The motor examination was remarkable for increased tone in her legs (left > right) with decreased strength of hip extension, knee extension, and flexion. There was persistent flexion and inversion at both ankles. Deep tendon reflexes were brisk throughout and plantar responses flexor. Sensory examination revealed
decreased temperature and pain sensation in face, trunk, arms, and legs. Proprioceptive loss was evident at distal interphalangeal, ankle, and toe joints. Coordination was impaired with pronounced dysmetria on finger-to-nose and heel-to-shin testing, dysdiadochokinesia with rapid alternating movements, and impaired checking responses. Truncal ataxia was present. Gait was ataxic and requiring two-hand support for ambulation.

**DISCUSSION**

This patient had a chronic progressive history of gait instability (see video, Case 58) and bulbar symptoms (including dysphagia, diplopia, and dysarthria on examination) suggesting a progressive cerebellar syndrome. Other symptoms and signs suggested the presence of extrapyramidal disease (resting tremor, restless legs syndrome, and dystonic posturing and pain), neuropathy (sensory disturbance and urinary dysfunction), and neurocognitive disturbance (depression and memory dysfunction).

Although pain was the chief complaint, this history and examination were dominated by disabling ataxia. While a number of diagnoses can be considered in the differential diagnosis (Table 58.1), only Wilson’s disease and spinocerebellar ataxia (SCA) are known genetic disorders. The family history suggesting an autosomal dominant disorder further limits the differential to an autosomal dominant cerebellar ataxia (ADCA). In this scenario, a diagnosis of SCA3 (or less likely SCA2) would best explain the multiplicity of traits indicated by history and examination, especially with the Portuguese heritage.

A screen for ADCAs would represent the best diagnostic test in this patient. When considering an autosomal dominant cerebellar ataxia (ADCA), the patient can be grouped into one of Harding’s clinical types1 (where ADCA I = cerebellar syndrome + other central nervous system (CNS) disorder (pyramidal, extrapyramidal, ophthalmoplegia, and dementia); ADCA II = cerebellar syndrome + pigmentary maculopathy; ADCA III = ‘pure’ cerebellar syndrome ± mild pyramidal signs). These categories can be used for narrowing the differential diagnosis. The patient was screened for inherited ataxias in the ADCA I category and was confirmed to have a SCA3 mutation (reflected by a CAG trinucleotide repeat \( n = 70; \) normal < 55) expansion).

Spinocerebellar ataxia type 3 (SCA3), also known as Machado-Joseph disease, is thought to be the most prevalent autosomal dominant cerebellar ataxia (ADCA) worldwide (20–28% of ADCAs)2 with perhaps the most variable phenotype. Typically, SCA3 begins in adulthood with cerebellar ataxia. It is seen frequently in affected families descended from Portugal. Early-onset SCA3 presents with extrapyramidal signs including parkinsonism and dystonia. In contrast, late-onset SCA3 may present with an apparently isolated peripheral neuropathy. The variability in presentation age and phenotype may camouflage the hereditary nature of the condition in some families (Machado disease and Joseph disease were thought to be separate conditions on this count, named after different families). Distinctive features in some patients include parkinsonism, restless legs syndrome, pseudoexophthalmus, faciolingual myokymia, dystonia, and loss of temperature sensation involving the limbs, trunk, and face (a relatively specific finding in SCA3).
This patient’s history was an excellent example of SCA3, because the patient’s pedigree (Figure 58.1) traced the disease back to an adopted grandmother from Portugal, demonstrating four consecutive generations with ataxia (since the patient’s diagnosis, her sister and father have been genetically confirmed to have SCA3). She also had several features commonly associated with SCA3 including parkinsonism, restless legs syndrome, dystonia, gaze-evoked horizontal nystagmus, and loss of pain and temperature sensation involving face, trunk, and limbs. Interestingly, she endorsed a significant morbidity throughout her life due to depression and anxiety, and remarked that the family members who had suffered from ataxia also suffered from depression. An increased incidence of anxiety and depression has been reported in SCA3.3, 4

A prominent feature of her neurologic condition was severe pain in the lower back and legs. While there are a vast number of causes for pain, painful dystonia should be suspected in certain neurologic conditions in which dystonia often occurs (Table 58.1). For instance, Parkinson’s disease frequently presents in younger patients with focal limb dystonia (writer’s cramp, ankle inversion with sustained exercise, and striatal toe are the most common); the focal dystonia is typically painful and ipsilateral to subsequent parkinsonian features.5 However, despite its association with many neurologic conditions, dystonic extrapyramidal pain is frequently misdiagnosed in patients with these conditions (as occurred in the current case). A common example is the patient with shoulder pain, or ankle pain, who was diagnosed with joint disease several months previously to being appropriately diagnosed with Parkinson’s disease plus painful rigidity–dystonia.

Unfortunately, the diagnosis of painful dystonia had not been entertained to explain this patient’s pain, despite her being seen by multiple physicians over the course of her disease (some of whom were neurologists). The dystonia mostly involved her legs and was associated with posturing at the ankles with prominent inversion and flexion. Dystonia has been reported in SCA36,7 and is thought to be associated with younger age of symptom onset and longer trinucleotide repeat lengths,8 both of which characterize this patient. The delay in diagnosis led to unnecessary suffering, wasted time and resources for the patient and

Table 58.1  Neurologic conditions frequently associated with dystonia

<table>
<thead>
<tr>
<th>Condition</th>
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<tbody>
<tr>
<td>Parkinson’s disease</td>
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<td>Corticobasal degeneration</td>
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<td>Multiple system atrophy</td>
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<td>Wilson’s disease</td>
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<td>Progressive supranuclear palsy</td>
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<td>Machado-Joseph disease</td>
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<td>Dopa responsive dystonia</td>
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<td>Multiple sclerosis</td>
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<td>Spinocerebellar ataxia</td>
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physician, and treatment with medications with potentially harmful side-effects and abusive potential.

Botulinum toxin is the mainstay of symptomatic treatment for focal dystonia in such patients. This patient’s pain was alleviated with botulinum injections to her quadriceps, gastrocnemius, and posterior tibialis. This relief was maintained with subsequent botulinum toxin injections every 3–6 months. Such a treatment should be considered in any patient with a substantial extrapyramidal pain syndrome without an otherwise direct treatment.

This case is instructive because it demonstrates the typical features of SCA3 as well as an approach to the patient with inherited ataxia. It also stresses the importance of recognizing that dystonia can cause severe and chronic pain and should be considered as a potential etiology in any individual with a disorder included in Table 58.1. As this case illustrates, the failure to recognize painful dystonia can result in unnecessary patient suffering and expense.
REFERENCES


Legend to video

Case 58 This demonstrates progression of the patient’s gait ataxia (increased base, irregular foot placement, imbalance, and veering) and appendicular ataxia on heel-to-shin testing from 3/2000 to 1/2005.
A woman with progressive ataxia and hallucinations

Sarah Pirio Richardson and David P Richman

CASE PRESENTATION

A 58-year-old woman with chronic obstructive pulmonary disease was admitted to the neurology service for inability to walk. Seven months prior to admission, she experienced hallucinations of seeing snakes or hearing babies cry. Three months later, the patient underwent a nocturnal polysomnogram for progressive daytime somnolence. The study demonstrated obstructive sleep apnea for which she was begun on continuous positive airway pressure (CPAP).

Four months prior to admission, she underwent an exacerbation of her pulmonary disease and was hospitalized for severe respiratory distress requiring intubation. At the time of discharge, the patient was noticed to have difficulty with gait and unspecified memory problems. A physical therapy consultant recommended a cane. Over the next few months, the hallucinations increased, as did the gait abnormality. By 2 weeks prior to admission, the patient could no longer walk and the family could no longer care for her. The patient’s family history was pertinent only for her mother having a history of sleep apnea, possible tremor, and death at age 56. The patient had never traveled outside of the United States and there was no history of blood transfusion, tissue transplant, or growth hormone exposure.

The patient’s general examination and vital signs were normal. She was alert but disoriented. Her Mini Mental State Examination (MMSE) score was 15/30. Her speech was fluent with frequent paraphasic errors. She was actively hallucinating. She had full but saccadic pursuit eye movements and moderate dysarthria. She demonstrated diffuse paratonia but strength was normal. She had an ataxic tremor with limb activation (see video, Case 59). She had spontaneous arrhythmic jerking movements of her limbs that were difficult to characterize but were slower than myoclonus. She had no startle myoclonus. The deep tendon reflexes were normal with flexor plantar responses. Grasp, glabellar, and snout reflexes were present. Sensation was normal. She had bilateral upper and lower limb dysmetria, worse on the left, as well as truncal and gait ataxia.

Magnetic resonance imaging (MRI) of the brain demonstrated increased signal on diffusion-weighted images (DWI), symmetrically, in the caudate, putamen,
medial and posterior thalamus, and cerebellum, and a mild increase in signal in fluid attenuated inversion recovery (FLAIR) sequences in some of the same areas (Figure 59.1). There was no enhancement. A second MRI scan was performed 4 days later, which revealed more involvement in the same areas (Figure 59.1). An electroencephalogram (EEG) performed during the first week of hospitalization showed bifrontal slow sharp waves and generalized slowing. A second EEG performed 1 week later showed generalized slowing with periodic triphasic waves. Cerebrospinal fluid (CSF) analysis showed mildly elevated total protein (64 mg/dl), a positive 14-3-3 protein assay, and an elevated neuron-specific enolase. CSF viral culture and serologies were negative. Paraneoplastic antibodies and Borrelia burgdorferi antibodies were negative. Serum evaluation showed negative or normal results for Wilson’s disease, toxins, heavy metals, vitamin B12, thiamine, liver function tests, serum glucose, thyroid function, erythrocyte sedimentation rate, antinuclear antibody, and human immunodeficiency virus. A blood smear was negative for acanthocytes.

DISCUSSION

This patient was diagnosed as having sporadic Creutzfeldt-Jakob disease (CJD), the Brownell–Oppenheimer form. The hallucinations improved with risperidone but her ataxia and dementia continued to worsen. She was discharged to home with hospice care and died within 1 month.

CJD is a rapidly progressive, fatal neurodegenerative disease. The majority of cases are sporadic. About 15% of CJD cases are familial. Rarely, CJD can be due to infection, as in variant CJD and iatrogenic exposures (< 1%). A methionine/valine polymorphism in codon 129 in the prion protein gene commonly occurs in the general population. The genotype at codon 129 appears to affect the phenotypic presentation in CJD cases, whether sporadic, familial, or transmitted by infection.¹

CJD can present with various combinations of the following findings: rapidly progressive dementia, cerebellar dysfunction, pyramidal and extrapyramidal signs, visual changes, myoclonus, language impairment, behavioral changes, and sensory symptoms.¹ While cerebellar dysfunction is a common symptom in many subtypes of CJD, predominant cerebellar ataxia was first described by Brownell and Oppenheimer as a subtype of CJD.² Sleep apnea, as was seen in this case, has also been reported as a presenting feature of CJD.³

MRI is a non-invasive aid to the diagnosis of CJD. Increased signal on DWI and FLAIR sequences, specifically, has been examined and followed through the course of the disease.⁴ The signal change in the basal ganglia and cortex, as was also seen in this case, is typical. Diffuse signal change in the cerebellum is a rare feature, but consistent with changes seen in other Brownell–Oppenheimer variant cases.⁵ Additional useful investigations in CJD include EEG and CSF examination. The EEG typically shows slowing and periodic sharp wave complexes.¹ CSF evaluation is typically normal with mild elevation in total protein possible. The increase in CSF 14-3-3 protein, although controversial, may add to the diagnosis.⁶ Definite diagnosis is made through brain biopsy or autopsy.

Quinacrine has been hypothesized to inhibit the conformational conversion of the normal prion protein to the abnormal prion protein. In spite of the fact
A woman with progressive ataxia and hallucinations that an open label study of quinacrine failed to demonstrate increased survival or pathological benefit, it is currently used on a compassionate-use basis to treat CJD.⁷

This case is instructive because it demonstrates the cerebellar presentation of CJD manifested by rapidly progressive limb and gait ataxia along with rapidly progressive dementia.

REFERENCES

Legend to video

Case 59  This demonstrates an ataxic tremor, upper extremity dysmetria, occasional myoclonic jerks, truncal ataxia, snout and grasp reflexes, and an exaggerated startle response.
A case of rhythmic abdominal movements

Stephan Bohlhalter, Masao Matsuhashi, Zoltan Mari, Keith Saxon, Hiroshi Shibasaki, and Mark Hallett

CASE PRESENTATION

An 18-year-old right-handed woman presented with involuntary rhythmic abdominal and tongue movements. She had been in good health until a prolonged ‘coughing attack’ with respiratory ‘spasms’ 2 months earlier. She had a feeling of tightness in her throat and shortness of breath (‘could not get air through’). She was hospitalized briefly and treated for an asthma attack. During another episode, she was suspected to be hyperventilating and was sedated. After awaking, she noticed rhythmic abdominal movements. They disappeared in 5 days, but reappeared 2 weeks later and had been present almost constantly since then, disappearing only while she was sedated or asleep. When the movements were more vigorous, they caused shortness of breath and exhaustion. They were frequently associated with epigastric discomfort and difficulty falling asleep. She complained of disabling fatigue, which interfered with daily activities. After another attack of dyspnea, she developed intermittent tongue movements. There were no other neurological symptoms. Clonazepam improved her symptoms significantly after many unsuccessful medication trials including carbamazepine and phenytoin.

On examination, she appeared well with no signs of respiratory distress. On neurological examination, there was no palatal tremor. There were intermittent rhythmic tongue movements of 2–4Hz accompanied by a snapping sound. (see video, Case 60). While holding the tone ‘eh …’ there was a staccato pattern of the voice. Pulsating movements of similar frequency were seen in the upper abdomen and chest symmetrically. The movements were not suppressed with distracting maneuvers and there was no entrainment or change in frequency with hand tapping. Deep inspiration, sniffing or breath holding only partially suppressed the movements. Swallowing was not affected by the involuntary movements. The neurological examination was otherwise normal.

Laboratory testing was normal including complete blood count, sedimentation rate, vitamin B12 and folate levels, and metabolic and immunologic panel. Cerebrospinal fluid (CSF) was normal without oligoclonal bands. Electrocardiography (ECG) and computed tomography (CT) scan of the chest were unremarkable.
Magnetic resonance imaging (MRI) of the brain and cervical spinal cord was normal, as was an electroencephalogram (EEG). Fluoroscopy of the diaphragm showed a slightly asynchronous diaphragmatic flutter at about 200/min. Fiberoptic examination of the upper airway demonstrated rhythmic vertical movements of the pharynx extending to the larynx. Rhythmic tongue movements against the posterior pharyngeal wall caused hypopharyngeal obstruction giving rise to a snapping sound. Phonation was tremulous, but vocal folds showed no paradoxical movement or obstruction during respiration.

Surface electromyography (EMG) showed rhythmic bursts of activity lasting 100-200 ms in the muscles of the neck (sternocleidomastoid), thoracic cage (external intercostal), abdomen (abdominal rectus), and floor of mouth (geniohyoid). The peak frequency of the EMG activity was 3 Hz and synchronous in most body parts except the geniohyoid muscle, which showed an independent EMG frequency of 4 Hz. The EMG discharges of the abdominal rectus muscle were continuous, but those of other muscles were intermittent. Externally paced right hand tapping did not affect the frequency of EMG activity in these muscles (Figure 60.1).

**DISCUSSION**

Respiratory myoclonus or Leeuwenhoek’s disease is a rare movement disorder characterized by rapid involuntary rhythmic contractions of the diaphragm and accessory respiratory muscles. It was first described by Anthony van Leeuwenhoek in 1723, who himself suffered from the disorder. Respiratory myoclonus can be paroxysmal or continuous, as seen in this case. The frequency (ranging from 60 to 200/min) and amplitude are variable and increase under emotional stress. The diaphragmatic movements either interfere with breathing or superimpose on normal respiration without influencing it. Epigastric pulsations are also typically present.

The clinical manifestations of respiratory myoclonus are heterogeneous, including dyspnea, fatigue, and abdominal or chest pain. Respiratory myoclonus may imitate hyperventilation syndrome or an asthma attack. The rhythmic movements usually disappear during sleep or sedation and decrease or stop with respiratory maneuvers (e.g., deep inspiration). The disorder may be restricted to the diaphragm but frequently involves accessory respiratory muscles such as the scalenes and intercostals. Therefore, the term respiratory myoclonus is often more appropriate than diaphragmatic myoclonus or flutter. The diagnosis of respiratory myoclonus is based mainly on the clinical presentation, chest fluoroscopy, and EMG. The EMG characteristics of respiratory myoclonus are similar to those of palatal tremor, showing longer burst durations (>50 ms) than typical myoclonus. Some have suggested that respiratory myoclonus may be a variant of palatal tremor and, as such, ‘respiratory tremor’ might be the more appropriate term rather than respiratory myoclonus.

The etiology is unknown in most cases of respiratory myoclonus. Symptomatic causes are frequently of central origin. Most common is encephalitis, followed by vascular lesions, tumors, and multiple sclerosis. Pathological excitation of the phrenic nerve, usually on the left side, by a mediastinal mass or cardiac disease should also be considered in the differential diagnosis. Based on the occasional
bizarre presentation, disappearance during sleep, and the influence of emotional stress, respiratory myoclonus may be misdiagnosed as a psychogenic movement disorder. Lack of entrainment with voluntary tapping, as seen here, helps to rule out a psychogenic cause. Although respiratory myoclonus is considered benign, it can be disabling by causing dyspnea and fatigue. Pharmacological treatment is empirical. Clonazepam can be effective, as demonstrated in this case. Phenytoin and carbamazepine have also been used successfully. Phrenectomy is considered a last resort for refractory cases.

Little is known about the pathophysiology of respiratory myoclonus, but it is likely a disorder of central respiratory control. In our patient, two types of rhythmic movements existed, involving respiratory and glossopharyngeal muscles. Both had similar though not synchronous frequencies, as detected by EMG (Figure 60.1). This finding points to segmental myoclonus with two different generators in respiratory centers of the lower brainstem. Loosely coupled oscillators in the brainstem behaving independently, with some influence on each other, have been described for symptomatic palatal and postural limb tremor. Furthermore, the view of separate oscillators, putatively located in the reticular formation, generating rhythmic glossopharyngeal and diaphragmatic movements, is supported by experimental data showing that the brainstem control of hypoglossal and phrenic activity is uncoupled during respiration.
This case is instructive because it demonstrates the clinical manifestations of respiratory myoclonus and the utility of the EMG evaluation to confirm the diagnosis.

REFERENCES


Legend to video

Case 60 First segment: high-frequency (around 3Hz) rhythmic abdominal oscillations involving the thorax, superimposed on normal respiration. At the beginning a snapping sound caused by the rhythmic tongue movements is audible. Second segment: abdominal movements demonstrating no entrainment with hand tapping. Third segment: high-frequency rhythmic pulsations of upper abdomen. Fourth segment: fluoroscopy showing high-frequency rhythmic movements of the diaphragm. Fifth segment: fluoroscopy demonstrating rhythmic glossopharyngeal movements interrupted by swallowing. Sixth segment: fiberoptic examination showing hypopharyngeal obstruction by tongue movements against the posterior pharyngeal wall producing a snapping sound. Seventh segment: laryngoscopy showing vocal folds during respiration with no paradoxical movement or obstruction. Note rhythmic movements of pharyngeal wall.
Parkinson’s disease: what to do when there seems nothing more to do

M Karimi, Joel S Perlmutter, J Dowling, and F Revilla

CASE PRESENTATION

A 37-year-old woman noticed the gradual onset of left hand tremor followed by difficulty arising from deep chairs. Soon she developed a shuffling gait and hesitation when initiating steps. Within 5 years her symptoms gradually progressed, with the extension of tremor to the right hand. At age 44, carbidopa/levodopa provided a dramatic response. Four years later, she developed occasional visual hallucinations and 9 years later experienced dyskinesias. A short duration response to individual doses of levodopa, dyskinesias, and drug-induced psychosis progressed over the next 15–20 years. She had been suffering from paranoid delusions and mood fluctuations since her 60s and had severe dyskinesias during all of her ‘on’ time. Reductions of levodopa to reduce psychosis produced unacceptable slowness, stiffness, and tremor. Neither quetiapine nor clozapine controlled psychosis when she was taking enough levodopa to provide acceptable motor benefit. A trial of electroconvulsive therapy provided no additional psychiatric benefit.

The patient was evaluated at our center at age 68, after a 31-year history of symptoms. At that point, carbidopa/levodopa took 45 minutes to provide benefit that lasted 1–3 hours, and there were frequent dose failures when it would not take effect. She had severe dyskinesias when ‘on’ but could feed herself with some spilling, and required assistance to stand. Her mood was low and she had suicidal ideation when ‘off’ but when ‘on’ her mood returned to normal. She had persisting hallucinations and delusions. During ‘off’ periods she had marked bilateral leg dystonia and severe generalized tremors, and was bedridden and unable to swallow or talk (see video, Case 61).

On examination she was disoriented and had a low mood with sense of hopelessness and helplessness and visual hallucinations. Her Unified Parkinson’s Disease Rating Scale (UPDRS) motor score when ‘off’ was 97.5, and when ‘on’ was 48.5 (108 maximum). We agreed with the diagnosis of idiopathic Parkinson’s disease (PD) with the following treatment-related complications: dose failures, short duration of benefit from individual doses of levodopa (wearing-off), severe
peak-dose dyskinesias, off-period dystonia, marked mood fluctuations, and
dopa-induced psychosis. Treatment was limited by drug-induced side-effects.
We recommended bilateral subthalamic deep brain stimulator implantation
given the severity of her condition and the limitations of drug therapy
due to side-effects. We simplified her medication regimen switching from a
combination of controlled release and immediate release carbidopa/levodopa to
just immediate release 25/100, one tablet four times per day. The psychosis
cleared and dyskinesias decreased but she was relatively slow, stiff, and
tremulous.

Within 1 month, she underwent deep brain stimulation (DBS). Targeting the
subthalamic nuclei was achieved with T2-weighted magnetic resonance imaging
(MRI) guidance and a stereotactic navigation system confirmed by limited
electrophysiologic mapping. Prior to activating the stimulators or changing
the presurgical medications, the ‘off’ UPDRS score was 68. This benefit was
presumably due to a ‘lesion’ effect of the surgical implantation. Activating the
stimulator decreased the ‘off’ score to 45 the same day. The lesion effect decreased
within 2 weeks with an off score of 74. But activating the stimulator and taking
50 mg levodopa improved the score to 26. Levodopa was gradually decreased to
50 mg four times a day over the next few months, thereby reducing dyskinesia.
During her 3-year follow-up, she has not demonstrated any persisting side-
effects. She experiences transient paresthesias for a few seconds when activating
the stimulators during programming sessions. During the last 3 years, she has
had minor increases in levodopa and several adjustments of stimulation settings.
However, she remains free of major dyskinesias with an ‘on’ UPDRS motor score
ranging between 20 and 30. She has not had mood fluctuations or psychosis
since programming the stimulators.

DISCUSSION

Several groups have published recommendations for selection of PD patients for
DBS surgery. Despite overall agreement on key issues, stringency and details
of inclusion and exclusion criteria vary from center to center. In our center at
Washington University, patients must fulfill diagnostic criteria for Parkinson’s
disease, since other parkinsonian conditions do not respond well to subthalamic
nucleus (STN) DBS. Dopa-responsiveness is a key criterion, and it is widely
accepted that patients do not improve beyond their best response to maximal
doses of levodopa. Other criteria at our center include wearing-off or dose
failure despite optimization of antiparkinsonian medications, which is often
limited by side-effects such as dyskinesias, psychosis, or delirium. Dopa-induced
psychosis and cognitive impairment, however, should be distinguished from
dementia. Dementia and psychosis unrelated to drugs are contraindications for
DBS surgery and regarded as predictors of poor post-surgical outcome.
Hence, we perform a preoperative neuropsychological evaluation to determine
whether any of these relative contraindications are present. Patients with bilat-
eral subthalamic nucleus DBS have less wearing-off and require lower doses of
levodopa. As a result, reduced levodopa leads to reduction of dyskinesia and
hallucinations as seen in our patient. However, disease progression in the future
may require increased doses of levodopa.
This case is instructive because it demonstrates that DBS of the STN can have a dramatic and sustained effect on PD, primarily improving the ‘off’ state. And, it emphasizes the necessity of careful patient selection as key for a successful outcome, with criteria including a definite diagnosis of PD, a good response to levodopa complicated by disabling ‘off’ time, and the lack of dementia.

REFERENCES


Legend to video

Case 61 In the first segment, the patient is ‘off’ prior to surgery. There is a severe rest tremor of all limbs, marked bradykinesia, hypomimia with an open mouth, and inability to get out of the bed without assistance. The second segment shows the patient 20 minutes after taking 50 mg of levodopa, still prior to DBS. The tremor has resolved and there is improvement in bradykinesia, but these have been replaced by severe dyskinesias. She is unable to arise from the chair without help, walks slowly with impaired balance, and loses her balance on the pull test. The next segment shows the patient 14 days after DBS of the STN. She is off levodopa but the stimulator is on. There is no tremor except when walking. There is marked improvement in bradykinesia as well as the ability to arise from a chair and walk. The last segment shows the patient after the stimulator has been turned off for 5 minutes. There is return of tremor and bradykinesia.
Is it PD or DLB? Timing is everything

Irene Hegeman Richard and Roger Kurlan

CASE PRESENTATION

An otherwise healthy 82-year-old right-handed woman presented for a second opinion regarding the diagnosis and treatment of Parkinson’s disease (PD). She had developed a resting tremor of the right hand approximately 9 months earlier and since developed difficulty with handwriting, buttoning, and other fine motor tasks. She had also become slower in general. She was diagnosed with PD and started on pramipexole, titrated up to her current dosage of 0.5 mg three times a day. This dopamine agonist reduced the tremor and improved her writing. Her family was concerned because she reported seeing children in her house at night even though she lived alone and had not actually had any guests.

On examination, while providing the history, she appeared to be alert, appropriate, and in a good mood. On mental status testing, however, she did not know the correct month or date, recalled only one of three objects at 5 minutes, and became confused attempting to draw a clock. Her language was normal and she was not apraxic. On probing, she believed that children came into her home at night and, although not frightening, she considered them a nuisance. The remainder of the neurologic examination was significant only for a bilateral upper extremity resting tremor (right greater than left), mild cogwheel rigidity in the upper extremities (right greater than left), and impaired finger taps (moderate on the right and mild on the left). She had mild bradykinesia overall and needed to use her arms to arise from the chair. Her gait was slightly stooped with reduced arm swing (mostly on the right). She had no postural instability.

DISCUSSION

The motor features in this woman are typical of PD (resting tremor, rigidity, and bradykinesia with an asymmetric onset), but the cognitive impairment within 1 year of onset of motor symptoms should raise the possibility of an alternative or additional diagnosis, since dementia related to PD generally occurs in the later stages. One should consider the possibility of dementia with Lewy bodies (DLB), particularly in light of the visual hallucinations. Spontaneous visual hallucinations and early cognitive impairment are hallmarks of DLB. Other features
of DLB include fluctuating cognition with pronounced variations in attention and alertness, and frequent falls. It is also possible that the patient does, in fact, have PD but the cognitive impairment is due to a second process. For example, she may have concomitant early Alzheimer’s disease (AD), vascular dementia, or a reversible cause, such as hypothryroidism or vitamin B12 deficiency. The lack of ‘cortical’ dysfunction (i.e. aphasia, apraxia) makes AD less likely. It would be important to determine the relationship between the onset of visual hallucinations and the introduction of pramipexole. If they started before the drug was begun, DLB is more likely. If the hallucinations started after pramipexole then DLB is still possible, but so is PD with drug-induced psychosis.1

Dopamine agonists can cause hallucinations, and patients who are older and cognitively impaired seem to be at greater risk. Regardless of the diagnosis, therapeutically, the first thing to do is to reduce or stop the pramipexole to see whether the hallucinations resolve. Since her motor status will likely worsen, she may need another antiparkinsonian medication. A trial of carbidopa/levodopa would be reasonable. This medication may also induce psychosis but probably does so to a lesser degree than dopamine agonists. If the hallucinations persist despite discontinuing pramipexole (or if they return after carbidopa/levodopa is started) it may be necessary to treat her with an atypical antipsychotic medication. Some of the ‘atypical’ antipsychotic medications (risperidone and olanzapine in particular) have been reported to worsen parkinsonian motor features.2 Preliminary studies suggest that quetiapine does not worsen motor function in PD, but results are mixed regarding efficacy.34 A small case series suggests that aripiprazole may be an effective and well-tolerated alternative,5 but there have been no controlled studies to verify this. Clozapine has been shown in a well-controlled clinical trial to be effective and well-tolerated for the treatment of drug-induced psychosis in PD.6 However, due to the risk of agranulocytosis, weekly (and eventually biweekly) blood monitoring is required. Unfortunately, this can be expensive and inconvenient. It is advisable to reassure patients and their caregivers that hallucinations are a known side-effect of antiparkinsonian medications.

In addition to treating the hallucinations, it is important to rule out reversible causes of cognitive impairment rather than assume that the dementia is an inevitable consequence of PD. This should include routine laboratory studies, vitamin B12 level, and thyroid stimulating hormone (TSH). If reversible causes of dementia are ruled out, consideration could be given to an acetylcholinesterase inhibitor. These medications have been shown to be effective and well tolerated in AD, and studies thus far suggest that they may be beneficial for patients with DLB (particularly for the behavioral features) and PD-related dementia.7

To date, the pathophysiology of dementia in PD has remained elusive, and the relationship between PD and DLB has been unclear. It had been suggested that cognitive impairment in PD was due to concomitant Alzheimer’s pathological changes. However, a recent study by Aarsland and colleagues revealed that the main substrate of dementia in PD is, in fact, Lewy body disease.89 This supports the notion that the clinical course (particularly the temporal course of cognitive dysfunction and hallucinations) is the main feature distinguishing PD with dementia from DLB.10
This case is instructive because: (1) it highlights the fact that DLB is in the differential for patients with parkinsonism with early visual hallucinations and cognitive impairment; (2) it emphasizes that hallucinations in DLB are part of the disease, whereas in idiopathic iPD they are drug-induced; (3) it reinforces the need to check for reversible causes of dementia in Parkinson’s disease; (4) it illustrates that inducement or worsening of psychosis is a side-effect of antiparkinsonian medications: older age and dementia may increase the risk for drug-induced psychosis, and dopamine agonists are associated with a particularly high risk of psychosis; (5) it increases awareness of the need to treat psychosis in PD with atypical antipsychotics, and that not all ‘atypical’ antipsychotics are equally tolerated, highlighting the need for evidence-based treatment strategies.

REFERENCES

CASE PRESENTATION

A 43-year-old man was referred to the movement disorders clinic for evaluation of possible Wilson’s disease. Approximately 1 year earlier, intermittent head tremor had appeared. Excessive fatigue also emerged and he noticed that he was moving slowly and ‘dragging my feet’. Over time his handwriting became smaller and he began to experience difficulty getting up from chairs and out of automobiles. His voice became softer and increased saliva with occasional drooling also became evident.

Approximately 7 months earlier, his primary care physician had referred him to a neurologist. An electroencephalogram showed diffuse background slowing, and magnetic resonance imaging (MRI) demonstrated ‘prominent high signal on T1 weighted sequencing involving the basal ganglia in a symmetric fashion’. He was placed on pramipexole and the dosage was titrated to 1 mg three times daily, without improvement in motor function.

He was subsequently referred for hepatological evaluation. On examination he was noted to have a palpable liver, a slightly distended abdomen, and ‘scattered spiders’. The hepatologist also noted that ‘his response to almost every question was many, many seconds of pausing prior to beginning speech’, and that his ‘affect was extremely flat and he showed no emotion’. There were mild elevations of liver enzymes, with aspartate aminotransferase (AST) 123 IU/l (normal 0–40) and alanine aminotransferase (ALT) 83 IU/l (normal 0–40); a mildly prolonged international normalized ratio (INR) of 1.5; total bilirubin slightly elevated at 1.3 mg/dl (normal 0.0–1.2); and significant thrombocytopenia of 63 000. The hepatologist considered these abnormalities to be consistent with cirrhosis.

Medical history was significant for intravenous drug use approximately 20 years previously, with subsequent development of chronic hepatitis C. Hypothyroidism had been diagnosed approximately 1 year ago and thyroid replacement instituted.

On examination in the movement disorders clinic, speech was very soft and verbal responses were delayed. A score of 25/30 was recorded on the Mini Mental State Examination (MMSE). Cranial nerve examination was unremarkable except for some limitation of conjugate upgaze. Kayser–Fleischer rings were not present. There was mild neck rigidity but no limb rigidity. Tremor was not
present, but there was moderate bradykinesia involving limbs and body in a symmetric fashion. Gait demonstrated mild parkinsonian features.

Laboratory evaluation included: serum ceruloplasmin 27 mg/dl (normal 17–54); 24-hour urine copper 49 µg/day (normal 3–50); and serum manganese 2.2 µg/l (normal 0.0–7.8). Liver function studies had not changed appreciably and remained mildly abnormal. Urine heavy metal and manganese levels were normal. Repeat MRI demonstrated increased signal intensity in the lentiform nuclei on T1-weighted images.

DISCUSSION

This patient was diagnosed as having chronic acquired hepatocerebral degeneration (CAHD) (see video, Case 63). It bears many of the clinical features of Wilson’s disease (WD), but can be distinguished by its lack of a genetic basis, normal ceruloplasmin levels, absence of any evidence of disordered copper metabolism, and the absence of Kayser–Fleischer rings. CAHD may have been first described by van Woerkom in 1914, but it was the report by Victor and colleagues in 1965, in which they described 27 patients with the disorder, that clearly established CAHD as a distinct clinical entity. CAHD is a rare disorder. It is possible, however, that many cases of CAHD go unrecognized in individuals with chronic liver disease, in whom neurological features, especially if mild, might simply be overlooked or attributed to hepatic encephalopathy. In support of this speculation, features of parkinsonism were present in approximately 22% of individuals with cirrhosis in one clinical study, while in another investigation over 50% of subjects with minimal hepatic encephalopathy were found on neurological examination to have features of extrapyramidal dysfunction.

CAHD typically emerges in individuals with advanced liver disease who have experienced repeated episodes of hepatic encephalopathy. However, this is not invariably the case, and CAHD has been documented in individuals who have never displayed any evidence of hepatic encephalopathy. It can also develop in persons who do not have actual liver disease, but rather other processes, such as portal vein thrombosis, that result in blood being shunted around the liver. In the series of Victor and colleagues, hepatic disease preceded the appearance of neurologic disease in 81% of patients. The ultimate neurological deficit that develops in individuals with CAHD is predicted by neither the severity nor the frequency of episodes of hepatic encephalopathy.

The clinical signature of CAHD is a combination of cognitive impairment and abnormality of movement; however, there is considerable variability. Cognitive features typically consist of executive dysfunction, apathy, slowness in responding, and reduced attention and concentration. Cortical findings, such as aphasia or apraxia, are generally not present. Victor and colleagues noted cognitive impairment in 80% of the patients they studied.

Abnormalities of movement in CAHD reflect a combination of basal ganglia and cerebellar dysfunction including parkinsonism, tremor, chorea, myoclonus, asterixis, dysarthria, and ataxia involving both trunk and limbs. Dystonia is uncommon. Episodes of hepatic encephalopathy may be superimposed on CAHD, and during such episodes asterixis and myoclonus may become noticeably more
pronounced. Although rest tremor may develop in individuals with CAHD, distal large-amplitude action or postural tremor is much more common. Orofacial, lip, and tongue tremors have also been described. Mild pyramidal tract findings may be evident in a minority of individuals, but frank myelopathy is rare.

The hallmark MRI feature of CAHD consists of bilaterally symmetric, hyperintense signal changes on T1-weighted images. These changes are most prominent in the globus pallidus, but involvement of the putamen, mesencephalon, and even cerebellum has been reported. Manganese deposition is believed to be responsible for these changes (Figure 63.1). Pathologically, CAHD is characterized by neuronal loss, polymicrocavitation, and astrogliosis with increased numbers of Alzheimer’s type II glia involving multiple brain regions.

The course and clinical features of CAHD were felt by Victor and colleagues to be progressive and largely irreversible, although responsiveness to levodopa has subsequently been described by some investigators. Resolution of dysfunction following liver transplantation has also been reported.

This case is instructive because it demonstrates the clinical and radiographic features of chronic acquired hepatocerebral degeneration. Recognition of CAHD in an individual with progressive hepatic failure may have treatment implications, and even influence the decision of whether liver transplantation is needed.

REFERENCES

Legend to video

Case 63 This demonstrates a number of parkinsonian features characteristic of chronic acquired hepatocerebral degeneration (CAHD) including hypomimia, a monotone voice of decreased volume, lack of spontaneous movement, and mild, symmetrical slowing of finger, hand, and foot movements.
Tricking a patient with oromandibular dystonia

Axel Schramm, Joseph Classen, and Markus Naumann

CASE PRESENTATION

A 63-year-old man presented for evaluation of involuntary facial movements. Symptoms started at age 57 with a feeling of stiffness of the perioral region during speaking. This was followed later by involuntary movements of the jaw, which worsened over a period of 1 year. He experienced mild blepharospasm. No other dystonic symptoms were reported. Medical history revealed mild hypertension but was otherwise unremarkable. There was no exposure to neuroleptics or antiemetics. The patient’s mother had blepharospasm; his sister also had mild oromandibular symptoms but details were not available and intake of neuroleptics could not be excluded.

Neurological examination showed mild blepharospasm, and involuntary contractions of perioral and jaw-opening muscles including the submentalis complex and the platysma during speaking. The remainder of the neurological examination was normal. Cranial magnetic resonance imaging (MRI) was normal except for a slight hyperintensity between the right putamen and external capsule. Further diagnostic work-up was normal including ceruloplasmin and urine copper, as well as routine laboratory diagnostics, cerebrospinal fluid analysis, electroencephalography (EEG), motor- and somatosensory-evoked potentials, and X-ray of the maxillary joint.

Treatment with tiapride (up to 600 mg), trihexyphenidyl (up to 12 mg), tetrabenazine (up to 75 mg), and pimozide (up to 12 mg) was ineffective. Initial treatment with local injections of botulinum toxin into the periorbital and perioral region, as well as the platysma did not lead to significant improvement of oromandibular dystonia. Additional injections into the lateral pterygoid muscles followed by a combined injection of the digastric muscle, the perioral region, and the platysma led to some improvement of symptoms.

The patient showed an effective sensory trick maneuver: when biting on a small wooden stick, his speaking improved by 50% on a subjective visual analog scale. Trick-related improvement was confirmed in a blinded analysis of an audio recording and amounted to 31% on the subscore for ‘speech’ of the Fahn–Marsden dystonia rating scale. There was a significant reduction of surface electromyogram (EMG) activity of dystonic muscles while biting on a
wooden stick (temporal −20%; perioral −48%; submental −39%). In contrast, jaw occlusion without biting on the stick produced no significant improvement by self-assessment (−17%), and there was no objective change in the audio analysis despite a significant (−19%) reduction of EMG activity in dystonic muscles.

As the patient experienced major relief of symptoms by application of the trick maneuver, he designed with his dentist a special device that could be easily mounted and dismounted on the lower teeth row (see video, Case 64). Biting on this device eased the dystonic spasms and improved speaking, just as the wooden stick did. In addition, a constant small gap between lower and upper teeth was maintained. This facilitated air-flow during speaking and was therefore favored over biting on the wooden stick. The use of this dental device has continued to be highly effective over a period of 3 years and favored by the patient compared to injection of botulinum toxin.

**DISCUSSION**

This patient has blepharospasm and oromandibular dystonia (OMD), a combination sometimes referred to as Meige syndrome. Both are likely idiopathic (primary) because of the typical clinical presentation with lack of tongue involvement or stereotypies, task specificity (speaking), positive family history, lack of neuroleptic intake, and normal additional diagnostic tests. We consider the slight abnormalities on MRI related to mild cerebral microangiopathy due to arterial hypertension rather than playing a role in the pathophysiology of OMD in this case. As sensory trick maneuvers are typically present in other forms of idiopathic dystonia, the effectiveness of a trick maneuver in this patient further supports an idiopathic etiology.

Oromandibular dystonia is characterized by involuntary movements of lower facial, labial, and lingual as well as pterygoid and submental muscles, resulting in mouth opening or closure, jaw deviations, facial grimacing, or tongue movements. Symptoms are often task-specific, presenting especially during speaking or chewing. Tardive forms of OMD following neuroleptic exposure are more often associated with tongue movements and stereotypies, whereas idiopathic forms are often associated with other forms of dystonia such as blepharospasm, cervical dystonia, or spasmodic dysphonia.

A well established treatment for OMD is the local injection of botulinum toxin into the masseter muscles or submentalis complex. This may lead to improvement in functional rating of 37–47%. The subtype of jaw-opening dystonia is more difficult to treat. Usually, a smaller functional improvement can be achieved at the cost of an even higher rate of complications such as dysphagia and dysarthria.

Another option to partially relieve symptoms in idiopathic dystonia is the use of sensory trick maneuvers. Slight sensory stimulation or manual pressure in the region of affected body parts leads to a 48% decrease in surface EMG activity of involved muscles. In OMD, some patients present with an effective sensory trick maneuver such as touching the lips, chin, or submental region as well as chewing gum or biting on a toothpick.

Trick application such as biting on a small wooden stick has been described before. It effectively improved objective as well as subjective parameters in this
patient. Perhaps unexpectedly, slight jaw occlusion without the stick was equally effective in reducing surface EMG activity, yet this did not translate into improvement of articulation as it was counteracted by deterioration of speaking by the jaw closure itself. This problem could be circumvented by the use of a specially designed dental device which enabled voluntary occlusion, while a slightly opened teeth row allowed for fairly natural speaking. This device therefore represents a highly practical and continuously effective form of sensory trick application. As therapeutic options including medication and local botulinum toxin injection might be of limited effect, especially in jaw-opening OMD,\textsuperscript{5,6} patients should be encouraged to explore the use of sensory trick maneuvers.

This case is instructive because it demonstrates the typical clinical features of oromandibular dystonia and illustrates the potential of utilizing sensory tricks for treatment.

REFERENCES

Legend to video

Case 64 Patient with jaw-opening oromandibular dystonia using a specially designed dental device as sensory trick maneuver. In the first sequence the patient speaks without use of the dental device, while using it in the second sequence clearly improves articulation.
Focal dystonia in a string musician: strumming the wrong tune

Mark F Lew

CASE PRESENTATION

A 47-year-old man was referred for a second opinion regarding difficulty playing his guitar, diagnosed as dystonic musician’s cramp. The patient had been a professional classical guitarist, touring the world and teaching college-level guitar for several decades. Approximately 5 years ago he noticed difficulty using his right hand to play: he was mis-stroking and hitting unintended strings. He also complained of involuntary, uncontrollable flexion of the middle finger as he played.

He developed a compensatory method of stroking the strings, which was still below his usual quality of playing. Recently he had noticed involuntary movements of the right thumb whenever his index finger moved. Over the last 6 months he experienced worsening of his symptoms and had become concerned about his capacity to continue touring.

Other pertinent history included involuntary grasping while shaking hands and while running (right side). He described difficulty relaxing his hand due to ongoing tightness, potentially worse in cold weather. He denied difficulty with other fine motor tasks, weakness, cramping, or involuntary movements in other body parts. He had no leg stiffness or slowness; there was no dysphagia or diplopia. He reported that he functioned well otherwise and was able to play the piano without similar problems.

There was, however, a history of difficulty with writing for more than 20 years. He described a tendency for his hand to tighten involuntarily while writing. He devised a compensatory method over 20 years ago by piercing a ping-pong ball in the center and running it down to the bottom of the pen and subsequently holding the ping-pong ball, allowing him to write more effectively. He also complained of some tremor on the right with action.

He had a long history of anxiety and depression for which he had been treated with neuroleptics briefly and intermittently since childhood, with no exposure for several decades. In the last year he was able to wean himself off benzodiazepines which he had taken for several decades. He also reported that for as long as he could remember he had had to buy pants that were relatively ‘baggy’
to accommodate the size of his calf muscles. He has a sister who is a dancer with a similar body habitus, and he could remember his father as being built similarly and having a tremor. He is of Russian/German descent. There was no history of trauma to the head, neck, or limbs.

His medical history was otherwise notable only for sleep apnea and loud snoring, for which he had had surgery. His current medications included escitalopram oxalate and zolpidem tartrate. While he quit tobacco smoking 20 years ago, he continued to chew nicotine gum regularly. He consumed 3–4 alcoholic beverages daily.

On neurologic examination he was pleasant but anxious with a normal voice. Cranial nerves were normal. Motor testing revealed hypertrophied gastrocnemii and quadriceps muscles. Strength was normal. He was observed gripping, writing, and playing guitar. His difficulty with movement appeared to be an inability of his muscles to relax. There was no involuntary posturing or dystonia evident. There was percussion myotonia in the gastrocnemii and thenar eminence. Gait, coordination, reflexes, and sensation were normal.

While observed playing the guitar (see video, Case 65), there was stiffness and inability to relax his fingers once flexed. While writing, he complained of tightness and stiffness of his right arm, but no specific involuntary movements were seen. Electromyography (EMG) revealed increased insertional activity with myotonic discharges. There was no evidence of motor unit action potentials at rest as might be seen with dystonia.

**DISCUSSION**

This case illustrates the importance of detailed history taking, careful examination, and critical review of a prior diagnosis. The referring neurologist diagnosed this patient with a focal, task-specific occupational dystonia. This typically occurs only when the affected person attempts to perform specific motor functions, such as playing a musical instrument or writing. Hand and finger muscles can flex or extend, diminishing the action or causing the exaggerated posture to persist.¹,² This patient not only described involuntary flexion of his fingers while playing guitar, but also noticed slowness of his fingers to regain their normal posture to repetitively strum the strings. The video clip (Case 65) confirms that there is no evidence of involuntary muscle pulling, twisting, or spasm of the hand and finger muscles as would be expected with dystonia. Rather, there is an inability of the hand muscles to relax, once contracted, characteristic instead of myotonia. The finding of hypertrophied gastrocnemii is consistent with this long-standing myopathic disorder. Additionally, he gave a history of long-standing difficulty with writing that encouraged his clever use of a ping-pong ball to fashion a compensatory writing aid to treat his inability to relax the muscles of his hand and fingers.

Myotonia congenita is a hereditary muscle disorder characterized by impaired relaxation of skeletal muscle after voluntary contraction. The phenotypic presentation can be varied, and there are both dominant and recessive forms. In this case, the patient’s history of his sister and perhaps father with similar phenotypes suggests a dominant inheritance. These inherited forms are due to an abnormality of skeletal muscle chloride channel gene.³ Men may be affected
more frequently, and age of onset can vary considerably, with recessive cases being diagnosed at a later age. Some patients report cold weather to worsen symptoms, and a brief ‘warm-up’ effect is also reported, with initial energetic exercise allowing a patient to have diminished myotonia. Neither of these symptoms was described by this patient.

Neuromuscular disorders, including specific neuropathies (typically entrapment neuropathies) can mimic focal limb dystonia. The most commonly diagnosed disorders in the differential diagnosis of limb/occupational dystonias are of musculoskeletal origin, including thoracic outlet syndrome, bursitis, and tendonitis. Musculotendinous overuse has become the leading etiologic factor in the development of occupational cramps, with time and intensity of practice portending a higher risk.

This case is instructive because it illustrates that other neurologic disorders may superficially resemble dystonia, in this case myotonia congenita. Furthermore, it enforces the importance of taking a detailed history, as listening closely to this patient’s history raised a number of red flags casting doubt on the referring diagnosis of musician’s dystonia. These doubts were confirmed on examination, which showed that the predominant motor disorder was failure to relax a contracted muscle, characteristic of myotonia, rather than a limb assuming an abnormal posture, as would be expected of dystonia.

REFERENCES

Legend to video

Case 65 This shows the patient playing his guitar with no evidence of dystonia. There is no involuntary pulling, twisting, or turning of muscles of the hand or arm. In the audio segment the patient provides commentary on his compensatory mechanism and inability to relax his finger muscles in time to make an appropriate stroke of the strings. This is consistent with myotonia.
An intractable movement disorder cured

Stephen E Grill

CASE PRESENTATION

A 48-year-old woman with an 8-year history of multiple sclerosis (MS) was referred for a movement disorder. MS presented with optic neuritis and paresthesias of the feet. Three years later, she experienced severe gastroparesis requiring a feeding tube, and she was placed on metoclopramide. Approximately 1 year later she began having involuntary trunk and hip movements described as ‘swaying’. She subsequently developed orofacial dyskinesias and she was diagnosed as having tardive dyskinesia. The metoclopramide was stopped and she was put on tetrabenazine which helped, but only for about 6 months. She was next treated with risperidone followed by clozapine, but the movements persisted and were severe enough to affect her gait, and she limited her social activities because of embarrassment. At the time of the initial visit, the movements had been present continuously during her waking hours for the past 4 years.

On examination (see video, Case 66) she had continuous lateral deviations of the jaw as well as pursing movements of the lips. While sitting, there were choreiform movements of the trunk and rhythmic flexion at the hips. The legs were continuously adducting and abducting, more severe on the right. The upper limbs were uninvolved. There was a waddling gait with exaggeration of hip sway.

In light of the severity of her movements and the failure of medical therapy, the patient opted to undergo bilateral implantation of deep brain stimulating electrodes into the globus pallidus internas (GPi). Four weeks later, the stimulators were turned on and programmed using a low stimulus rate of 60 pulses per second starting with the left stimulator. After trying several electrode settings, the movements on the right side were essentially abolished, as were the movements on the left when the right stimulator was programmed (see video). She then had 5 days with virtually no involuntary movements, but returned for further programming on two occasions because the movements had returned to some extent. Since then, she has been largely free of the tardive dyskinetic movements.
Tardive dyskinesia (TD) is an iatrogenic condition of involuntary abnormal movements following chronic use of agents which block central dopamine receptors. The offending agents include antipsychotics and, as demonstrated in this case, antiemetics such as metoclopramide. The abnormal movements may include orolingual dyskinesias, chorea, athetosis, dystonia, and tics. Any body part may be involved, with the mouth being the most common. In some individuals the movements improve or resolve when the offending agent is stopped, but they are often permanent. Women, the elderly, and those with affective disorders (as opposed to schizophrenia) are at highest risk of developing tardive dyskinesia. The risk is increased with the use of classical antipsychotics (between 15 and 25% prevalence at 5 years) and is rare with atypical neuroleptics such as clozapine and olanzapine (1% per year). In a double-blind study, the risk of developing tardive dyskinesia was much less for olanzapine (0.52%) compared to haloperidol (7.45%).

The pathophysiology of TD is unknown. Hypotheses have included neuroleptic-induced denervation hypersensitivity of striatal dopamine receptors, γ-aminobutyric acid (GABA) ‘insufficiency’, and neurotoxic-induced structural changes in basal ganglia–thalamocortical circuits. Although some pathological changes have been reported in the brains of persons with TD (involving the inferior olive and basal ganglia), the findings are not universal.

The best treatment for TD is prevention, by avoiding the use of neuroleptics (and dopamine receptor-blocking antiemetics) whenever possible, using the lowest dose possible, and choosing atypical neuroleptics which have a lower risk of development of TD. Once present, a change from a conventional to an atypical neuroleptic should be considered. While medications remain the first treatment of choice for tardive dyskinesia, including tetrabenazine, reserpine, and others, for refractory cases (including tardive dystonia), deep brain stimulation has been demonstrated to be safe and highly effective.

This case is instructive because it demonstrates the potential of deep brain stimulation to treat medically refractory, disabling tardive dyskinesia.

REFERENCES


Legend to video

Case 66 In the first part of the video, there are choreiform abduction and adduction movements of the legs. While standing, she marches in place. There are also characteristic orolingual dyskinesias. In the second part of the video, bilateral globus pallidus interna (GPi) stimulators have been implanted and the patient is shown immediately after the initial programming session. While limb movements are absent, there is some persistence of the orolingual dyskinesias.
CASE PRESENTATION

A 52-year-old man reported an 8-month history of slowed movements in both upper extremities, associated with mild hand tremor present at rest and with action. He also dragged his right leg while walking, and had stiffness in both legs. The patient’s father-in-law had a long-standing history of Parkinson’s disease (PD) and took levodopa. The patient diagnosed himself with PD, and began taking his father-in-law’s medications. He had minimal benefit from carbidopa/levodopa 25/100-mg tablets, and so titrated the dosage on his own to 25/250 mg every 2 hours for a total of 8–10 tablets per day. He began ordering the medication over the Internet without a prescription and without consulting a physician. Three months later, he began experiencing involuntary restless movements that interfered with ambulation. These worsened as each dose of carbidopa/levodopa wore off and at the end of the day.

Motor examination revealed prominent choreiform movements in the distal upper and lower extremities at rest that increased with distraction (see video, Case 67). No rigidity or bradykinesia was appreciated. There was a mild bilateral action and postural tremor. Gait was broad-based due to persistent abnormal movements, and had a ‘goose-stepping’ character. There was no retropulsion on the pull test.

DISCUSSION

In this relatively young man, high doses of levodopa (up to 2500 mg/day) produced generalized dyskinesias within a few months after onset of therapy. Patients with young-onset PD are more likely to develop choreiform dyskinesias (75.8% vs 49.5%), dystonia (82.3% vs 49.0%), and motor fluctuations (90.1% vs 68.1%) compared to those with onset at a typical age. In a retrospective review, an inverse relationship between age at onset of PD and incidence of levodopa-induced dyskinesia (LID) was found: 52% of patients with PD onset at 50–59 years had LID during the first 5 years of treatment, whereas 26% of those with onset at 60–69 years and 16% of those with onset at 70–79 years had experienced LID in the same time period. Another study found that
100% of young-onset PD patients had developed LID and motor fluctuations by 10 years.4

Predictors of LID included age, female sex, body weight, Hoehn–Yahr score, age at onset of PD, duration of the disease, duration of levodopa treatment, and levodopa dose, in one sample of patients.5 The dose-dependent nature of LID was confirmed in a study of 361 patients with rigorously defined early-stage untreated PD.6 Here, 16.5% of patients treated with 600 mg/day of levodopa for 40 weeks developed LID, while only 2.3% of patients taking 150 mg/day and 3.3% of patients taking 300 mg/day did so. Although the higher doses of levodopa resulted in greater clinical benefit, the risk of developing motor complications was felt to be detrimental, and the authors recommend that lower doses (150 mg or 300 mg/day) are more appropriate initial targets in patients with early PD.

Because of the concern of precipitating motor complications with levodopa therapy, recent strategies in pharmacologic management of PD have centered on early treatment with dopamine agonists, although this strategy is not universally accepted.7 Most movement disorder specialists, however, probably agree that delaying the onset of levodopa therapy, particularly in young-onset PD, is prudent practice. In a study of ropinirole vs levodopa for 5 years in early PD, the cumulative incidence of dyskinesia was 20% (36 of 177 patients) in the ropinirole group and 45% (40 of 88 patients) in the levodopa group.8 The hazard ratio for remaining free of dyskinesias while taking ropinirole was 2.82 (95% confidence interval (CI) 1.78–4.44; p < 0.001). Similarly, initial pramipexole treatment resulted in significantly less wearing-off, dyskinesia, or on–off motor fluctuations (28%) compared with levodopa (51%) (hazard ratio 0.45, 95% CI 0.30–0.66; p < 0.001).9 In this study, levodopa resulted in greater reduction in total Unified Parkinson’s Disease Rating Scale (UPDRS) scores from baseline to 23.5 months, but at the expense of motor complications. However, it should be noted that some series of early-PD patients have reported development of LID as early as 5–6 months after beginning therapy.10

Therapeutic strategies that employ continuous dopaminergic stimulation have been advocated. Several studies have provided evidence that levodopa (with its short half-life) and short-acting dopamine agonists both result in pulsatile dopamine receptor stimulation, which in turn may precipitate motor fluctuations and LID.11 In animal models, the use of levodopa with catechol-O-methyltransferase (COMT) inhibitors at low and frequent doses has resulted in reduced dyskinesias and motor complications by simulating a more physiologic manner of dopamine receptor activation.12,13

This case of Parkinson’s disease with dyskinesias is instructive because it highlights the following clinical points: (1) LID and motor fluctuations may occur early in the course of levodopa-treated PD; (2) recent evidence suggests that levodopa is a reasonable option for management of early PD symptoms, but higher doses are associated with an increased risk of motor complications and low, frequent doses of levodopa are preferable; and (3) prescription medications may be obtained over the Internet and patients may not always reveal having done so.
REFERENCES


Legend to video

Case 67 In the first segment, the patient has mild, generalized choreiform levodopa-induced dyskinesias. He readily acknowledges self-dosing with levodopa as well as acquiring it over the Internet without a prescription. In the second segment, after a medication adjustment downward, the patient admits that he is doing better. There are few stigmata of PD. As he walks, there is decreased arm swing.
An elderly lady with ataxia and neuropathy

Joohi Shahed and Joseph Jankovic

CASE PRESENTATION

A 78-year-old woman presented with a 4-year history of dizziness when looking up (without vertigo) and loss of balance. In the last year she had developed numbness in her hands and feet. Her fine motor skills had deteriorated, with difficulty buttoning, doing needlework, and sewing. She was told that she had a cardiac arrhythmia, but no evidence of heart enlargement or failure. Her family history was significant for two of four sons with Friedreich’s ataxia (one with onset at age 38 years and a triplet repeat expansion of 275, and the other with symptom onset at age 40 years); a third has diabetes. The patient’s husband had a history of schizophrenia and was not in contact with the family. There was no history of consanguinity.

Neurologic examination showed intact cranial nerves without nystagmus, and normal speech, strength, and coordination. Sensation to all modalities was decreased in a length-dependent fashion in all four extremities. Reflexes were 1+ and symmetric with absent ankle jerks and absent Babinski signs. Gait was wide-based with short steps, and had an antalgic quality due to some knee pain. Romberg’s sign was present.

Nerve conduction studies showed a sensorimotor axonal neuropathy with markedly reduced amplitudes but normal latencies and velocities. Electromyography showed mildly reduced recruitment patterns and mild polyphasia. Work-up for reversible causes of neuropathy included erythrocyte sedimentation rate (ESR), rheumatoid factor (RF), antinuclear antibody (ANA), rapid plasma reagin (RPR), serum protein electrophoresis (SPEP), and vitamin B12, which were all normal. A prior evaluation for diabetes was negative. Brain magnetic resonance imaging (MRI) showed minimal periventricular white matter ischemic changes without evidence of cerebellar atrophy.

DISCUSSION

Friedreich’s ataxia (FA) is the most common autosomal recessive ataxia. It is a neurodegenerative disorder that typically presents before the age of 25 years and is characterized by progressive ataxia, dysarthria, sensory loss, absent
reflexes, and pyramidal weakness.\textsuperscript{1} The phenotype of FA, however, has been broadening since discovery of the causative gene, and includes hyperreflexia and spasticity as well as a variety of hyperkinetic movement disorders, including tremors, dystonia, and myoclonus.\textsuperscript{2} Associated features include cardiomyopathy, diabetes, scoliosis, and optic atrophy. It is diagnosed by demonstrating a GAA triplet repeat expansion in the X25 gene on 9q13–21 that encodes frataxin, a mitochondrial protein whose deficiency results in intramitochondrial iron accumulation and free radical damage. The majority of patients harbor homozygous mutations in the range of 70–1300, but a small percentage are compound heterozygotes with a point mutation on one allele and a triplet expansion on another.

This patient’s genetic testing revealed 1069 GAA repeats on allele 1 and 71 on allele 2 (Athena Diagnostics, Inc; normal $\leq$33, intermediate 34–66, expanded $\geq$67), indicating that she is homozygous for triplet repeat expansions on the X25 gene, and is likely to be affected with FA.

Repeat length in FA correlates with age at onset of symptoms and severity of the phenotype.\textsuperscript{3} However, the shorter allele expansion (GAA1) is the main determinant of the phenotype, while the longer expansion (GAA2) is poorly predictive.\textsuperscript{4} Thus, a patient with one allele that has a relatively short (<500) triplet repeat length is more likely to have a later age at onset, a longer disease duration before wheelchair dependence, and preserved tendon reflexes, regardless of whether the second allele has a larger repeat number. The phenomenon of ‘pseudodominant’ inheritance, similar to that seen here, has been well described.\textsuperscript{5} In a kindred with consanguinity, two brothers with the typical FA phenotype and childhood onset were homozygous for an expansion with 700–800 repeats, while two other siblings in a different generation with a late-onset phenotype and slow progression over decades had 250 repeats on one allele (paternally inherited) and 700 repeats on the other (maternally inherited).\textsuperscript{6} In other cases, heterozygote parents of affected children have been found to manifest mild ataxic features.\textsuperscript{7} Unstable transmission of allele size is well documented, such that genetic anticipation in subsequent generations is not uniform.

Age-related variants of FA include late-onset FA (LOFA) and very late onset FA (VLOFA). Patients with LOFA have essentially the same clinical features as those with typical FA, but the phenotype overall is milder, onset is between 25 and 39 years of age, and there is a slightly slower rate of progression.\textsuperscript{8} VLOFA cases are defined as having onset after age 40 years, and are also quite heterogeneous. In one review of the literature, repeat length combinations (GAA1/GAA2) ranged from 117/250 to 835/1200.\textsuperscript{9} Of the nine reviewed cases, one had cardiomyopathy, two had definite evidence of diabetes, eight had posterior column dysfunction, and all had ataxic features. The authors suggest that the diagnosis of VLOFA should be considered in those with onset of ataxia in the 5th or 6th decade.

McDaniel et al reported two brothers with mild ataxia and proprioceptive loss without cardiomyopathy or diabetes, whose symptoms began between ages 60 and 70.\textsuperscript{10} Genetic testing revealed 120–130 GAA repeats. Similar findings have prompted other authors to conclude that smaller repeat lengths are more likely to be associated with atypical disease.\textsuperscript{11}
The neuropathy of FA is typically sensory, with the posterior columns preferentially affected clinically. Electrophysiologic studies generally reveal normal or low-normal motor conduction velocities and absent sensory potentials.\(^{12,13}\) Cases of sensorimotor neuropathy mimicking Charcot–Marie–Tooth disease are described.\(^{14}\) In another series, sural nerve biopsy showed a severe loss of large myelinated fibers; teased nerve fiber preparations showed shortened internodes.\(^{15}\) No correlation was seen between electrophysiologic findings, histologic abnormalities, and clinical disability. Active denervation and signs of remyelination are typically absent. Unaffected family members were found to have mild neuropathic changes on electrophysiologic studies.

This patient was referred to our center for evaluation of FA. Her case is unusual because of the late age at onset of her symptoms and the presence of a sensorimotor axonal neuropathy. However, genetic testing demonstrates that she carries dual FA gene expansions. GAA1 in this patient, though lower than expected in typical FA cases, is nonetheless in the abnormal range. Her husband is an obligate carrier of the disease, and thus each of her children will at least also be a carrier of an abnormally expanded gene. Her two affected sons have otherwise typical LOFA.

This case of very late onset Friedreich’s ataxia is instructive because: (1) it demonstrates that FA should be considered in the differential diagnosis of ataxia at any age of onset, including the elderly; (2) it demonstrates a familial clustering of LOFA/VLOFA with ‘pseudodominant’ inheritance; as some authors have suggested, the presence of milder symptoms in parents does not preclude a diagnosis of FA in subsequent generations; (3) it demonstrates that cases with late onset FA can have a milder phenotype with less evidence of cardiac or endocrine involvement. And, finally, it demonstrates that widely differing repeat lengths can cause homozygosity for expanded FA alleles, and illustrates that the smaller of the two alleles, the GAA1 repeat number, is the more likely determinant of the disease phenotype. Treatment with high doses (45 mg/day) of the antioxidant idebenone has been shown to be well tolerated and result in a modest improvement in neurological function and activities of daily living.\(^{16}\)

REFERENCES


Leg and back cramps: psychogenic or organic?

Neil Mahant and Anthony E Lang

CASE PRESENTATION

A 56-year-old woman presented with a 3-year history of progressive ‘cramping’ in her left leg and back, associated with poor balance. Her symptoms had started with intermittent posturing of the left foot. At the time she was under consider-
able stress at work and at home. There was plantar flexion at the ankle and clawing of the toes while walking, which evolved to a fixed posture of the foot. She had been unable to put the foot flat on the floor for 2 years. Occasionally, the left leg would twitch involuntarily, mainly with kicking movements. There was pain involving the lumbar region and left leg. Mobility was impaired, including difficulty walking (especially if there was nothing to reach out to for support) and activities such as getting in and out of a car. She had multiple falls despite the use of a walking stick.

One year prior to our assessment, she had a severe ‘spasm’ while getting out of a car, with excruciating pain in the back and down the legs, and was unable to walk or get back into the car, lasting many minutes. Soon after this, she noticed that the left leg would kick and become stiff for about 30 seconds if she heard an unexpected noise. This was very painful. She stopped driving and became unable to walk without a walking aid. Clonazepam and baclofen were started, with an initial improvement in foot posture and resolution of the noise-induced spasms, although the symptoms gradually returned. She had also tried levodopa and trihexyphenidyl, without benefit. She tried withdrawing the clonazepam, but the symptoms again worsened and she began to fall backwards both spontane-
ously and in response to startle. One fall resulted in a wrist fracture. The right leg started to be affected 2 months prior to our seeing her, worsening her mobility so that she had marked difficulty arising from a chair and initiating walking, and was unable to walk without assistance. By this time, she could hardly bend the left knee.

She had lost 5 kg over the previous 6–12 months, and was recently diagnosed with subclinical hypothyroidism. She denied symptoms of major depression. She was taking clonazepam 2mg four times a day, paroxetine 20mg, and multivitamins. The patient was not pursuing legal action, or seeking compen-
sation or disability support. The family history was significant for her
82-year-old father being diagnosed with Parkinson’s disease and her mother with hypothyroidism.

On examination she was a vague historian, giving tangential answers lacking relevant detail. The affect was reactive and she did not look systemically unwell. All movements of the upper limbs were slow, without fatiguing or interruption of movement. Tone in the upper limbs was normal and the reflexes were normal to brisk. The paraspinal muscles were very firm, but not rock hard. The abdominal muscles were not overactive. The right ankle was fixed in near-maximal plantar flexion, and there was clawing of the interphalangeal joints of toes 2–5 bilaterally. There was intermittent extensor posturing of the great toes. The leg muscles were firm. Lower limb tone was markedly increased, with a lead-pipe rather than clasp-knife quality. There was no clonus. The left plantar response was flexor, and the right was equivocal. Leg movements were very slow, with little voluntary movement at the right ankle. The sensory examination was normal. She was unable to rise from a chair without help. She was unable to stand or walk unaided, and walked very slowly and cautiously on a broad base with the leg movements appearing very stiff; there was prominent plantar flexion of the ankles. In response to a loud unexpected handclap, while leaning forward against the examination bed, she jerked backwards and would have fallen if not caught. The remainder of the examination was normal. Some features of the initial examination are shown in the video (Case 69, first segment). Prior investigations were normal, including an electromyogram (EMG), and magnetic resonance imaging (MRI) of the brain and spinal cord.

We admitted her to hospital for a diagnostic work-up. After cautious withdrawal of clonazepam the clinical signs became more marked, and mobility deteriorated so that she became almost bed-bound. The startle response increased markedly. The abdominal and paraspinal muscles were rock hard, as were selected leg muscles. Tone in the legs increased to the point where it was very difficult to move the right knee or ankle at all (see video, second segment).

Physiologic testing demonstrated continuous motor unit activity in antagonistic muscles while attempting to relax the leg. Exteroceptive reflexes in response to tibial nerve stimulation were positive, with responses in leg and paraspinal muscles; there was a short latency response in trapezius following supraorbital nerve stimulation. These responses were at short latency, less than that required for a cortical relay and much less than voluntary reaction time.

High titer anti-GAD (glutamic acid decarboxylase) antibodies were found in serum and cerebrospinal fluid (CSF). Screening for diabetes was negative. The TSH (thyroid stimulating hormone) was mildly elevated, with a normal free T4 (thyroxine). Thyroid antibodies were negative. No other autoantibodies were detected.

With re-introduction of clonazepam, there was a slow but marked symptomatic improvement over 3-4 days. She was treated with intravenous methylprednisolone 500mg daily followed by oral steroids, tapering over 6 weeks to 10mg on alternate days. When re-assessed 6 weeks later, her condition had improved further and she was able to walk more than 100m with a quad stick. For the first time in approximately 12 months, she was able to walk several steps without any aid. The startle response disappeared and the pain markedly
improved. The abdominal and paraspinal muscles were soft to palpation and there was no startle response to handclap (see video, third segment).

**DISCUSSION**

The clinical, electrophysiologic, and immunologic findings in this patient supported the diagnosis of stiff person syndrome (SPS). SPS has been subdivided into classical stiff person syndrome, stiff limb syndrome (SLS), and progressive encephalomyelitis with rigidity and myoclonus (PERM). The clinical features of these conditions overlap, and patients may progress from SLS to classical SPS to PERM. The common feature is painful muscle spasms, typically with an exaggerated startle response, superimposed on an abnormal posture of the affected region – such as hyperlordosis of the spine or plantar flexion of the ankle. The startle reaction, spasms in response to unexpected stimuli, bears some similarity to hyperekplexia. Continuous motor activity in the affected muscles produces stiffness with features of both spasticity and rigidity, and muscles become hard to palpation. Reflexes are often increased. It may be possible to observe a startle response during the examination. Other clinical signs may be present – slowness resembling parkinsonism, brainstem myoclonus in the ‘jerking stiff man syndrome’, specific phobias, and tremor. Respiratory muscle involvement may cause dyspnea and mimic a panic attack. Other non-neurological and neurological diseases may coexist (including diabetes, thyroid disorders, vitiligo, pernicious anemia, cerebellitis, retinitis, and myasthenia gravis) – often associated with organ-specific autoantibodies.

Many patients with SPS are misdiagnosed with a psychogenic movement disorder. There are good reasons for this. First, features suggesting psychogenicity often accompany SPS. Many patients have stressful life events immediately prior to the development of permanent symptoms. Personality profiles may be abnormal and many patients have prior psychiatric diagnoses or substance abuse, possibly due to dysfunction of cerebral γ-aminobutyric acid (GABAergic systems). Second, many of the characteristic features of SPS resemble psychogenic disorders: exacerbation by stress, bizarre symptoms and signs, the presence of fixed posturing, and a level of disability out of proportion to the physical signs.

SPS should not be regarded as a diagnosis of exclusion – the clinical features and targeted investigations should enable an accurate diagnosis in most patients. Benzodiazepines may mask important clinical and electrophysiologic signs, and examination off medications should be attempted if possible. Appropriate investigations to rule out other diagnoses (e.g. imaging of brain and spinal cord, needle electrode examination of affected muscles to detect neurogenic discharges), to confirm the diagnosis of SPS (anti-GAD assays, electrophysiologic studies), and screen for associated conditions (e.g. diabetes, thyroid diseases, vitamin B12 level) should be performed. Psychiatric evaluation may be helpful in selected cases, but should not be used to diagnose or exclude psychogenic factors.

The differential diagnosis includes neuromuscular disorders (e.g. neuromyotonia, myotonia, and amyotrophic lateral sclerosis), spinal cord lesions, parasagittal
lesions, and extrapyramidal disorders (e.g. dystonia, lower-limb onset corticobasal degeneration). Satoyoshi’s syndrome is a rare multisystem disorder, characterized by painful muscle spasms associated with alopecia, gut, endocrine, and skeletal abnormalities. There may be some overlap between Satoyoshi’s syndrome and SPS - it often responds to immunotherapy, and anti-GAD antibodies have been reported in one patient.

The presence of high titer anti-GAD antibodies in 50–75% of cases, the association with other autoimmune conditions, and the response to immune suppression all suggest an autoimmune etiology of SPS. GAD is the rate-limiting enzyme of GABA synthesis, and serum from SPS patients inhibits GAD activity in vitro. However, GAD is an intracellular enzyme, and it is unclear whether the antibodies are directly pathogenic or a marker of an autoimmune response against GABAergic neurons. There is no apparent difference between patients with and without anti-GAD antibodies, clinically or in terms of response to treatment. Low titer anti-GAD antibodies may be present in other diseases, primarily type 1 diabetes. Various immunomodulatory therapies may be effective for SPS, including steroids, intravenous immunoglobulin, and plasma exchange. The result is reduced GABAergic transmission, primarily in the spinal cord, although brain GABA levels are low on magnetic resonance spectroscopy. Medications enhancing the GABA system give effective symptomatic benefit.

Benzodiazepines are the mainstay of symptomatic treatment, but very high maintenance doses may be required, and severe spasms may require large doses of intravenous benzodiazepines. Other GABAergic medications may also be effective, including baclofen, valproate, and vigabatrin. Intrathecal baclofen may be particularly effective, though abrupt withdrawal may be life-threatening.

There are few data concerning the prognosis of SPS. Without immunomodulatory therapy, the course may stabilize but is often progressive. High dose intravenous corticosteroids followed by maintenance oral steroids may induce a lasting partial or complete remission. Some patients require repeated courses of steroids. Regular cycles of intravenous immunoglobulin or plasma exchange are needed because the response is transient.

Paraneoplastic SPS may affect primarily the upper limbs or may progress over a few months to severe contractures, but may be indistinguishable from conventional SPS; antibodies may be directed against GAD or amphiphysin. It may respond poorly to benzodiazepines. Responses to immunotherapy and tumor treatment have been reported.

This case is instructive because it demonstrates that:

- SPS and its variants are difficult to diagnose, the most frequent misdiagnosis being a psychogenic disorder. SPS often has features suggestive of a psychogenic disorder, and conversely psychogenic disorders may mimic SPS.
- The differential diagnosis of SPS includes: Satoyoshi’s syndrome, paraneoplastic syndromes, spinal cord lesions, amyotrophic lateral sclerosis, and others.
sclerosis, and parkinsonian disorders such as corticobasal degeneration or, less often, symptomatic dystonia.

- The hallmark of SPS is painful spasms on a background of muscle stiffness. Other features that raise the possibility of SPS are: startle-induced spasms or falls, fixed posturing, atypical spastic mono- or diplegia, a history of muscle stiffness responding to GABAergic medication, and ‘parkinsonism’.
- A wide range of neurologic and immunologic disorders may accompany SPS.
- Helpful diagnostic tests for SPS include anti-GAD antibodies and electrophysiological testing (to document the presence of continuous motor unit activity and pathological exteroceptive reflexes).
- SPS may respond to immunomodulatory treatment. Intrathecal baclofen can be used under close supervision. Symptomatic treatment with high doses of benzodiazepines should not be withheld. All forms of treatment are most effective at reducing the spasms, and less effective at reducing the background level of stiffness.

REFERENCES

Legend to video

Case 69  First segment: initial assessment. The patient is taking clonazepam 9 mg/day. A stiff appearing gait with abnormal posturing of the trunk and legs is characteristic. She is unable to stand without support. A handclap-induced startle response led to a fall. The lumbar paraspinal muscles are well defined and firm to palpation. There is abnormal posturing of the ankles and toes, with impaired voluntary movement. Second segment: assessment on admission to hospital. The clonazepam has been tapered and stopped, the last dose taken 24 hours prior to the video. The patient describes her worsened symptoms. Voluntary movements are slower and more stiff in appearance and the truncal muscles have become rock hard. Third segment: follow-up 6 weeks after intravenous steroids. The patient describes the changes following treatment. There is improvement in posture and stiffness. The gait has improved to the point of her being able to take several steps without aid.
Early-onset chorea progressing to an ataxic syndrome

Thamer Al-Khairallah and Anthony E Lang

CASE PRESENTATION

This 18-year-old girl was a product of normal term pregnancy and uneventful perinatal period. She attained normal developmental milestones. Beginning at age 3 years her family noted abnormal ‘dance like’ movements primarily involving the limbs. Over the next 5 years, she was also noticed to have problems with coordination, especially riding a bicycle, printing, and in gym classes. Motor problems did not significantly interfere with her day-to-day living, and she progressed in school with above average grades, and interacted normally with her peers. The complaints were steadily, yet slowly, progressive. Over the course of follow-up, incoordination gradually became more prominent and disabling than the original abnormal limb movements.

Family history was significant for an uncle with similar symptoms, but no further details could be ascertained as he was estranged from the family. She was the only child of a consanguineous relationship. Both parents were healthy. She had had no history of frequent infections or other serious illnesses.

When we first saw her at age 8 (see video, Case 70, first segment), there was normal cognitive function for age. She could read well and follow complex commands. Eye movement examination was significant for slow, hypometric saccades. She used head thrusts to permit rapid re-fixation of vision. She had prominent saccadic pursuit. The remainder of the cranial nerve examination was unremarkable. Her speech was normal except for rare breaks associated with generalized chorea, which was of moderate severity and affected all limbs in addition to her trunk. Motor examination was otherwise unremarkable. She had generalized hyporeflexia with flexor plantar responses. There were no significant cerebellar signs. Gait was characterized by excessive arm movements, and tandem gait was mildly impaired apparently because of the chorea.

By age 18 she had developed limb and gait ataxia and cerebellar dysarthria. She continued to demonstrate chorea, ocular motor apraxia, and gaze-evoked nystagmus, and also had mild dystonic posturing of her feet (see video, second segment). She had no telangiectasia, musculoskeletal deformities, xanthomata, or palpable nerves. General physical examination was normal.
Investigations included normal levels of α-fetoprotein and vitamin E, normal chromosomal breakage studies and radiosensitivity testing, and normal antinuclear and anticardiolipin antibodies, serum copper, ceruloplasmin, and 24-hour urine copper. Her chemistry profile showed hypoalbuminemia and hypercholesterolemia. Her brain magnetic resonance imaging (MRI) revealed mild cerebellar atrophy. Electromyography (EMG) and nerve conduction studies demonstrated a mild sensory axonal polyneuropathy.

**DISCUSSION**

This patient suffers from a slowly progressive neurodegenerative syndrome that is characterized by chorea, ataxia, ocular motor apraxia (OMA), and polyneuropathy that started at the age of 3 years. There is perhaps a family history of similar illness, and her parents, although neurologically normal, are related, suggesting an autosomal recessive mode of inheritance. Ataxia–telangiectasia (AT) and Friedreich’s ataxia (FA) are among the most well known autosomal recessive cerebellar ataxia (ARCA) syndromes. Ataxia–telangiectasia patients have ataxia, OMA, and polyneuropathy. Our patient does not have immunodeficiency, telangiectasia, or susceptibility to ionizing radiation, and her α-fetoprotein level is normal, which makes this diagnosis unlikely. FA is the most common ARCA. However, our patient’s clinical presentation is not typical of FA, especially the ocular motor disturbances; the extraneurological features of FA are lacking (such as cardiomyopathy, diabetes, and scoliosis); and she has cerebellar atrophy on MRI of the brain which is not a feature of FA. Ataxia- and polyneuropathy-associated vitamin E deficiency is a readily treatable, though rare, condition, and as such should be considered in patients with undiagnosed ataxia.

Chorea was the predominant presenting feature, coupled with ocular motor apraxia. Huntington’s chorea was considered, but was felt to be unlikely as her disease evolved into an ataxic syndrome without much behavioral or cognitive decline. Benign hereditary chorea is excluded, given her prominent ataxia and ocular motor abnormalities. Autoimmune causes of chorea were ruled out with appropriate laboratory tests.

Our patient’s disorder fits the clinical description of ataxia oculomotor apraxia type 1 (AOA1). This is an autosomal recessive ataxia with onset range between ages 2 and 18 years (mean 6.8±4.8 years). Chorea may be prominent at onset but fades with time, and as the disease progresses it is dominated by ataxia and peripheral neuropathy. All patients with AOA1 should eventually have cerebellar ataxia, cerebellar atrophy on MRI, axonal sensory motor neuropathy which may become pronounced, and some degree of cognitive impairment that typically develops later in the course of the illness. Hypoalbuminemia and hypercholesterolemia also develop as the disease progresses. In one case series, ocular motor apraxia was present in 86%, low albumin in 83%, chorea at onset in 79%, and high cholesterol in 75% of patients. The disease is steadily but slowly progressive, and patients eventually become wheelchair-bound in a mean of 11.6 years. Patients with AOA1 typically lack musculoskeletal or other extraneurological features.
Earlier literature referred to this disorder as early-onset cerebellar ataxia with ocular motor apraxia and hypoalbuminemia (EAOH). The discovery of mutation in the gene APTX on chromosome 9q13, which encodes the protein apraxatin, has encouraged the use of the single term AOA1. A second form of AOA (AOA2) demonstrates gait ataxia, OMA, dystonia, and strabismus. It is generally a milder form of ataxia with an older age of onset (around 15 years), and takes longer until a wheelchair is required (around 16 years). It is associated with high α-fetoprotein levels. AOA2 is inherited as an autosomal recessive trait; the gene has recently been identified (sentaxin) on chromosome 9q34.

This case is instructive because it provides the clinical and diagnostic approach to autosomal recessive cerebellar ataxia. Some of these conditions are treatable and others have complications that are preventable and/or treatable if detected early. This case is also an example of how chorea can sometimes be a presenting feature of ataxic syndromes.

REFERENCES

Legend to video
Case 70  First Segment: this clip shows the subject at 8 years. Chorea is the dominant feature with very mild limb ataxia. She also has ocular motor apraxia (not shown). Second segment: this was taken at age 17 years. She has ocular motor apraxia, prominent cerebellar ataxia, mild dystonic posturing, and chorea.
Hemisensory syndrome with an ‘upgoing toe’

Niall Quinn

CASE PRESENTATION

In late 1976 at the age of 44 this woman complained of a numb feeling in her right leg below the knee. A few days later her right face became involved and then her right arm, then the left leg. She was seen as an outpatient by Queen Square consultant number one who found only increased reflexes on the right with an extensor right plantar response. When admitted for investigation no hard signs were found. Despite the complaint of numbness on her right side, no sensory loss was demonstrated. Cerebrospinal fluid (CSF) showed no oligoclonal bands, and visual-evoked potentials were normal, as were sensory and motor nerve conduction. A diagnosis of probable demyelination was made.

In May 1977 she saw Queen Square neurologist number two who noted an increase in tendon jerks on the right and an equivocal right plantar, and again diagnosed probable demyelination. In February 1978 she saw Queen Square neurologist number three who again considered demyelination most likely. In 1980 she saw Queen Square neurologist number four who again found the right tendon jerks brisker than the left and agreed with the probable diagnosis of demyelination. In 1981 she saw Queen Square neurologist number five who found no objective neurological signs and suggested she see a psychiatrist.

In January 1984, she again saw Queen Square neurologist number four, who this time elicited a history of tremor of the right arm and leg at rest for the last 2 years. The plantar responses were equivocal, facial expression was diminished, and arm swing was absent on the right. Repeat CSF showed no oligoclonal bands, and copper studies and computed tomography (CT) scan were both normal. Magnetic resonance imaging (MRI) of the brain was normal.

DISCUSSION

Parkinson’s disease was diagnosed 7 years after the initial symptom of hemi-numbness. I first encountered this lady in 1988 and continue to follow her. She has relatively benign levodopa-responsive tremulous Parkinson’s disease, now of 29 years’ duration, with motor fluctuations and dyskinesias, and is currently being worked up for the possibility of deep brain stimulation.
Parkinson’s disease typically begins unilaterally or asymmetrically, and aching or pain syndromes, particularly frozen shoulder, may be common presenting features.\(^1\) In addition to pain and aching, other sensory symptoms are not uncommon in Parkinson’s disease\(^2\)–\(^7\) and, as in this case, it may present with a hemisensory syndrome. Although sophisticated techniques may reveal subtle sensory abnormalities, sensory impairment on routine clinical bedside testing (with the exception of olfaction) does not occur in Parkinson’s disease. Reflexes are commonly slightly brisker on the more affected side, and the difficulty of distinguishing the striatal toe from a true Babinski response is well recognized.

This case is instructive for three reasons. First, it illustrates that Parkinson’s disease should be in the differential diagnosis of a patient presenting with an unexplained hemisensory syndrome. Second, it emphasizes that sensory symptoms, including pain, are common in Parkinson’s disease, and may be the presenting complaint (Table 71.1). Third, it indicates that even neurologists at Queen Square are not always right, at least first time around!

### Table 71.1  Sensory manifestations of Parkinson’s disease

<table>
<thead>
<tr>
<th>Sensory manifestation</th>
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</thead>
<tbody>
<tr>
<td>Cramps (especially leg)</td>
</tr>
<tr>
<td>Pain</td>
</tr>
<tr>
<td>Painful dystonia (especially of the foot)</td>
</tr>
<tr>
<td>Restless legs syndrome</td>
</tr>
<tr>
<td>Paresthesias, numbness, and burning</td>
</tr>
<tr>
<td>Internal tremor</td>
</tr>
<tr>
<td>Akathisia</td>
</tr>
<tr>
<td>Dyspnea</td>
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<tr>
<td>Fatigue</td>
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</table>

**REFERENCES**

Rapid-onset dystonia-parkinson in a brother and sister

Allison Brashear

CASE PRESENTATIONS

A 15-year-old girl with severe hearing loss from childhood meningitis was admitted to a psychiatric unit due to behavior disturbance. At discharge 4 weeks later, the family noted a gaping mouth, drooling, and a clumsy gait. Over the next month her symptoms progressed until she was unable to walk, use her arms to sign, or swallow. She became bedridden and was admitted to hospital.

On examination she had normal eye movements, drooling, and a gaping mouth with a sardonic grin. She was unable to stand or eat. Severe dystonic spasms in the arms and hands made it impossible to sign, and the legs were extended making walking difficult. Treatment with carbidopa/levodopa 75/750 per day resulted in mild improvement allowing her to use her hands to eat and sign. She required a gastrostomy tube due to persistent aspiration of solids and liquids. Over the last 15 years she has had some improvement on dopamine agonists. When pergolide was weaned she reported increased painful spasms in the arms and legs. Initiation of ropinirole and diazepam resulted in fewer leg spasms, but she remains wheelchair-bound and unable to communicate beyond rudimentary sign language.

The brother of the woman described above reported stiffness in his legs at age 16 years. Over 5 weeks he began falling and developed leg and arm spasms, dysarthria, and dysphagia. Examination demonstrated dysarthria, normal limb strength and dystonic spasms affecting the entire body. There were frequent dystonic spasms affecting the entire body. His arms would internally rotate and deviate behind his back with such force that he was unable to pull them back in front of him. The patient was unable to walk independently and had significant postural instability.

Imaging studies were normal. Cerebrospinal level of the dopamine metabolite, homovallinic acid (HVA), was low at 27.2 ng/ml (normal 72.0 ± 10.2 ng/ml), with normal levels of norepinephrine and serotonin metabolites. A trial of carbidopa/levodopa gave minimal improvement, but 2 weeks after the addition of pergolide he began to talk and eat. Walking remained significantly impaired.
Since the admission at age 16 the patient has stopped both levodopa and pergolide due to lack of sustained effect, and he reported that levodopa caused headaches. His current examination is unchanged compared to 15 years ago, with severe dysarthria, dysphagia, postural instability, and dystonic spasms in the arms and legs. With sensory tricks of moving his arm in circles (see video, Case 72) he is able to speak and walk without assistance.

DISCUSSION

These siblings have a rare condition known as rapid-onset dystonia–parkinsonism (RDP). It is characterized by the abrupt onset of dystonia and parkinsonism over days to weeks with little response to levodopa or other medications. In July 2004 we reported six different mutations in the ATP1A3 gene as the cause of RDP in seven families worldwide. RDP is the first neurologic disease to be caused by the α3 subunit of the Na/K adenosine triphosphatase (ATPase).

First described in a single family, classic RDP has been characterized as an autosomal dominant disorder with variable penetrance, presenting in the second or third decade usually after a physiologic stressor. Typical RDP presents over hours to days with stabilization over weeks and little or no improvement thereafter, although more recent cases suggest mild improvement in some and abrupt exacerbations in others.

While RDP is the first disease to be associated with ATP1A3, two neurologic diseases are associated with mutations in ATP1A2: infantile seizures and familial hemiplegic migraine (FHM). Missense mutations in chromosome 1q23 in the ATP1A2 gene encoding Na/K ATPase α2 subunit have been reported in four families with familiar hemiplegic migraine type 2.

The mechanism of familial hemiplegic migraine type 2 associated with the ATP1A2 subunit mutations has been proposed to be related to other genetic forms of migraine caused by the CACNA1A mutation (gene responsible for FHM type 1) through the interaction of the Na+/Ca2+ exchanger. If the ATP1A2 gene is impaired then an impaired clearance leads to elevated extracellular K+ and increased intracellular Na+. The elevated intracellular Na+ leads to increased intracellular Ca2+ through the nearby Na+/Ca2+ exchanger. The investigators of the ATP1A2 mutation propose that this increase in intracellular Ca2+ is responsible for the phenotypic similarity to FHM type 1, where the mutation of the α subunit of the voltage-gated P/Q-type calcium channel encoded by CACNA1A have been identified. How this abnormality in the ATP1A2 gene applies to the ATP1A3 gene mutations associated with RDP is unclear.

These cases are instructive because they illustrate the presentation of classic RDP, which should be considered in the differential diagnosis of atypical dystonia–parkinsonism syndromes. While RDP is rare, the known cases in the world were previously incorrectly diagnosed for years. The discovery of several cases of de novo mutations challenges previous thoughts that a family history is required for diagnosis. The Na/K ATPase α3 subunit mutation as the cause of RDP is the most recent dystonia gene to be described.
REFERENCES


Legend to video

Case 72. The first segment shows the proband with rapid-onset dystonia-parkinsonism. She is wheelchair-bound. There is severe dystonia involving all limbs and lower face with jaw-opening dystonia. She requires assistance to arise from the wheelchair, stand, and walk. There is severe impairment of postural righting reflexes. The second segment shows the brother of the proband, also in a wheelchair. There is severe dystonia involving all limbs, the trunk, and neck. He is eventually able to stand unsupported.
A young man with psychosis, ataxia, and signal changes in the splenium

SH Subramony, L Langford, and L Voulters

CASE PRESENTATION

This 39-year-old African-American man was referred for progressive ataxia and pontocerebellar atrophy seen on magnetic resonance imaging (MRI) scan. Until age 31 he had been a high achiever, having obtained more than one college degree, and worked for the Texas state government. At that time he was admitted to the Mississippi State Hospital with a ‘nervous breakdown’. The details of this admission were unavailable. He has received psychotropic medicines since then. He subsequently developed progressive imbalance, speech difficulties, and impaired coordination. Increasing dysphagia and significant weight loss followed. A percutaneous endoscopic gastrostomy (PEG) tube had been placed shortly before the referral. His responses had become slower, but the mother maintained that he was cognitively intact. His medications at the time of examination included haloperidol, benztropine, cyclobenzaprine, and olanzapine. His medical history and review of systems were notable only for an old abdominal gunshot wound. He smoked cigarettes and did not drink alcohol. The family history was sketchy, but his mother was not aware of any similar illness on either her side or the father’s side of the family.

When examined at age 39, he was alert, attentive, and oriented in all spheres. Questions focused on recent and remote events were answered correctly but after a long delay. His insight into his illness and reasons for further medical evaluation was appropriate. Cognitive decline was excluded by detailed neuropsychological testing. There was no language abnormality but speech was severely dysarthric with both spastic and scanning qualities. The cranial nerve examination revealed normal fundi and visual fields. Eye movements were normal except for constant saccadic intrusions into pursuit. There was no nystagmus or any abnormalities of saccades. He tended to keep his jaw open. Motor examination was characterized by normal bulk and strength in all muscle groups. Tone was diffusely increased. Kinetic tremor and dysmetria of limbs were noted. Sensory examination revealed no abnormalities. Deep tendon reflexes were normal and symmetric and plantar reflexes were flexor. Stance was broad-based and gait very ataxic, requiring support of considerable nature.
Review of the MRI that accompanied the patient showed pontocerebellar atrophy (Figure 73.1A). In addition, FLAIR (fluid attenuated inversion recovers) sequences revealed a high signal change in the splenium of the corpus callosum (Figure 73.1B) that was less clearly visible on T2 images.

DISCUSSION

The differential diagnosis of an ataxic syndrome in a young man associated with pontocerebellar or cerebellar atrophy is broad (Table 73.1). In general, apparent sporadic, idiopathic ataxia is more likely to be seen in the elderly, but at no age can a genetic etiology be ruled out completely. In patients with young adult- or childhood-onset ataxia, a genetic etiology is likely, despite the absence of a family history. Such genetic disorders include a number of autosomal dominant and recessive diseases that can be defined by DNA based tests as well as many diseases that can be diagnosed by more traditional ‘biochemical’ analyses.

The type of evaluation indicated in a patient with ataxia is to some extent determined by the accompanying features, but in the patient we saw there were no outstanding clues as to the direction to be taken. We explained the situation to the family that the precise underlying etiology was not clear, and a variety of tests of differing complexity and expense could be obtained. Some could lead to potentially useful therapy; others would allow more precise genetic counseling. As a preliminary exploration, we obtained a complete chemistry panel, thyroid function, vitamin B12 levels, complete blood count (CBC), rapid plasma reagin (RPR), human T-cell lymphotrophic virus type 1 (HTLV 1) serology, human immunodeficiency virus (HIV) antibody, serum lactate and pyruvate, ceruloplasmin levels, serum long chain fatty acids, and an ataxia DNA panel. All of the laboratory values were normal except for the serum very long chain fatty acids, done by the Kennedy Krieger Institute in Baltimore, Maryland. The C26:0 value was 0.980µg/ml (normal 0.24±0.14) and the C26/C22 and C24/C22 ratios were
Psychosis, ataxia, and signal changes in the splenium  303

Table 73.1  Some of the differential diagnostic considerations in a young man with ataxia

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Clinical clues</th>
<th>Diagnostic tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Friedreich’s ataxia</td>
<td>Abnormal sensory nerves; proprioceptive loss; areflexia (not universal)</td>
<td>MRI: no cerebellar atrophy but spinal cord atrophy; FA gene test</td>
</tr>
<tr>
<td>SCA1, 2, 6, 7, 10, 17, and MJD</td>
<td>Usually clear AD history Diminished DTR in SCA2; visual loss in SCA7; seizures in SCA10</td>
<td>MRI: pontocerebellar atrophy; CAG repeat expansion analysis</td>
</tr>
<tr>
<td>Mitochondrial diseases</td>
<td>Myopathy with PEO; retinal changes; exercise intolerance</td>
<td>Serum/CSF lactate and pyruvate; mtDNA mutation analysis; muscle biopsy</td>
</tr>
<tr>
<td>Ataxia with isolated vitamin E deficiency</td>
<td>Associated neuropathy; retinal changes</td>
<td>Vitamin E levels</td>
</tr>
<tr>
<td>Ataxia/oculomotor apraxia</td>
<td>Oculomotor apraxia; not all patients have this</td>
<td>Aprataxin mutation test; senataxin mutation analysis</td>
</tr>
<tr>
<td>Cerebrotendinous xanthomatosis</td>
<td>Tendon xanthoma</td>
<td>Serum cholesterol</td>
</tr>
<tr>
<td>PDHC deficiency</td>
<td>Episodic symptoms</td>
<td>PDHC activity in fibroblasts</td>
</tr>
<tr>
<td>Adrenoleukodystrophy</td>
<td>White matter changes on MRI; Addison’s disease</td>
<td>Serum very long chain fatty acids; X-ALD gene mutation analysis</td>
</tr>
<tr>
<td>Wilson’s disease</td>
<td>Basal ganglia features and liver disease</td>
<td>Serum copper/ ceruloplasmin</td>
</tr>
<tr>
<td>Toxic ataxias</td>
<td>Alcohol/solvents use/ dilantin use</td>
<td></td>
</tr>
<tr>
<td>Immune/infectious causes</td>
<td>HIV; related to anti-GAD antibody (usually diabetic women)</td>
<td>HIV serology; anti-GAD antibody</td>
</tr>
</tbody>
</table>

SCA, spinocerebellar ataxia; MJD, Machado-Joseph disease; AD, autosomal dominant; DTR, deep tendon reflexes; PEO, progressive external ophthalmoplegia; CSF, cerebrospinal fluid; mtDNA, mitochondrial DNA; PDHC, pyruvate dehydrogenase complex; X-ALD, X-linked adrenoleukodystrophy; HIV, human immunodeficiency virus; GAD, glutamic acid decarboxylase.

abnormally elevated (0.031 and 1.396 with normal being 0.01 ± 0.003 and 0.78 ± 0.10). These were consistent with the biochemical defect of adrenoleukodystrophy/adrenomyeloneuropathy (ALD/AMN). A repeat specimen was sent to the laboratory with the same results.

The patient unfortunately did not return for follow-up despite our efforts, but was admitted to a rehabilitation facility where he died of medical complications. No mutation analysis of the X-ALD gene was performed, and adrenal function was not assessed. In retrospect, the features that may have pointed to this diagnosis included a history of a psychotic disorder, which often occurs at initial presentation in adult-onset cases, and the abnormal white matter in the splenium of the corpus callosum. His course of relatively rapid decline to a completely dependent stage and death in 8 years after onset also was atypical for the more common autosomal dominant and recessive ataxias such as the spinocerebellar ataxias (SCAs) and Friedreich’s ataxia.
X-linked adrenoleukodystrophy most commonly presents as a childhood cerebral form with behavior changes, rapid progression to disability, and cerebral white matter changes on MRI. Yet it, and adrenomyeloneuropathy (AMN) with spastic paraparesis, may also present in young adulthood, or even later, in which case the MRI is abnormal in less than half the cases, and both are associated with adrenal insufficiency.2 There are patients who can have the cerebral form of disease, but with adolescent or adult onset; others may have adrenal insufficiency only or be asymptomatic.2 Some female heterozygous carriers may also exhibit a phenotype resembling AMN. Different phenotypes can occur in the same family and there are no specific phenotype–genotype correlations.3 Rare cases of ALD presenting as a ‘spinocerebellar ataxia’ have been reported.4–6 No MRI findings have been reported in these cases, but computed tomography (CT) scan showed pontocerebellar atrophy in one case, and in another cerebellar and brainstem white matter was preferentially affected at autopsy.

This case is illustrative because it emphasizes the need to keep adrenoleukodystrophy in the differential diagnosis of a progressive cerebellar syndrome in children as well as adults even when the MRI does not show typical changes in the white matter.

REFERENCES
An unusual jaw tremor

Dan Tarsy and Susie I Ro

CASE PRESENTATION

A healthy 66-year-old woman reported the sudden onset of jaw tremor 4 years previously, which had progressed slowly to the present time. It occurred only when speaking (especially the letter ‘s’) or attempting to drink from a glass, and disappeared when eating or at rest. It did not interfere with chewing or swallowing and she was unaware of voice tremor or dysarthria. The tremor was embarrassing, was aggravated by stress, and improved following a glass of wine. There was no family history of tremor or dystonia and no exposure to neuroleptic drugs. A swallowing study was normal.

On examination there was no jaw tremor at rest with her mouth closed or when held wide open. With her mouth held partially open there was a rhythmic 5-Hz tremor of the mandible with an amplitude of up to 2 cm. It increased while speaking or holding a cup of water to her lips, and could be suppressed by closing her mouth. Tremor also appeared when holding a pen near her mouth with her jaw slightly open. Her voice was slightly tremulous. There was no palatal, head, trunk, or extremity tremor. There were no signs of dystonia or parkinsonism and the remainder of the neurological examination was normal.

Two-channel electromyography showed an absence of spontaneous muscle activity with the mouth closed and relaxed. With slight jaw opening, a 5-Hz rhythmic tremor was present, with an alternating pattern of activity in masseter and digastric muscles (Figure 74.1). Tremor was similar while holding a cup to her lips (see video, Case 74). Tremor amplitude was 100μV and equal in digastrics and masseters with optimal electrode placement. There was normal reciprocal inhibition in that further jaw opening was associated with increased digastric and reduced masseter activity while the reverse occurred with jaw closing. Tremor was absent with jaw clenching or maximal jaw opening.

Botulinum toxin (BOTOX®) injections into digastrics (10 units bilaterally) and masseters (45 units bilaterally) on six occasions have produced marked relief of jaw tremor, lasting for 3 months.

DISCUSSION

Jaw tremor occurs in a number of unrelated conditions, including Parkinson’s disease, dystonia, essential tremor, palatal tremor, drug-induced tremor, geniospasm, and shivering.1 In these conditions it is typically associated with tremor in
other body areas, and other motor findings are present. Isolated jaw tremor is unusual, and has only rarely been reported.\textsuperscript{2,3} This patient’s tremor was absent at rest and appeared only with speaking, when holding the jaw slightly open, or when drinking from a glass. Its positional sensitivity resembles tremors involving the arm or hand, such as primary writing tremor in which writing or even assuming a posture of holding a pen activates hand tremor. Such tremors are sometimes also task-specific in that other manual tasks requiring a similar posture may be unaffected.\textsuperscript{4} In our patient, tremor was not task-specific but predictably occurred when the jaw was held partially open, regardless of the task. Electromyography was helpful in this case by identifying the antagonist muscles affected by tremor, and by demonstrating normal reciprocal inhibition between these muscles, thereby excluding dystonia or dystonic tremor.\textsuperscript{4}

Miles et al reported a similar patient with 6-Hz jaw tremor which occurred only when drinking from a glass or bringing the teeth together but not while speaking or eating.\textsuperscript{2} Unlike our patient, tremor was limited to the digastric muscles while sparing the masseters. Because speaking and eating were unaffected, they felt that the tremor was task-specific, and most closely resembled primary writing tremor. No treatment was reported. In our patient the clinical and electromyographic features were more consistent with a position-sensitive tremor. Another patient with focal jaw tremor with different clinical features has been reported.\textsuperscript{3} This was a 16-Hz jaw tremor which resembled chattering of the teeth. Tremor was present at rest, was intermittent, and could be suppressed by clenching or opening the jaw widely. Electromyography showed synchronous

![Figure 74.1 Tremor recording with needle electrodes in right masseter and right digastric muscles.](image-url)
An unusual jaw tremor

rather than alternating activation of antagonist muscles, and, because of its high frequency, it was thought to be a variant of primary orthostatic tremor.

This case is instructive because it considers the differential diagnosis of jaw tremor\(^5\) and provides an example of a rare form of focal, position-sensitive tremor responsive to treatment with botulinum toxin. Whether this is a variant of essential tremor or a unique form of focal tremor is a matter of speculation at this time.

REFERENCES


Legend to video

**Case 74** Position-sensitive tremor activated by slight opening of jaw and sipping from a cup. Two-channel needle electromyography shows 5-Hz jaw tremor with alternating pattern of activity in right masseter and digastric muscles.
What looks like Huntington’s disease but isn’t?

Sanjay S Iyer, John C Morgan, Jason Speir, and Kapil D Sethi

CASE PRESENTATION

A 41-year-old African-American woman presented with a ‘nervous condition’ that had begun approximately 2 years previously. Her family described her as constantly moving, fidgety, jerky, and unable to sit still. The abnormal jerks also complicated her gait. They also reported a gradual personality change over 2 years, citing new episodes of impulsivity and rage. She was a college graduate and had worked in a supervisory position. She reported that her job performance had deteriorated because of difficulties with memory and multitasking. She eventually had to move into her mother’s apartment and relinquish control of her finances because of multiple mistakes she had made with bills.

She had no other medical problems and denied a family history of a similar illness. Her mother, age 67, was healthy. Her father was described as very irritable and impulsive. He often ‘squirmed around’ and was very ‘nervous’. He had abandoned the family 15 years prior and died in a nursing home of ‘some brain disease’ not further characterized. She has three children, all currently asymptomatic. The patient denied use of tobacco, alcohol, or illicit drugs and denied exposure to dopamine blocking agents.

On examination, she was oriented to person and month. Her Mini Mental State Examination (MMSE) score was 16/30. She had 1/3 delayed recall and was unable to repeat a sentence, follow a three-step command, copy interlocking pentagons, write a sentence, or do serial subtractions. She had slow saccades and jerky pursuit in all directions. Her strength was normal but she demonstrated motor impersistence on tongue protrusion and arm extension. She had quick, intermittent jerky movements in her hands, shoulders, and trunk that seemed to flow into other body parts and worsened with action (see video, Case 75). She also had bilateral milkmaid’s grip. The reflexes and sensory examination were normal. Her gait was unsteady and ambulation worsened her choreic movements.

Previous work-up by the referring physician included a negative test for the Huntington’s disease (HD) gene, normal copper and ceruloplasmin, normal lactate and pyruvate, and no abnormalities of organic acids. There was mild cortical and caudate atrophy on coronal magnetic resonance imaging (MRI).
We ordered tests for dentatorubropallidoluysian atrophy (DRPLA), the testable spinocerebellar ataxias, a rheumatologic panel to rule out systemic lupus erythematosus (SLE), blood smears for acanthocytes, and α-fetoprotein for ataxia–telangiectasia. All tests were normal/negative.

**DISCUSSION**

Although this patient’s clinical presentation was highly suggestive of HD, the initial work-up was non-diagnostic. We decided to have her tested for Huntington’s disease-like (HDL) conditions by Dr Russell Margolis at Johns Hopkins University. Her gene test came back positive for Huntington’s disease-like 2 (HDL2).

Huntington’s disease (HD) was first formally described by George Huntington in his work ‘On Chorea’ (1872): ‘Hereditary chorea . . . confined to certain and fortunately a few families, and has been transmitted to them, an heirloom from generations away back in the dim past. It is spoken of by those in whose veins the seeds of the disease are known to exist, with a kind of horror. There are three marked peculiarities of the disease: 1. Its hereditary nature. 2. A tendency to insanity and suicide. 3. Its manifesting itself as a grave disease only in adult life.’

Huntington disease’s (HD) is an autosomal dominant, neurodegenerative disease that usually leads to death within 15–20 years of onset. Dementia and psychiatric problems frequently develop in parallel with abnormal movements, especially chorea, dystonia, parkinsonism, and ataxia. A CAG repeat expansion in the important transcript gene (IT15) on the short arm of chromosome 4 results in production of the abnormal protein huntingtin.

Huntington’s disease-like patients may have a phenotype identical to HD but do not possess the classic mutation seen in HD. To date, there are four described HDL conditions. A 192-nucleotide insertion in the region of the prion protein gene (PRNP) on chromosome 20 is responsible for HDL1. HDL2 is caused by a CTG/CAG repeat expansion within the junctophilin-3 gene on chromosome 16. HDL3 has not been definitely characterized beyond the clinical description. HDL4, now known to be SCA17 is due to an expanded trinucleotide repeat of the TATA box-binding protein on chromosome 6.

Huntington’s disease-like 2 (HDL2), first described in 2001, is a progressive, autosomal dominant, neurodegenerative disorder with marked clinical similarities to HD; indeed, MRI and autopsy findings are consistent with HD. To date, every HDL2 pedigree is either of definite or potential African descent. The causal mutation in HDL2 is a CTG/CAG expansion on chromosome 16q24.3 in a variably spliced exon of junctophilin-3 (JPH3). One theory proposes that the increased number of trinucleotide repeats interferes with normal JPH3 protein function as a regulator of intracellular calcium flux. An alternative theory suggests that trinucleotide repeat expansion results in JPH3 splice variants toxic at the RNA or protein level.

This case is instructive because it considers the differential diagnosis of a Huntington’s disease phenotype, including the recently described Huntington’s disease-like disorders—specifically HDL2.
What looks like Huntington’s disease?

REFERENCES


Legend to video

Case 75 The patient exhibits distal chorea and proximal jerks that worsen with action and complex mental tasks. She also shows poor concentration and is quickly frustrated when asked to do serial subtractions.
CASE PRESENTATION

A 71-year-old man had been healthy until his early 30s when he noticed tremor in his right hand while writing and in both hands when holding objects. The tremor gradually worsened. In his 40s he developed tremor of the head while upright that resolved when supine. Tremor of jaw and tongue appeared later. He was treated with beta-blockers (propranolol 80mg twice a day or nadolol 20mg daily) and a carbonic anhydrase inhibitor (methazolamide 50mg three times a day) for years, without obvious benefit. He experienced increased difficulty coordinating hand movements and was no longer able to write legibly. He required assistance cutting food, frequently spilled from glasses, and required a straw to drink. His speech became progressively slurred and he eventually developed dysphagia. In his 50s, the patient developed mild gait unsteadiness which progressed. He frequently steadied himself on walls or furniture. Prominent upper limb tremor and incoordination prevented effective use of a cane or walker. He fell frequently. In his mid-60s, family members observed slight memory impairment that progressed. In his 70s he developed bowel and bladder incontinence and light-headedness. He was admitted to hospital following a syncopal episode for which no cause, other than his neurological disorder, was found. He was transferred to a nursing home and was no longer able to walk. He required support while seated to prevent him from falling. His brain magnetic resonance imaging (MRI) 6 years ago and head computed tomography (CT) following syncope revealed diffuse atrophy of cerebral cortex and cerebellum with compensatory ventriculomegaly.

The patient’s childhood development had been normal. He graduated from high school, married, fathered two children, and worked full-time as a custodian until age 62, when prominent tremor and gait unsteadiness prompted retirement. His medical history was otherwise unremarkable. His mother developed hand tremor in her 40s and a progressive gait disorder in her 50s, and died at 59. His daughter developed a tremor in hands and head in her mid-20s. Relatives in each generation have exhibited a similar, progressive neurological disorder.
When he was first examined, at age 65, supine blood pressure (BP) was 166/90, pulse 76, and seated BP was 138/90 with a pulse of 64. He was oriented, his use of language and memory were normal, and he scored 26/28 on the Mini Mental State Examination (MMSE). Eye movement examination revealed square-wave jerks, mildly saccadic pursuit, and hypometric horizontal saccades. Cranial nerves were otherwise normal. He was diffusely hyperreflexic with a brisk jaw jerk. A Babinski sign was present on the right but equivocal on the left. He exhibited glabellar and rooting responses, bilateral grasp reflexes, and Hoffman signs. His arms and legs were paratonic. There was a mild paucity of spontaneous movement. Action tremor (both postural and kinetic) was prominent in hands, arms, head, and protruded tongue (see video, Case 76). Tremor of his mandible occurred intermittently and attenuated with speaking. Tremor of both legs was seen occasionally while he was seated but not standing. Finger-to-chin movements were moderately dysmetric and heel-to-shin less so. Handwriting appeared effortful and demonstrated a large amplitude tremor. A rapid, myoclonic-like movement was present occasionally at the termination of hand movements. He was able to arise from a chair and walk without assistance but could not perform tandem walking. His gait was moderately broad-based and ataxic. Arm swing was normal to mildly increased bilaterally.

The patient was re-examined at age 71. He was alert and in no distress. Supine BP was 120/68 without a significant orthostatic drop. Language was normal. He knew his name, his wife’s name, and the name of his state, but was disoriented to place and time. Registration of three objects was normal but he recalled none. MMSE score was 13/28. Pseudobulbar affect was manifested by emotional lability. There was motor impersistence. Cranial nerve examination revealed saccadic pursuit eye movements, hypometric saccades, and mildly reduced hearing. Reflexes were 3+ in the arms and legs and the jaw jerk was brisk. Withdrawal of feet from plantar stimuli and plantar grasp responses precluded confirmation of the extensor plantar response seen 6 years previously. Muscle bulk was diffusely and symmetrically reduced. No fasciculations were seen. Paratonia was noted in arms and legs and there was prominent gegenhalten in the upper limbs. His brow was usually furrowed. Action tremor of upper extremities, head, and tongue were increased in amplitude compared to his first examination. There was an intermittent tremor of the mandible. Finger-to-chin movements were markedly dysmetric. Lower extremity movements were moderately dysmetric. Speech was moderately dysarthric but intelligible. He needed help to sit up but could not ambulate, even with assistance.

**DISCUSSION**

This gentleman exhibits a slowly progressive familial disorder characterized by a postural and kinetic tremor, gait and limb ataxia, dysarthria, dysphagia, parkinsonism, hyperreflexia, and dementia. He and several family members were initially diagnosed with essential tremor and treated with beta-blockers that produced little benefit. Following development of additional neurological signs, the diagnosis of multiple system atrophy was considered. The family history and examination suggested an autosomal dominant spinocerebellar disorder. Genetic testing revealed spinocerebellar ataxia type 12 (SCA12). This patient is a
member of the American kindred (of German descent) in which this disorder was first identified. SCA12 has since been recognized in at least 25 kindreds in Northern India, but is otherwise rare. Indian patients with SCA12 are clinically similar to American SCA12 patients, but cognitive dysfunction is not prominent in Indian families and some have subclinical sensory and motor axonal neuropathies. Haplotype analysis supports a common founder for SCA12 in the Indian population. The causative mutation in SCA12, a CAG repeat expansion in the probable promoter for a regulatory subunit of protein phosphatase 2A (PP2A), likely occurred independently in American and Indian patients.

SCA12 typically includes action tremor of the arms and head appearing in the 20s–30s followed by progressive arm-more-than-leg dysmetria, gait ataxia, dystartrhia, dysphagia, mild parkinsonism, autonomic dysfunction, and cognitive decline that affects memory, spares language, and may include parietal lobe dysfunction (an ‘alien limb’ sign was seen in the proband). Brain imaging of SCA12 reveals atrophy of the cerebral cortex and cerebellum with generalized ventriculomegaly ex vacuo. Autopsy on the proband, who died at age 64 of urosepsis, revealed neuronal loss and intraneuronal inclusions in cerebellar Purkinje cells, substantia nigra, and cerebral cortical neurons with no evidence of Parkinson’s or Alzheimer’s disease.

ACKNOWLEDGMENTS

The author thanks the patient and family members who have participated in our investigations of SCA12, R Margolis and S Holmes for ongoing collaboration on SCA12, and M Molliver and S Reich for helpful discussion. This work was supported by National Institutes of Health (NIH) NS42930 and the National Ataxia Foundation.

This case is instructive because upper extremity tremor occurred initially in isolation, suggesting essential tremor. Subsequent development of hyperreflexia, dysmetria, and ataxia made that diagnosis incorrect. SCA12 may also mimic multiple system atrophy (MSA), but the longevity and a positive family history should itself rule out MSA, which is sporadic. Although SCA12 is rare, the diagnosis should be considered in patients (especially of Indian descent) with upper extremity and/or head tremor plus additional neurological signs, including gait ataxia, limb dysmetria (arm > leg), dystartrhia, abnormal eye movements, hyperreflexia, parkinsonian features, autonomic dysfunction, or cognitive abnormalities.

REFERENCES


Legend to video

Case 76  The first examination of this patient at age 65 demonstrates a postural and kinetic tremor of the upper extremities, head, protruded tongue, and legs. He also has a mixed tremor of his mandible. Upper extremity movements are moderately dysmetric. Dysdiadochokinesia and handwriting tremor are apparent. His gait is moderately ataxic and he cannot perform tandem walking. He is mildly parkinsonian. On examination 6 years later, the patient’s ataxia has increased and he is no longer able to walk independently. His tremors, dysmetria, and dysdiadochokinesia have increased. He is cognitively impaired and displays a pseudobulbar affect. His brow is chronically furrowed. During recitation of the alphabet, mild-to-moderate dysarthria and variability in the volume of his voice are audible.
Painful involuntary neck movements in a 45-year-old woman

Kathleen M Shannon

CASE PRESENTATION
A 45-year-old rural mail carrier had developed neck pain and stiffness following an upper respiratory infection at the age of 38. Her osteopathic physician prescribed a neck brace. She subsequently noticed involuntary tilting of her head to the right shoulder and rotation of her chin toward the left shoulder. She was seen by a chiropractor, and then had acupuncture without benefit. Six years into her illness, she tripped over her dog and fell down the stairs, injuring her right elbow. Following these injuries, she experienced increased neck and right shoulder pain, and the tilting and rotation of her head worsened. She noticed that she could improve the neck spasm by gently touching the back of her neck with her right hand. She was evaluated by a neurologist who diagnosed cervical dystonia. Treatment with clonazepam, trihexyphenidyl, baclofen, and lorazepam were not helpful. The medical and family histories were non-contributory.

On neurological examination, there was involuntary turning of her head to the left shoulder with tilting toward the right shoulder. There was mild pulling of the head backwards. There was palpable spasm in the right sternocleidomastoid, right splenius capitus, and right levator scapula muscles (see video, Case 77). She responded well to electromyogram-directed injections of botulinum toxin into the left splenius capitus and longissimus muscles, and the right sternocleidomastoid, splenius capitus, trapezius, and levator scapulae muscles. She has continued to benefit from these injections for 13 years.

DISCUSSION
This patient developed involuntary twisting and tilting movements of the head associated with muscle pain in middle adulthood. She has a sensory trick, or geste antagoniste, that temporarily suppresses the spasms: touching her hand to the back of her neck. The stereotyped, slow, and torsional nature of the movements and the presence of geste antagoniste are characteristic of dystonia.
Dystonia was defined by an ad hoc working group for the Dystonia Medical Research Foundation as 'a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures.' Because the movements and postures are localized to the neck, the diagnosis is focal cervical dystonia. Torticollis (twisted neck) and spasmodic torticollis are more colorful pedestrian terms for this movement disorder. Patients with cervical dystonia often wait years and see multiple physicians or other healthcare providers before the condition is diagnosed. Some patients become aware of cervical dystonia following minor trauma or illness, but the trauma may merely bring attention to the underlying illness. In this case, the prior infection and trauma are likely unrelated to the development of the dystonia.

The estimated prevalence of cervical dystonia is 5.7–11.5/100,000. The disorder is more common in women. The mean age at onset is 40.8 years. Familial aggregation occurs in about 20–34% of cases, depending on diagnostic certainty. Patients with cervical dystonia usually present with sustained rotation of the head to one side (torticollis), pulling of the chin to the chest (antecollis) or the vertex toward the back (retrocollis), and shift of the neck to one side (lateral shift) or to the front or back (anterior and posterior sagittal shift, respectively). Many patients with dystonia have superimposed fast movements or tremor. A more normal head posture returns when the patient is supine or prone or when the head is supported by a headrest or wall, but longstanding disease may result in muscular contractures. The geste antagoniste is usually a touch with a finger to the cheek on the side ipsilateral to the direction of head movement. In patients with an effective geste antagoniste, abnormal electromyographic activity can be reduced by applying the geste with the hand or a plastic stick, when the examiner touches the face, or when the patient imagines touching the face. Tricks are least effective when the head is in the maximally deviated position, and are most effective at stabilizing a neutral or slightly overcorrected head position. More than half of patients have multiple gestes, which improve head position in an average of 60% and completely restore normal head position in almost 30% of patients.

Pain, sometimes severe, is experienced by 70% of patients with cervical dystonia. There may be prominent hypertrophy of the sternocleidomastoid, splenius capitus, trapezius, or levator scapula muscles. Some patients also have a personal or family history of postural tremor in the arms. Dystonic movements may hamper normal swallowing, and about 50% of patients with cervical dystonia have abnormal videofluoroscopy studies. Although cervical dystonia is a common manifestation in patients with generalized dystonia, it is only rarely the presenting sign. Cervical dystonia has an impact on quality of life that is similar to that of Parkinson’s disease, multiple sclerosis, or stroke.

Most cases of adult-onset cervical dystonia are primary, that is, dystonia is the ‘disease’, but it can rarely be on a secondary basis. The differential diagnosis of cervical dystonia includes Wilson’s disease, basal ganglia infarction, systemic lupus erythematosus, multiple sclerosis with midbrain plaque, ataxia–telangiectasia, congenital or acquired cervical spine abnormalities, septic cervical arthritis, pharyngeal abscess, oropharyngeal malignancies, tumors, compensation for diplopia or vertigo, and hiatal hernia with gastroesophageal reflux (Sandifer’s syndrome). When a structural lesion is to blame, the cerebellum
and brainstem are the most common locations (primarily in children), followed by the cervical spinal cord and basal ganglia. Routine cerebral neuroimaging is generally normal or shows spurious findings. However, secondary spinal complications, such as spondylosis, myelopathy, disc herniations, fractures, vertebral subluxations, or radiculopathy, occur in up to 40% of cases, and abnormalities typical of these secondary conditions may be seen in spine neuroimaging. Research neuroimaging studies, such as voxel-based morphometry, have shown changes in gray matter density of uncertain significance.

The etiology of cervical dystonia is unknown. There have been no conclusive findings on neurophysiology or neuropathology. Up to 25% of patients have a positive family history, and there are a number of potentially important genetic loci including DYT17, DYT13, and polymorphisms in the dopamine D5 receptor gene. The role of trauma is somewhat controversial. In some cases, trauma likely unmasks a subclinical dystonia. However, there appears to be a distinct subgroup of patients who develop very painful treatment-resistant cervical dystonia shortly after cervical trauma.

The pathophysiology of cervical dystonia is incompletely understood. Blink and masseter reflex studies suggest hyperexcitability of brainstem interneurons. The vestibulo-ocular reflex is also abnormal in cervical dystonia, but it is not clear whether this is a primary or a secondary abnormality. Studies of reciprocal innervation between forearm flexors and extensors reveal reduced inhibition, suggesting a more widespread nervous system dysfunction than the clinical degree of involvement would indicate.

Studies using transcranial magnetic stimulation suggest that the map for the hand is spread or displaced over the cortex, and that this abnormality may improve after botulinum toxin therapy. Positron emission tomography (PET) studies suggest increased glucose metabolism in the basal ganglia, thalamus, premotor and motor cortices, and cerebellum. Single photon emission computed tomography (SPECT) studies suggesting abnormalities of dopamine receptors and cholinergic striatal neuronal density require independent confirmation.

There is a poor evidence-base for the treatment of cervical dystonia. Although anticholinergics, baclofen, benzodiazepines, and dopaminergic and antiparkinsonian medications have traditionally been used, these agents are only modestly effective in adults, and only high-dose anticholinergic use in younger patients is supported by evidence. A recent evidence-based review concluded that botulinum toxin injections were effective for the treatment of cervical dystonia. Repeated botulinum toxin injections remain effective for up to 10 years, and lead to increased employability. Complications of botulinum toxin injection include the development of blocking antibodies, transient dysphagia, neck pain or weakness, anaphylaxis, and flu-like symptoms. A recent randomized, double-blind comparative study of botulinum toxin serotypes A and B found that the serotypes are equivalent in efficacy, though the benefit from type A lasts a bit longer. Patients who fail to respond to botulinum toxin injections or who develop secondary resistance to botulinum toxin may benefit from electromyogram-directed 2% phenol blocks or selective peripheral denervation. Two small studies of bilateral pallidal deep brain stimulation (DBS) in treatment-refractory cervical dystonia patients suggest improvements of up to 80% in objective
measures. Unlike the immediate improvement seen in DBS for Parkinson’s disease, the improvement following DBS in dystonia evolves over a period of months.

As in other focal dystonias, there is about a 10–20% chance of spontaneous remission in cervical dystonia; however, recurrence is likely. Remission is most common within 1 year of onset and is more common in younger patients. The severity of cervical dystonia may gradually worsen over several years, but generally remains stable after the first 5 years or so.

This case is instructive because it illustrates the typical clinical presentation of cervical dystonia, which is important because it is common for patients with cervical dystonia to see multiple care providers before the diagnosis is made. The case also demonstrates how difficult it is to treat cervical dystonia with oral medications, but that substantial long-term improvements can be achieved with botulinum toxin injections.

REFERENCES

Legend to video
Case 77 This patient has an abnormal head posture, with her head tilted toward the right shoulder (lateral collis) and her chin rotated towards the left shoulder (torticollis). There is a minor degree of lateral shift toward the right side. She shows elevation of her right shoulder. When asked to count backwards, one can see some superimposed more rapid movements (dystonic tremor). There is hypertrophy of the right sternocleidomastoid muscle.
A stimulating treatment for essential tremor

Rajesh Pahwa and Kelly E Lyons

CASE PRESENTATION

A 74-year-old man presented for evaluation of severe tremor of both hands that had begun at age 35. Initially the tremor was not bothersome and he did not seek medical attention. His tremor progressively worsened and at age 42 he was evaluated by a neurologist and was diagnosed with essential tremor. His tremor improved with alcohol, and both his parents had essential tremor. As the tremor was bothersome, his neurologist started him on propranolol LA (long-acting) 60mg per day. The tremor did not improve at this dose and the patient had difficulty maintaining an erection and therefore discontinued propranolol. His neurologist then initiated primidone 25mg at night which was gradually increased to 50mg three times a day. The patient had some improvement in tremor at this dose; however, he developed sleepiness and discontinued primidone. The patient did not want to try any other medications.

The tremor was relatively stable until age 66 and then became progressively worse, and he presented for treatment options. At that time, he could not feed himself with utensils and was restricted to finger food. He had to use a straw to drink liquids and two hands to shave using an electric razor. He required assistance to button his shirt and could not write due to hand tremor. His medical history was unremarkable and he was not taking any medications. His neurological examination was unremarkable except for tremor. He had a slight voice and head tremor. There was no resting tremor in either hand but he had a severe postural and kinetic tremor in both hands (see video, Case 78). He had marked difficulty in writing and drawing Archimedes spirals with either hand, and could not pour water with either hand. As the patient had marked disability due to his hand tremor and had not been able to tolerate medications he underwent left brain thalamic stimulation.

DISCUSSION

Essential tremor is one of the most common movement disorders. There are approximately 10 million persons in the United States with essential tremor, and approximately 1.3–5.1% of the population over the age of 60 years. Essential
tremor is believed to be an autosomal dominantly inherited disorder, and a family history of tremor is reported in 68–96% of patients. Both postural and kinetic tremors are commonly seen in essential tremor, although either form of tremor can occur in isolation. Essential tremor is usually present in the hands (70%), but also affects the head (40%), voice (18%), lower extremities (14%), face (3%), trunk (2%), and tongue (1%). Essential tremor is a monosymptomatic disorder without any neurologic signs or symptoms other than tremor. It presents insidiously and progresses slowly over years. There are no tests available to confirm the diagnosis. The diagnosis of essential tremor is made by the presence of bilateral, largely symmetric postural or kinetic tremor of the hands and forearms that is visible and persistent, or isolated head tremor without evidence of dystonia (e.g., abnormal posturing). In addition, the patient should not have any other abnormal neurologic signs, presence of known causes of enhanced physiologic tremor (e.g., drugs, anxiety, hyperthyroidism), evidence of psychogenic tremor, sudden onset or stepwise progression, primary orthostatic tremor or isolated voice, tongue, chin, or leg tremor, or isolated position-specific or task-specific tremors.

The treatment of essential tremor is symptomatic. There is no cure for essential tremor, nor are there any medications that slow disease progression. Treatment is initiated when tremor causes functional impairment or embarrassment. Tremor severity varies, and is often worse under periods of stress and anxiety. If the tremor is disabling only at certain times, propranolol and benzodiazepines can be used on an as-needed basis. Primidone and propranolol are used as first-line drugs for the treatment of disabling tremor. Propranolol can be used as either an immediate or a long-acting preparation. Propranolol is started at 10 mg three times a day and propranolol LA is initiated at 60 mg once a day. The dose of propranolol can be increased gradually to 320 mg per day. Primidone is usually initiated at 25 mg at bedtime and the dose is titrated gradually to 250 mg three times a day. If a patient has suboptimal control with one medication, a combination of propranolol and primidone can be used. β-Adrenoceptor antagonists such as atenolol or metoprolol can also be tried. The response of medications other than propranolol and primidone has not been consistently documented in essential tremor. Benzodiazepines such as clonazepam or antiepileptics including gabapentin and topiramate can be beneficial in some patients. Botulinum toxin injections into the muscles may provide relief for disabling head and voice tremor. Multiple other medications have been tried in essential tremor with questionable efficacy, and these include carbonic anhydrase inhibitors (e.g., methazolamide), phenobarbital, calcium channel antagonists (e.g., nimodipine), isoniazid, clonidine, clozapine, and mirtazapine.

If the patient continues to have disabling tremor after the use of medications, especially propranolol and primidone, or they cannot tolerate these medications, surgical options can be considered. Thalamotomy and deep brain stimulation of the ventral interomedial nucleus of the thalamus are the surgical options commonly used. Patients with disabling tremor and no cognitive impairment are candidates for these procedures. Surgical morbidity and mortality for these procedures is low, with a risk of major complications being approximately 1%. Both procedures have similar efficacy, although fewer complications have been
reported with deep brain stimulation. These surgical options provide adequate tremor control in approximately 90% of patients, with 90% improvement in tremor in the targeted limb. Deep brain stimulation of the thalamus is the procedure of choice in patients undergoing bilateral surgeries, due to the higher risk of complications seen with bilateral ablative procedures. Axial tremor such as head and voice tremor can improve with unilateral thalamic stimulation; however, bilateral procedures are usually required. Long-term studies have reported that the majority of patients continue to have control with thalamic stimulation.

This case is instructive because it illustrates the typical history and examination of essential tremor and discusses medical therapies. It also demonstrates the efficacy of treatment with deep brain stimulation of the thalamus for patients with disabling tremor uncontrolled with optimal medical therapy.

REFERENCES


Legend to video

Case 78  In the first segment, prior to deep brain stimulation, there is a severe essential tremor. It is absent at rest. There is a bilateral, large amplitude postural and kinetic tremor as well as a vertical tremor of the head. He is unable to lift a cup with water and handwriting is severely impaired. Following deep brain stimulation, there is significant improvement in the right upper limb tremor to the extent that he can now pour water and write.
The coat hanger sign

Stephen G Reich

CASE PRESENTATION

A 50-year-old previously healthy man was seen for the first time in December 2004 for decreased motor skills as well as problems with bowel and bladder. He first noticed that his gait was 'a little unstable' in 2002. About the same time he noticed erectile dysfunction and a change in his voice: hoarseness. He was seen by an otolaryngologist and had a reportedly normal laryngoscopy. Under a neurologist’s care he underwent an MRI scan of the head and neck, reportedly normal, as were evoked potentials. Within one year, he developed constipation, alternating with large bowel movements followed by ‘almost uncontrollable diarrhea,’ with rare fecal incontinence. Concurrently, he experienced urinary urgency, frequency, occasional incontinence and enuresis as well as occasional lightheadedness, especially on a second flight of stairs.

His gait continued to deteriorate and he saw a second neurologist who performed an extensive evaluation. An MRI scan demonstrated pontine and cerebellar atrophy but on personal review there was no signal change in the basal ganglia or a ‘hot cross bun’ sign. He was found to have a slightly low vitamin B12 level but replacement did not improve his symptoms. He had a spinal tap which was normal as was an intestinal biopsy. He underwent a screen for inherited ataxias which was negative.

By the time of his initial visit, the patient had had 3 falls. His wife reported that he would get clammy during exercise. She also reported that in 2002, the patient fell out of bed several times while enacting a dream and his arms would often flail during sleep. She described that while asleep, he would take several breaths and then have a ‘jerk’ but she had not observed apnea.

On examination, the patient had a hoarse somewhat ‘squeaky’ voice (see video, Case 79). Blood pressure supine was 162/101mmHg and after standing for 2 minutes, 125/90mmHg. Mental status was normal. He had difficulty arising from a chair. His gait was moderately ataxic and he could not tandem walk. There was dysmetria with finger-to-nose, dysdiakinesia, and ataxia with heel-to-shin. There was no bradykinesia, tremor or rigidity but blink rate was diminished. Oculomotor examination demonstrated overshoot saccades and saccadic pursuit.

The diagnosis of multiple system atrophy was made (MSA-cerebellar type) based on the presence of a cerebellar syndrome with autonomic failure including
constipation, urinary symptoms, erectile dysfunction and orthostatic hypotension. The history also suggested a REM sleep behavioral disorder and sleep apnea both of which are common in MSA. The latter was confirmed by a sleep study and he started using CPAP with an improvement in daytime sleepiness.

This patient has continued to progress particularly with regard to speech and gait and now uses a walker or motorized scooter. Although a urologist recommended intermittent catheterization, he is managing fairly well with diapers. By making accommodations and showing great determination, he continues to work and travel. In 2007 during a vacation in Italy, he had a syncopal episode: to avoid having to urinate during a ferry ride he had purposely limited his fluid intake; it was a hot day and he passed out after ascending a flight of stairs. Previously, he experienced occasional lightheadedness and also described episodes of posterior cervical and shoulder discomfort while standing (see video) relieved by sitting or lying down. His orthostatic hypotension has been managed with a combination of water and salt intake, sleeping with the head of the bed propped, midodrine, caffeine in the morning, and avoiding situations known to precipitate low blood pressure such as arising quickly, straining at stool, eating a large meal or being in a hot environment.

**DISCUSSION**

Multiple system atrophy is a sporadic ‘synucleinopathy’ which typically begins between ages 50–60, affecting men and women equally. It comes in two main types depending on which motor features are dominant. MSA-P (Parkinson) is characterized by parkinsonian features including bradykinesia, rigidity, tremor and imbalance which are poorly responsive to levodopa, at least as the disease evolves, as there may be benefit initially. In contrast to PD, the parkinsonism of MSA-P is usually symmetrical and is less likely to include a classic resting tremor. When cerebellar features predominate, it is referred to as MSA-C. The diagnosis of MSA requires either parkinsonism or cerebellar ataxia along with autonomic dysfunction including orthostatic hypotension or urinary incontinence/incomplete bladder emptying and erectile dysfunction in men. As this case illustrates, the diagnosis of MSA is often not considered leading to unnecessary testing and unhelpful therapies. MSA-P is more common than MSA-C and often misdiagnosed as PD. Admittedly, it may be very difficult and sometimes impossible to make a distinction during life, emphasizing that the autopsy is needed for a definitive diagnosis.

To improve the likelihood of diagnosing MSA, it is not sufficient to be familiar with established criteria. Equally important is to reconsider the appropriateness of the diagnosis of PD or ‘idiopathic’ cerebellar ataxia at each visit and to actively look for ‘red flags.’ While the parkinsonian features and signs of ataxia are overt, autonomic dysfunction may go unrecognized, therefore, missing an opportunity for a correct diagnosis of MSA. For instance, men will often not volunteer that they are experiencing erectile dysfunction and must be asked directly. Similarly, patients cannot be expected to recognize that their bladder symptoms are neurologic in origin and they may have been
incorrectly attributed to prostatism (and treated as such with surgery) or the effects of normal aging, and as such, they must be queried about their presence.

Orthostatic hypotension (OH) is a criterion for MSA and defined as a systolic drop of at least 30 mmHg or diastolic of at least 15 mmHg after standing for 3 minutes from being supine. When OH presents with typical symptoms of postural dizziness, lightheadedness or actual syncope then it is readily recognized, but OH may be asymptomatic or manifested only by less distinctive symptoms emphasizing that one cannot rely on symptoms alone to rule out OH and the blood pressure must be measured. Less appreciated symptoms of OH include blurred or tunnel vision, weakness, fatigue, and difficulty thinking or concentrating.

This patient (see video) describes another common symptom of OH: posterior cervical, occipital and shoulder discomfort when upright, known as the coat hanger sign given its ‘coat hanger-like’ distribution and the sensation of being ‘suspended’ from a hanger. This discomfort may occur in isolation or co-exist with other symptoms of OH. It has been reported to occur more often in the morning, after meals, with warm temperatures, during exertion and straining to have a bowel movement. The coat hanger sign has been ascribed to localized hypoperfusion.

This case is instructive because it presents a typical example of MSA, the cerebellar type. It also emphasizes the necessity of actively seeking out the symptoms and signs of MSA, especially features of autonomic dysfunction, which may not be volunteered by patients and are often overlooked or incorrectly ascribed by physicians. This patient aptly describes the coat hanger sign of orthostatic hypotension characterized by posterior cervical pain when standing. Recognition of the autonomic features of MSA not only leads to an earlier and accurate diagnosis but also presents an opportunity for treatment to alleviate symptoms and improve quality of life.

REFERENCES

Legend to video

Case 79 This patient with MSA-C is describing the coat hanger sign of orthostatic hypotension. Note the characteristic hoarse, ‘squeaky’ voice of MSA and the fact that when he experiences posterior cervical discomfort, there are few if any other more obvious symptoms of OH. During the visit in which he described this symptom, his BP went from 140/90mmHg supine to 100/70mmHg standing.
Lewy body Parkinson’s disease in a familial case: what is idiopathic Parkinson’s disease?

Peter P Pramstaller and Christine Klein

CASE PRESENTATION

At the age of 49 years, this right-handed carpenter first noticed a slight resting tremor in both arms that spread to both lower limbs 3 years later. At this stage, generalized bradykinesia and rigidity had also developed, and a diagnosis of Parkinson’s disease (PD) was made. He was started on levodopa (100mg three times a day), resulting in marked and long-standing improvement of his signs and symptoms that were very slowly progressive. Fourteen years later, now aged 63 years, his gait had worsened and was complicated by frequent freezing episodes. At the same time, he began to experience motor fluctuations consisting of wearing-off, random on–off episodes, and mild peak-dose dyskinesias.

His medical history was unremarkable; in particular, there was no history of head trauma, meningoencephalitis, or exposure to toxins or drugs capable of inducing parkinsonism. He had smoked 15 cigarettes a day until 3 years ago and consumed small amounts of alcohol on a regular basis. He was married with three children. His mother also suffered from parkinsonism as did four of his nine siblings, including three brothers and one sister (Figure 80.1). The three brothers responded well to levodopa. In his extended family, several other members were affected with either PD or an isolated postural upper limb tremor.1,2

On neurological examination, at the age of 65 years, he showed a postural instability–gait disturbance (PIGD) type of PD (see video, Case 80), along with a moderate 4-6-Hz resting tremor in both upper limbs and the right lower limb (Hoehn–Yahr stage III, Unified Parkinson’s Disease Rating Scale (UPDRS; motor part–rated in ‘off’ score 68). In his ‘on’ phase, he had mild oromandibular and lower limb dyskinesias. There were no cerebellar or pyramidal signs, and no dysautonomia or cognitive dysfunction. A computed tomography (CT) scan was normal, as was all routine laboratory testing. Fluorodopa–positron emission tomography (PET) showed a uniform pattern of decreased presynaptic fluorodopa uptake, most prominently in the posterior part of the putamen.3 The patient’s parkinsonism remained slowly progressive. He died at the age
of 73 years due to a pulmonary embolism after surgery for oropharyngeal cancer.

Histological examination of the brain revealed moderate nerve cell loss and Lewy bodies in the substantia nigra and the locus coeruleus that stained positively with antibodies against α-synuclein (Figure 80.2). α-Synuclein-positive inclusions were present in neurons of the dorsal nucleus of the vagus and nucleus ambiguous, as well as in neuronal cell processes.
DISCUSSION

Although our patient’s clinical picture, PET scan, and autopsy all suggested idiopathic PD, there were two notable exceptions, leading to an alternative diagnosis. First, parkinsonism began earlier than usual, but more important, there was a strong family history which was atypical for idiopathic PD. Instead, this patient featured some of the clinical findings typically associated with Parkin parkinsonism, which was confirmed by sequence and gene dosage analysis of the Parkin gene that revealed compound heterozygous mutations (del exon 7 and 1072delT). Additional information from the autopsy was that surviving neurons stained with antibodies to the N-terminus of Parkin but not the ‘IBR’ domain, which had been deleted by both mutations.

Mutations in the Parkin (PARK2) gene are the most common known single factor responsible for early-onset parkinsonism (EOP), and mutations in this gene account for about 50% of EOP with a positive family history. Mutations in the Parkin gene have been found in numerous families of different ethnic backgrounds worldwide. The wide spectrum of Parkin mutations includes alterations in almost all exons. More than 50% of mutation carriers have exon rearrangements that, in the heterozygous state, are not detectable with conventional screening methods. Parkin is expressed in processes and cell bodies of neurons. The Parkin protein is a ubiquitin ligase characterized by a ubiquitin-like domain at its N-terminus and two RING finger domains flanking an In-Between-RING (IBR) domain at its C-terminus.

Carriers of Parkin mutations tend to have an earlier age of onset of PD, slower disease progression, more symmetrical onset, and more frequent dystonia as initial sign, hyperreflexia, and a tendency towards a better response to levodopa despite lower doses, compared to patients without Parkin mutations. However, in many patients with Parkin mutations, the clinical picture is indistinguishable from idiopathic PD.

Postmortem findings in Parkin-associated PD are variable, but may include neuronal loss and typical Lewy bodies. The similarities between Parkin-associated parkinsonism and idiopathic PD may extend beyond the clinical picture, as illustrated by our patient, who showed classic fluorodopa-PET findings of PD as well as Lewy body pathology. Our patient confirms that the earlier view of ‘no Lewy bodies as a hallmark of Parkin-related disease’ needs to be revised.

The family history of our patient was strongly suggestive of a hereditary form of parkinsonism. However, since his mother and five out of nine siblings were affected, the transmission initially appeared dominant rather than recessive. Both his mother and his affected sister carry a single heterozygous mutation only, supporting the notion of a possible role of heterozygous mutations as a susceptibility factor for PD. Our patient was compound heterozygous for both known types of Parkin mutation, thus stressing the need for comprehensive mutational screening including gene dosage analysis.

ACKNOWLEDGMENTS

We would like to thank Drs K Hedrich and F Scaravilli for providing the figures.
This case is instructive for three reasons:

1. **Role and diagnosis of Parkin-associated parkinsonism:** Parkin-associated parkinsonism may mimic idiopathic PD at many levels, and a clear-cut diagnosis cannot be established solely on clinical or pathologic grounds. Parkin mutations should be considered in the differential diagnosis of EOP, where they account for about 10% of all cases, as well as in other cases with hereditary parkinsonism.

2. **Treatment and counseling of patients:** Although the individual clinical course cannot be predicted in a specific Parkin mutation carrier, the majority will progress more slowly and respond better to treatment than patients without mutations. Genetic testing is cumbersome and expensive and does not affect treatment, and genetic counseling is complicated by the possible role of heterozygous mutations as susceptibility factors.

3. **General considerations:** Due to its many similarities to idiopathic PD, our case raises the important question of a better definition and classification of idiopathic PD and other parkinsonian syndromes. Parkin-related parkinsonism may serve as a model for idiopathic PD, resulting in an improved understanding of shared pathogenetic pathways between Parkin-linked parkinsonism and idiopathic PD.

**REFERENCES**


**Legend to video**

**Case 80**  Patient at the age of 65 years with predominant akinetic-rigid Parkinson’s disease, on and off dopaminergic therapy. When ‘off’, there is freezing and imbalance. In the ‘on’ phase, the patient displays mild choreiform dyskinesias with significant improvement in mobility.
A cerebellar syndrome without cerebellar signs
Joy Muthipeedika, Sarah Furtado, and Oksana Suchowersky

CASE PRESENTATION

The patient was first seen by one of us (OS) at the age of 56 years, with a 7-year history of right-sided bradykinesia, rigidity, and rest tremor. He had a 10-year history of abnormal posturing of his right hand during writing, suggestive of a dystonic writer’s cramp. Physical examination at the initial visit revealed right-sided bradykinesia and rigidity, mild bilateral rest tremor, and dystonic writer’s cramp. Eye movements were normal, as was the rest of the neurological examination, and there were no cerebellar signs. A diagnosis of Parkinson’s disease (PD) was made. The patient exhibited a good response to carbidopa/levodopa.

He was followed regularly in our movement disorders clinic and continued to demonstrate a beneficial response to levodopa, and later to dopamine agonists. By age 62, motor fluctuations with ‘wearing-off’ and levodopa-induced dyskinesias were present. He developed dysarthria and apraxia of eyelid opening. At the most recent follow-up at age 65, he was on carbidopa/levodopa (50/200) six times a day, and pramipexole 4.5 mg. He was receiving injections of botulinum toxin for apraxia of eyelid opening, with good benefit. He was observed to have a mild gait ataxia (see video, Case 81).

During the initial visit it was noted that the patient’s mother and maternal aunt had also been diagnosed with PD. Information was later obtained that the patient’s son had been seen by another neurologist and was also found to have features of PD. His symptoms began at 31 years of age and responded well to levodopa. The patient’s brother was also seen in our clinic, with levodopa responsive parkinsonism. A more detailed family history was obtained, revealing that a number of individuals over three generations had had neurodegenerative disorders, including six with parkinsonism and two with dementia.1

Because of the extensive family history of parkinsonism, a genetic cause was sought. The patient was tested for mutations in the Parkin, α-synuclein, and tau genes as well as spinocerebellar ataxia type 3 (SCA3) and SCA2. This revealed expanded repeats of 39 for SCA2 (normal 14–31). Similar expansions were found in other affected family members. The patient and his son underwent a positron emission tomography (PET) scan of the brain using 6-[18F]fluoro-L-dopa (FD)
Movement Disorders

and [11C]raclopride (RAC) to study the integrity of the nigrostriatal dopaminergic system and dopamine D2/D3 receptor density, respectively. Scanning results showed a pattern of reduced FD uptake in a rostrocaudal gradient and normal raclopride binding in striatum, characteristic of idiopathic PD. Magnetic resonance imaging (MRI) of the brain was normal.

DISCUSSION

Spinocerebellar ataxia type 2 (SCA2), one of the autosomal dominant cerebellar ataxias, is due to an expanded CAG trinucleotide repeat on chromosome 12q23–24. Diverse ethnic origins are seen among SCA2 kindreds, and significant phenotypic variability has been described. Typical features include ataxia, ophthalmoparesis, and sensory peripheral neuropathy. Postural tremor, action tremor, myoclonus, and hyporeflexia may also be seen. The frequency of several clinical signs such as myoclonus, dystonia, and myokymia increases with the number of CAG repeats, whereas the frequency of other signs is more related to disease duration. Slow saccades are only found in patients presenting younger than 35 years of age.

Parkinsonism associated with SCA2 may be accompanied by ataxia, a progressive supranuclear palsy-like presentation, restless legs syndrome, dystonia, motor neuron disease, postural tremor, and dementia. There may also be phenotypic variability within family members. In general, the age of onset of SCA2 is younger than in idiopathic PD, and patients with SCA2 parkinsonism may or may not respond to levodopa. However, patients with SCA2 presenting as isolated levodopa responsive parkinsonism is unusual. A review by Furtado et al of patients with parkinsonism-predominant SCA2 suggested that the prevalence of SCA2 among cases of familial parkinsonism ranged between 1.5 and 8%.

The patient satisfied criteria for the diagnosis of idiopathic PD with all three cardinal features, asymmetry at onset, and levodopa responsiveness. He had a normal MRI of the brain and a PET scan compatible with PD. However, the presence of dystonia, apraxia of eyelid opening, and a strong family history of parkinsonism were suggestive of another etiology.

The case is instructive because it demonstrates that SCA2 should be considered in the differential of autosomal dominant parkinsonism. Cerebellar signs typical of SCA2 may not be present even after many years of illness. It also demonstrates that a strong family history, while occasionally seen in PD, should raise the possibility of an alternative diagnosis.

REFERENCES

A cerebellar syndrome without cerebellar signs  335


Legend to video

Case 81 This 65-year-old patient has had symptoms of levodopa responsive parkinsonism for 17 years. The video is taken in the ‘on’ state. There is evidence of mild cerebellar dysfunction as well as mild bradykinesia and dyskinesia. There is a shuffling gait. The most prominent features are of parkinsonism. Cerebellar dysfunction only became evident over the past year.
Facial twitches in an elderly man

Joy Muthipeedika, Scott Kraft, and Oksana Suchowersky

CASE PRESENTATION

A 75-year-old man presented with a 3-year history of involuntary movements consisting of frequent eyelid closure and twitching of the nose. The movements were present throughout the day and were partially suppressible, but he developed an uncomfortable sensation around the nose when attempting to suppress them. The movements were absent in sleep. No sensory tricks could be used to attenuate the movements. The movements started shortly after a fall with injury to his face. Following the fall, he experienced nasal congestion with rhinorrhea and was treated with a variety of decongestants and antihistamines. He then underwent nasal septal surgery. The movements did not vary in location, frequency, or severity over the 3 years.

There was no previous history of any movement disorder, specifically motor or vocal tics, in childhood or adulthood. There was no history of exposure to drugs that could cause a tardive disorder. There was no history to suggest obsessive-compulsive disorder, or family history of Tourette’s syndrome or obsessive-compulsive traits.

On examination he exhibited frequent forceful closure of the eyelids, and synchronous stereotyped movements around the nose causing either upward or downward deviation of the medial cheek area. His ears twitched with the facial movements. These movements were suppressible (see video, Case 82). There were no vocalizations. The rest of the neurological examination was normal.

A diagnosis of an adult-onset motor tic disorder was made. Treatment with clonidine resulted in some benefit but was discontinued due to side-effects. He was treated with botulinum toxin type A injections into the frontalis, orbicularis oculi, procerus, and lateral nasii muscles. He has continued with regular 3-monthly treatments for 2 years and has had significant improvement in his symptoms.

DISCUSSION

This patient had features characteristic of tics, including a premonitory urge to move. Execution of the movement relieved the tension around the nose, and he could voluntarily suppress the tics for a short time. Other dyskinesias in the differential include myoclonus and dystonia; however, these movements are
not suppressible and not associated with premonitory urges. No sensory tricks improved the movements, as is often seen with dystonia.

Most tic disorders are either hereditary or idiopathic. Much less frequent causes include head trauma, encephalitis, carbon monoxide poisoning, hypoglycemia, cerebrovascular disease, and choreic disorders (neuroacanthocytosis, Sydenham’s chorea, Huntington’s disease). Drugs such as levodopa, central nervous system (CNS) stimulants (cocaine), and neuroleptics have also been reported to induce tics.

Chouinard and Ford found that 22 out of 411 patients presented with tic disorders for the first time after the age of 21. In nine patients, detailed questioning disclosed a history of childhood transient tic disorder, but in 13 patients, the adult-onset tic disorder was new. Among the new-onset cases, six developed tics in relation to an external trigger, and thus would be considered secondary tic disorders. The remaining patients had idiopathic tic disorders. Adults with new-onset tics were more likely to have a symptomatic or secondary tic disorder, which in this series included infection, trauma, cocaine use, and neuroleptic exposure. Adult-onset tic disorders may be more common than is generally appreciated or reported.

Our patient is interesting in that he reportedly developed motor tics following an injury to the face, raising the question of a post-traumatic etiology. Trauma is an unusual cause of tics. Fahn reported a case in an 18-year-old man who sustained a head injury with loss of consciousness. Though the patient recovered completely from the injury, he developed asymmetrical facial twitching 3 months later, and many years later he developed generalized motor and vocal tics. There was a family history of tics in this patient, and it was assumed that the head trauma precipitated a Tourette’s-like syndrome in a genetically predisposed individual.

Singer et al described a 27-year-old man who developed exclusive motor tics several weeks following head trauma. He did not have a family history of Tourette’s syndrome or obsessive–compulsive disorder. In this patient, the tics were only partially suppressible. Factor and Molho described two cases of peripheral injury associated with tics, including one case with bilateral facial twitching beginning hours after the facial injury.

This case is instructive because it demonstrates that tic disorders may begin in adulthood, even in the elderly. Secondary causes need to be explored in adult-onset cases. Trauma is an unusual but possible precipitating factor for tics.

REFERENCES
Facial twitches in an elderly man


Legend to video

Case 82  This depicts facial tics manifested by abrupt, rapid, repetitive movements including blinking tics, flaring of the nostrils, and synchronous stereotyped movements around the nose causing either upward or downward deviation of the medial cheek area. His ears twitch with the facial movements.
A man with quick jerks, inappropriate vocalizations, chronic anxiety, and compulsions

Saima Athar and Jorge L Juncos

CASE PRESENTATION

The patient is a 59-year-old man with a history of facial twitches, throat clearing noises, and grunting sounds that began at age 4 years. As the symptoms evolved he exhibited frequent grimacing, jerking of the head, and twirling when walking. Snorting, barking, and throat clearing worsened gradually to become at times loud noises, short phrases, and, occasionally, foul language (coprolalia) (see video, Case 83). In spite of this, was able to work, marry, and raise a family.

Early in school he was given a series of medical and psychiatric diagnoses ranging from seasonal allergies (the snorting tics), to situational anxiety, to attention-seeking behavior. He was considered in need of more discipline. At age 12 years he was first diagnosed with Tourette’s syndrome (TS). Until then, the confusion generated by incorrect diagnoses had been interpreted by the patient as evidence of personal failings, leading to serious problems with self-esteem and depression.

The most physically damaging problem was ritualistic self-mutilating tics that included various forms of self-abuse. In a case of ‘self-mutilation by proxy’, as an adolescent he repeatedly placed the barrel of his brother’s BB gun to his orbit until his brother pulled the trigger one day, enucleating his globe. He has worn a glass eye since. About 10 years ago he developed a new tic. He repeatedly hit his abdomen with his elbow until he ruptured his appendix. To this day he continues to hit his knees against each other, resulting in chronic arthritis. The most socially disabling tics have been a tendency to spit his food at the table, and the coprolalia. Over the years he has managed to transform (‘sublimate’) the latter into more the socially acceptable: ‘… may God bless you; I love you’. The tics peaked during adolescence, ebbed in early adulthood, and then peaked again at age 35 and have remained severe since. At age 35 he went through a divorce and had to take a leave of absence from his regular job. He has since been on disability.

He began to exhibit symptoms of generalized anxiety disorder (GAD) in elementary school. By adolescence he had developed obsessive–compulsive disorder (OCD). He has rituals associated with virtually every activity of daily...
living, and obsessively ruminates over conversations for weeks. After more than 20 years, the anticipatory anxiety that precedes each disability review starts 5 months before. The stress generated by the OCD symptoms leads to tic flare-ups that are very difficult to control. When relaxed he is able to suppress the tics enough to socialize in familiar surroundings. As a child he was told he had attention deficit disorder (ADHD), with severe distractibility, impulsivity, and irritability. A lifetime of depression manifests as loss of initiative and motivation, irritability, apathy, and troughs in self-esteem.

His medical history is remarkable for hypothyroidism and gastroesophageal reflux disease. There is no family history of tics. However, his mother has symptoms suggestive of OCD, though she has never been formally diagnosed. His father has alcoholism.

It is beyond the scope of this to list all of the medications tried with this patient. In brief, for tics he has been treated with typical and atypical antipsychotics to maximum tolerated doses. Most typical antipsychotics produced unacceptable levels of extrapyramidal symptoms, mainly akathisia and parkinsonism. Atypical antipsychotics proved too sedating, and he was not able to afford them. These drugs have had a modest-to-moderate tic suppression effect that has generally faded after a few years. The internal tenseness that accompanies the tics has not responded to these agents. For OCD he has received clomipramine, various selective serotonin reuptake inhibitors (SSRIs), and a select number of tricyclic antidepressants. These medications have helped the anxiety symptoms but produce sedation, dizziness, or non-specific odd feelings that have led to their discontinuation.

His current medications are amitriptyline 150mg/day, thiothixine ≤ 6 mg/day, a typical low potency antipsychotic, and diazepam 20mg/day. Amitriptyline keeps the depression at bay and helps reduce anxiety without doing much for the OCD. By now he has developed tolerance to diazepam, but he does not exhibit drug-seeking behavior. At an early age, stimulants consistently worsened his tics, and he has been reluctant to try them since. More recently the non-stimulant tricyclic atomoxetine had a similar effect.

**DISCUSSION**

Tourette’s syndrome is a chronic neurologic, developmental disorder with motor, phonic, and behavioral manifestations. The known pathophysiology of the illness was recently reviewed in comprehensive monographs. Although clearly a familial condition, its genetics remain elusive and complex, with the most recent data suggesting that TS may associated with various genes, each with variable and incomplete penetrance subject to environmental influences.

Tics peak around adolescence and tend to stabilize or decrease thereafter. Approximately half the patients develop comorbid attention deficit hyperactivity disorder (ADHD) and/or OCD, as illustrated in this case. Typically, ADHD develops before entering school and tics shortly thereafter. Anxiety and OCD symptoms begin between ages 8 and 12. ADHD and OCD symptoms may persist into adulthood, leading to chronic personal, occupational, and psychosocial stress. This case is unusual due to the level of symptom severity, which is much higher than for most patients in any clinic.
Quick jerks, inappropriate vocalizations, chronic anxiety, and compulsions

From a therapeutic standpoint the patient is also unusual in that he has been intolerant to many of the conventional drugs used in TS. In most patients, small doses of fluphenazine, haloperidol, or pimozide can control symptoms with minimal sedation or extrapyramidal symptoms. Atypical antipsychotics are currently under investigation, with reports suggesting that risperidone, aripiprazol, and ziprasidone may be helpful. Clonidine and clonazepam are helpful at controlling mild-to-moderate tics and improving sleep. Other agents to consider in selected cases are baclofen, metoclopramide and tetrabenazine.

This patient’s response to stimulant therapy was problematic but not typical. Contrary to reports published more than 10 years ago and the prevailing assumptions then, ADHD symptoms can be treated successfully in TS with the careful use of stimulants and atomoxetine. Regardless of these well controlled studies, it is important to consider that, as in this case, some TS patients may experience sustained worsening of TS symptoms. To minimize this risk, stimulants should be titrated more slowly in TS than in ADHD children without TS.

Management of OCD is beyond the scope of this brief report and the authors refer readers to a recent review. This patient would be a candidate for deep brain stimulation that could address the tics and OCD, but he is simply too anxious to consider this option. Reference 11 details specific recommendations from the Tourette Syndrome Association in the selection of surgical patients, and provides a cautionary note for those contemplating this still experimental procedure.

This case is instructive for several reasons. First, it reviews the clinical features of Tourette’s syndrome, including motor and vocal tics as well as the frequent comorbidities of OCD, anxiety, and ADHD. Second, it demonstrates graphically the impact that Tourette’s syndrome can have on a patient’s self-image, relationships, occupation, and functioning in society. Third, it reviews the many treatment options available for Tourette’s syndrome, and finally, emphasizes the harm that may come from an incorrect or delayed diagnosis.

REFERENCES

For more information, and support for patients with Tourette Syndrome, please see http://tsa-ura.org.

**Legend to video**

**Case 83** This demonstrates many of the patient’s tics including continuous circling and marching, vocalizations such as noises and repetition of phrases (palilalia), arm rotation, sudden neck and trunk extension, and rapid banging of the knees. It also demonstrates the result of self-injurious behavior including loss of the right eye and tooth loss.
A young man with a jerky hand

Ramon L Rodriguez, Steven Eisenschenk, Hubert H Fernandez, William Ondo, and Michael S Okun

CASE PRESENTATION

A 17-year-old right-handed man with a previous history of a complex partial seizure disorder since age 5 years presented to an outside institution with ‘jerky’ movements limited to the left upper extremity. These movements were predominantly in the fingers, wrist, and elbow. He had been seizure-free for 3 years prior to presentation and was on therapeutic levels of valproate. One week following presentation he noticed his left upper extremity was developing a flexed posture at the wrist, elbow, and fingers. He continued to experience twitching as well as jerks of his left proximal and distal upper extremity (see video, Case 84). There was no alteration in consciousness associated with the symptoms. He was tried on multiple anticonvulsants, including gabapentin 1500mg three times daily and tiagabine 16mg three times daily, but they failed to improve the movements. His electroencephalogram (EEG) and magnetic resonance imaging (MRI) of the head were reportedly normal at the time of initial examination. After failing therapy with antiepileptic medications, an alternative diagnosis of myoclonus-dystonia syndrome was presumptively assigned, and he was tried on maximal doses of anticholinergics, beta-blockers, levodopa, and botulinum toxin, all of which failed to result in benefit. Deep brain stimulation of the right globus pallidus was also unsuccessful at improving his symptoms.

His past medical history included complex partial seizures with motor activity in the right side of his body. There was no history of recreational drug use or exposure to toxic substances. His mother reported a normal pregnancy with an uncomplicated vaginal delivery. He had achieved all developmental milestones appropriately.

His general physical examination was unremarkable. The neurologic examination revealed 4/5 weakness of the left deltoid, biceps, triceps, and hand intrinsics. There was also 4/5 weakness in the left quadriceps and hamstrings. He also had wrist and finger flexion dystonia that lessened over time. Dedifferentiation was noted when performing finger taps in the left hand. He was noted to have a startle response predominantly involving his left upper extremity. He also had myoclonic movements involving the left shoulder, arm, and hand that were stereotyped and somewhat rhythmic. There appeared to be similar and simultaneous movements in his left toe and foot.
Repeat evaluation 6 months after initial assessment with EEG demonstrated electrographic activity seen over the right frontocentral region consisting of 4–6-Hz sharply contoured theta. MRI revealed cortical thinning in the right mesofrontal region, probably the focus of his abnormal involuntary movement. The diagnosis in this case was epilepsia partialis continua (EPC).

**DISCUSSION**

Epilepsia partialis continua is characterized by prolonged focal seizures that may not be associated with an alteration in consciousness. It is often the result of structural brain damage or encephalitis, and may present both diagnostic and treatment challenges. The motor manifestations of epilepsia partialis continua may mimic a focal hyperkinetic movement disorder. Multiple presentations for EPC have been reported, including tremor, dystonia, chorea, and myoclonus. The variable presentations may be a source of confusion and misdiagnosis, as was the case in this patient.

Dystonia–myoclonus syndrome, in contrast to EPC, is an autosomal dominant disorder characterized by myoclonus, dystonia, or both, and usually presents in young patients and is commonly responsive to alcohol. It results from a mutation in the ε-sarcoglycan (SCGE) gene. Other cases have been associated with mutations in the dopamine D2 receptor (DRD2) gene. The lifespan for dystonia–myoclonus is usually normal. Subjects seem to respond to benzodiazepines, and in severe cases to deep brain stimulation of the globus pallidus interna. The clinical presentation, along with the EEG and imaging studies, differentiated EPC from myoclonus–dystonia in this case. EPC should be considered in any new-onset predominantly unilateral presentation with myoclonus or ‘jerky tremor’.

This case is instructive because it demonstrates that epilepsia partialis continua may mimic a movement disorder. It also emphasizes the importance of an accurate diagnosis prior to consideration of deep brain stimulation.

**REFERENCES**

Legend to video

Case 84  There is continuous, dysrhythmic jerking of the left hand, forearm, and arm as well as a mild left hemiparesis with slowness and incoordination of finger movements.
An unusual cause of stuttering

Juan G Puig, Rosa J Torres, Alfonso Verdu, and H A Jinnah

CASE PRESENTATION

This patient had been born at term without complications. There had been no difficulties during the prenatal period or immediately following birth. Stuttering speech was apparent from the time he began using words at 1 year. He did not walk unassisted until 2 years, and his gait was always slightly clumsy. Cognitive impairment was noticed early in childhood, and he was initially thought to have a mild form of cerebral palsy. Despite his impairments, he functioned well and was able to live independently as an adult, supporting himself by selling lottery tickets.

When seen at age 37 years, the most obvious problem was prominent ‘stuttering’ (see video, Case 85) accompanied by involuntary jaw opening. Simultaneously, there was often overactivity of other facial muscles including the frontalis, orbicularis oculi, orbicularis oris, and platysma. Overactivity was observed only with speaking. Limb tone was normal and there was no tremor. Skilled movements of the hands and fingers were normal. His gait had a stiff, spastic-like appearance, with slight exaggeration of the lumbar lordosis and reduced flexion of the knees when stepping. He could not run normally, and when doing so the stiffness was exaggerated. Despite a spastic-like appearance to the gait, tendon reflexes were normal, there was no clonus, and the plantar responses were flexor.

At age 4 years, he was noticed to have an increase in serum uric acid to 8.5 mg/dl. Persistent hyperuricemia led to subsequent investigations revealing a reduction in fibroblast hypoxanthine–guanine phosphoribosyltransferase enzyme activity to approximately 7.5% of normal at 7 years. Molecular studies demonstrated two point mutations in the gene encoding the enzyme, T128G and G130A, predicting two amino acid substitutions in the protein. These findings are diagnostic of a mild form of Lesch–Nyhan disease (LND), associated with less than complete loss of enzyme function.

DISCUSSION

LND typically presents during the first year of life with motor delay. By 2 years, most patients develop generalized dystonia, sometimes accompanied by choreoathetosis and spasticity. The motor disorder is sufficiently severe that patients
are usually unable to walk, have severe dysarthria and dysphagia, and require assistance with most activities. By 4 years, cognitive delay becomes more apparent, and most patients achieve intelligence quotient (IQ) scores indicative of moderate mental retardation. This pattern often leads to a diagnosis of extrapyramidal cerebral palsy, and LND is usually not suspected until more specific manifestations become apparent. Two important diagnostic clues include self-injurious behavior, which usually emerges by 3 years, but may be delayed until the later teenage years. A second clue is elevated serum uric acid or the development of uric acid kidney stones.

LND is inherited in an X-linked recessive manner, due to heterogeneous mutations of the gene encoding the enzyme hypoxanthine-guanine phosphoribosyltransferase. This enzyme plays a key role in purine metabolism, recycling the purine bases hypoxanthine and guanine back into usable purine nucleotides. In the absence of this enzyme, these bases cannot be recycled. Instead, they are degraded to uric acid, and lost purines must be replaced by alternative synthetic pathways. It is the failed purine recycling together with augmented purine synthesis that leads to overproduction of uric acid and hyperuricemia. However, the degree of hyperuricemia can sometimes be small, and readily escapes notice in routine clinical testing.

Particularly challenging are patients with incomplete enzyme deficiency leading to clinical syndromes that are mild or lacking characteristic features. Similar attenuated or late-onset presentations have been reported for many other inborn metabolic disorders as well. Because these disorders may be unusually mild or lacking the expected clinical manifestations, a delay in diagnosis is common. The current case lacked a characteristic feature of classic LND: self-injurious behavior. His motor disorder was mild, being limited to stuttering due to oromandibular dystonia, and a mildly abnormal gait, as opposed to the usual severe, generalized dystonia. It was the identification of mild hyperuricemia that provided the initial clue leading to the diagnosis.

Stuttering is a common disorder that may present at any age. It is often a transient problem in early childhood, and occurs with increased frequency in conditions such as attention deficit hyperactivity disorder or Tourette’s syndrome. It may also emerge in older adults, in association with stroke or neurodegenerative disorders such as Parkinson’s disease. The different clinical manifestations and various associations of stuttering suggest that it may have diverse etiologies. Some studies suggest that stuttering arises from a defect in speech and language centers of the cerebral cortex, whereas others suggest that it represents primarily a subcortical defect involving the basal ganglia. Some forms of stuttering have also been classified as a task-specific dystonia. In the current case, the stereotypical overactivation of the jaw muscles together with overflow activation of multiple other facial muscles suggested that his stuttering was a task-specific dystonia. This interpretation is consistent with observations that the major motor defect in other more severely affected patients with LND is dystonia and is also consistent with the known pathology of LND, which involves prominent dysfunction of basal ganglia dopamine systems.

In addition to the stuttering, another unique feature in this case is the gait disorder. Although his gait resembles a spastic paraparesis, he did not have the expected findings of spasticity, weakness, hyperreflexia, clonus, or extensor
An unusual cause of stuttering

plantar reflexes. Instead, his gait, as well as the exaggerated lumbar lordosis, likely reflects dystonia which is universal in more severely affected patients with LND.²

This case is instructive for several reasons. First, it demonstrates several of the features of LND including developmental delay and dystonia, which can be easily mistaken for cerebral palsy. Second, it emphasizes some important diagnostic clues for LND including self-injurious behavior and hyperuricemia. Third, it demonstrates that oromandibular dystonia can manifest as stuttering. And fourth, it teaches that inborn errors of metabolism, which typically present in childhood, also need to be considered in adults.

REFERENCES


Legend to video

Case 85 As the patient attempts to speak there is either single or repetitive jaw opening often associated with blepharospasm, neck flexion, and contraction of the platysma. He walks slowly with a spastic-like gait. There is a mildly exaggerated lumbar lordosis.
CASE PRESENTATION

A 78-year-old man was referred for ‘trouble walking’ and difficulty ‘getting started’. On the background of excellent health, his gait disorder had begun insidiously 5 years before presentation. The first neurologist suspected Parkinson’s disease, but there was no improvement with antiparkinsonian medications. A second neurologist considered normal pressure hydrocephalus. The first of several spinal taps offered slight improvement, but not subsequent lumbar punctures. There was never an abrupt change to suggest a stroke. The patient had noticed that it was easier to get started with a visual cue such as stepping over a special bar added to the bottom of his cane, or holding the cane upside down and stepping over the handle. He occasionally used a motorized cart. He reported slight loss of dexterity in the upper limbs. There was no cognitive impairment.Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain showed mild age-appropriate atrophy without hydrocephalus or significant signal changes in the white matter. Cervical MRI showed degenerative changes without canal stenosis.

On examination, the patient was in a wheelchair but otherwise looked well. There were no abnormalities on mental status testing. His voice volume was mildly decreased with slightly slurred speech. He was able to arise from the wheelchair under his own power and his posture was upright. He had a great deal of difficulty initiating walking. His gait was slightly broad-based with a waddling quality. He would suddenly freeze, especially during turns, and had a great deal of difficulty starting (see video, Case 86). He was unable to recover spontaneously on the pull test. He was able to stand on his toes and heels. Romberg’s sign was not elicited. Limb strength was full. Rapid repetitive movements were normal and there was no dysmetria. Deep tendon reflexes were 2–3+ and symmetrical and there was no Babinski sign. The cranial nerves were normal with the exception of mild hypomimia. Specifically, vertical eye movements were full.

DISCUSSION

This case represents primary progressive freezing (akinesia) gait. The term primary indicates that the gait freezing/akinesia was not the result of another
The distinction between these different causes of freezing gait is important, as treatment and prognosis are different. Freezing of gait associated with PD should be treated with dopaminergic medicine, which generally improves stride length, cadence, and freezing. Yet, freezing in PD may prove resistant to dopaminergic medication unless it is confined to ‘off’ time. Some patients with PD freeze even when ‘on’. In contrast to PD, freezing secondary to other parkinsonian disorders does not respond to dopaminergic medication.

Patients with non-PD gait disturbances characterized by freezing should be evaluated for etiologies amenable to specific therapies, such as small vessel vascular disease, which would require risk factor modification, normal pressure hydrocephalus, and the rare structural lesion. There is a subset of patients who have a primary gait problem for whom an underlying etiology is not found.
The case of the freezing man

It has been proposed that this subset be referred to as having primary progressive freezing gait. This group of patients is found to share some features with PD, but never develop the complete syndrome, and all experience progressive difficulty with gait over the course of several years. Some of these patients, if followed for long enough, may eventually develop additional signs to allow a more specific diagnosis, particularly progressive supranuclear palsy.

This case is instructive because it illustrates the features of freezing gait, discusses the differential diagnosis of freezing, and demonstrates the distinction between freezing due to PD and that associated with other etiologies.

<p>| Table 86.1 | Clinical characteristics of Parkinson’s disease (PD) compared with higher order gait disorders |</p>
<table>
<thead>
<tr>
<th>PD</th>
<th>Higher order gait disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shortened steps</td>
<td>Yes</td>
</tr>
<tr>
<td>Freezing episodes (start hesitation, turn hesitation, hesitation in narrow spaces)</td>
<td>Yes</td>
</tr>
<tr>
<td>Arm swing retained</td>
<td>No</td>
</tr>
<tr>
<td>Base of support while walking</td>
<td>Normal or narrow</td>
</tr>
<tr>
<td>Trunk movement</td>
<td>Reduced</td>
</tr>
<tr>
<td>Eversion of toes while walking</td>
<td>No</td>
</tr>
<tr>
<td>Response to dopaminergic medication</td>
<td>Good</td>
</tr>
</tbody>
</table>

REFERENCES

Legend to video

Case 86  The first segment shows a 78-year-old man with a complaint of progressive difficulties in walking. He complained of frequent episodes of being stuck to the floor, and has difficulty starting his steps. He has found that his walking is better when using a cane. The second segment shows a 54-year-old man with Parkinson’s disease who initially complained of tremor in his right hand. Over the last several months he has had increased difficulty initiating walking, with his feet being stuck to the floor.
A stridorous woman

Babak Tousi and Thyagarajan Subramanian

CASE PRESENTATION

A 73-year-old woman was referred to our movement disorders clinic for evaluation of tremor. Her symptoms had started 1 year prior to presentation with a postural tremor as well as an intermittent rest tremor of her right hand. These symptoms worsened over time and affected her handwriting. She was treated with dopaminergic agonists in adequate doses, with no significant benefit, which were discontinued due to side-effects. She had dysphonia, preceding the onset of tremor by several years, that was initially diagnosed as spasmodic dysphonia. Over the prior 3 months she had had more trouble with her voice and difficulty breathing, which was stridorous at rest. She had experienced urinary stress incontinence for 6 years and urge incontinence for the past 1 year. She denied difficulty walking or falls, but had trouble standing from the sitting position and rare incidents of freezing while walking. She also complained of fatigue, and trouble swallowing her pills. She had no history of infection, toxin exposure, or use of medications known to cause a parkinsonian syndrome and no family history to suggest a hereditary neurodegenerative disease.

On examination the patient’s affect was depressed and she had impaired attention. There was a purplish hue of both feet, and on subsequent visits the hands as well were cold and dusky. Eye movements were normal with the exception of saccadic pursuit. There was diminished facial expression. Speech was hypophonic. There was normal muscle strength but increased tone with rigidity. Deep tendon reflexes were brisk throughout and a jaw jerk was present. There was a mild, symmetrical postural and kinetic tremor of the upper limbs but no rest tremor. There was very mild dysmetria of the right hand on finger–nose–finger testing. Rapid alternating movements were decreased in both upper extremities. She could stand without assistance, but her gait was bradykinetic and she had mild difficulty with tandem gait walking.

Because of stridor she underwent indirect laryngoscopy which revealed true vocal cord paralysis (Figure 87.1 and see video, Case 87) necessitating an emergent tracheostomy.

External anal sphincter electromyography (EMG) revealed a markedly decreased number of motor unit potentials firing at a slow rate, with little alteration in the number of motor unit firings on attempted relaxation and contraction.
Urodynamic studies showed reduced bladder capacity of 245 ml with stress urinary incontinence. During the voiding phase, the patient could not sustain continuous detrusor contraction and only voided 20 ml.

We initiated treatment with carbidopa/levodopa 25/100, which was gradually titrated up to one tablet three times a day, resulting in mild improvement of her tremor but without other significant benefit.

**DISCUSSION**

The patient’s symptoms and signs are diagnostic of probable multiple system atrophy–parkinsonism (MSA-P).\textsuperscript{1–3} The differential diagnosis includes Parkinson’s disease (PD) and progressive supranuclear palsy (PSP). The symmetry, vocal cord paralysis, cold, dusky extremities, and lack of significant response to levodopa are all ‘red flags’\textsuperscript{4} making PD unlikely. The lack of vertical gaze palsy and no history of spontaneous falling points away from PSP.

Multiple system atrophy is a sporadic, progressive, synucleinopathy characterized by a combination of: autonomic failure including orthostatic hypotension,
urinary incontinence, constipation, and erectile dysfunction; parkinsonism with a poor response to levodopa; cerebellar dysfunction; and corticospinal signs.\textsuperscript{2,3} When parkinsonism dominates the clinical picture, it is referred to as MSA-P, and MSA-C designates the cerebellar prominent form. Pathologically, MSA is characterized by neuronal loss with other features of degeneration as well as oligodendroglial cytoplasmic inclusions (GCIs) in a variety of structures including the substantia nigra, basal ganglia, pontine nuclei, Purkinje cells, and autonomic nuclei in the brain stem and spinal cord.

MSA-P is characterized by progressive bradykinesia, rigidity, with a jerky postural tremor, and, infrequently, a rest tremor. Patients may have a characteristic high-pitched dysarthria. Recurrent falls at disease onset are unusual in MSA in contrast to PSP. A fully developed picture of MSA-P evolves within 5 years of disease onset, allowing a clinical diagnosis during follow-up visits. MSA-C is characterized by predominant gait ataxia, limb kinetic ataxia, dysarthria, and oculomotor disturbances.\textsuperscript{3}

Magnetic resonance imaging (MRI) of MSA may show basal ganglia abnormalities such as putaminal atrophy, a hyperintense putaminal rim, putaminal hypodensity, and cerebellar and/or brain stem atrophy (hot-cross-bun sign).\textsuperscript{3} Quinn and others have described a number of clinical ‘red flags’ that cast doubt on the diagnosis of PD as the cause of parkinsonism, and point towards MSA. These include the lack of resting tremor, symmetry, antecollis, poor response to levodopa, early and prominent dysautonomia, cerebellar signs, and cold, dusky extremities, among others.\textsuperscript{3,4}

A particularly important sign of MSA is inspiratory stridor, which can develop at any time during the course of the illness and may be the presenting feature of MSA.\textsuperscript{5-7} As in this case, it may be apparent while awake but more often occurs only during sleep, and therefore may be unrecognized unless the bed partner is questioned specifically about this symptom. Other sleep-related disorders in MSA include apnea (both central and obstructive) as well as rapid eye movement (REM)-sleep disorder.\textsuperscript{7} Stridor may be due to either vocal cord paralysis with bilateral laryngeal abductor weakness\textsuperscript{5-7} or excessive adductor activation during inspiration, likely the result of dystonia.\textsuperscript{8} Treatment options include continuous positive airway pressure or tracheostomy.\textsuperscript{7}

This case is instructive because it demonstrates many of the characteristic features of MSA-P. It also highlights the serious complication of stridor, which can be the presenting sign of MSA, and emphasizes the necessity of paying careful attention to sleep and airway symptoms in patients with MSA.

REFERENCES


Legend to video

Case 87  This is an image looking down at the larynx. The bottom of the screen is anterior and the flat structure is the epiglottis. The top of the screen is posterior, representing the esophageal inlet. As the patient inspires, the paralyzed vocal cords do not abduct, producing stridor. Normally the vocal folds open widely (abduct) during inspiration and close during phonation.
CASE PRESENTATION

A 55-year-old man was seen in 2001 for ‘imbalance’, which had been noticed initially 5 years before presentation but especially during the preceding year. He had also experienced a mild change in his handwriting and a subtle change in his speech, but despite these symptoms he was functioning at a normal level. His medical history included only mild hypercholesterolemia for which he was taking pravastatin. The patient’s 80-year-old mother was diagnosed as having ‘ataxia’ in 1980 and had been wheelchair-bound for the past 3 years. No one else in the family was known to have ataxia and the patient had no siblings or biological children.

On examination, the mental status was normal. There was mild scanning dysarthria. There was modest gait ataxia as well as mild incoordination with finger-to-nose and heel-to-shin as well as dysdiadokokinesia, but normal limb strength and sensation. The reflexes were brisk, including a jaw jerk, but the toes were down. There was primary position downbeating nystagmus with ocular overshoot dysmetria, saccadic pursuit, and a hypoactive vestibulo-ocular reflex (VOR) and impaired VOR cancellation. A magnetic resonance imaging (MRI) scan demonstrated pan-cerebellar atrophy but was otherwise unremarkable. A genetic screen for autosomal dominant spinocerebellar ataxia (SCA) was done.

The patient’s mother was seen on one occasion only, in 2003. At that time, she was 81 years old and reported that she had become symptomatic at age 40. She related that her mother was probably also affected as she required a cane and then a walker to ambulate, and eventually developed dementia. Her father had died in his 40s, but until then was not obviously affected. On examination (see video, Case 88), she was in a wheelchair and unable to stand without assistance and could not walk. There was moderately severe dysarthria as well as evidence of mild dementia and inappropriate jocularity. There was mild dysmetria with finger-to-nose and moderately severe dysdiadokokinesia. Oculomotor examination demonstrated downbeating nystagmus, saccadic pursuit, overshoot dysmetria, and a hypoactive VOR. She died in 2007 after becoming more demented.

Her son continues to be followed. He has progressed from a walking stick to a motorized walker. He retired due to disability in 2004, after a period of gradually reducing work hours. Aside from dysphagia and brisk deep tendon reflexes, the prominent features remain largely restricted to cerebellar signs (see video).
DISCUSSION

This patient presented in middle age with a relatively pure, slowly progressive cerebellar syndrome with an inheritance pattern suggesting autosomal dominant (AD) transmission. Of the autosomal dominant SCAs, this phenotype is most suggestive of SCA6,¹–⁶ which was confirmed by genetic testing demonstrating 22 CAG repeats. Yet, the SCAs are very heterogeneous; SCA6 can have extracerebellar features, and other SCAs may present with a relatively pure cerebellar syndrome. As such, it is not possible to rely on the phenotype to predict the genotype, and therefore, when evaluating an ataxic patient, it is usually necessary to conduct a comprehensive ataxia screen.

Like several other SCAs, SCA6 is due to an expanded trinucleotide (CAG) repeat. The gene, CACNA1A on chromosome 19p, encodes the α1A subunit of a P/Q-type voltage-dependent calcium channel.⁷–⁹ Although the role of this gene is not known, the P/Q calcium channels are widely distributed throughout the body, especially in the cerebellar Purkinje and granular cells, and are essential for neuronal function.¹⁰ Normal genes have 6–17 repeats whereas SCA6 has 21–30. Point mutations in this same gene cause episodic ataxia type 2 and familial hemiplegic migraine.¹,⁹ Several, but not all, studies have demonstrated anticipation in SCA6 with a younger age of onset in successive generations,²,³ but no correlation between repeat length and clinical features or the rate of progression.³

Pathologically, SCA6 is characterized by degenerative changes largely confined to the cerebellum with severe loss of Purkinje cells.²,¹¹ The mechanism(s) by which alterations in the α1A subunit of a P/Q-type voltage-dependent calcium channel cause neuronal death is not known. Obviously, SCA6 may be a channelopathy, and, as recently reviewed by Kordasiewicz and Gomez,¹⁰ the mutated subunit can form functional channels with altered function and kinetics and, depending on the experimental model, cause either an increase or a decrease of calcium entry into cells. Alternatively, or possibly in conjunction with an alteration in calcium channels, cells may die due to a toxic ‘gain of function’ as a result of normal cleavage of the C-terminus of the α1A subunit, which contains the SCA6 expansion.¹⁰

Studies in several distinctive geographic regions have demonstrated that SCA6 accounts for about 10% of autosomal dominant ataxias.³,¹²,¹³ In contrast, SCA6 was found in only 2% of a series of AD ataxias from France.⁶ Schöls et al.¹⁴ demonstrated that 7% of apparently sporadic adult-onset ataxia was due to SCA6, although in the French series, none of 146 cases of sporadic ataxia had SCA6.⁶ The prevalence of the SCA6 expansion has been estimated as 4–5/100 000.¹⁵

SCA6 typically has a later age of onset and more gradual rate of progression than most of the SCAs. It usually becomes symptomatic between ages 40 and 50, but may present as early as the 20 or after age 60.²,³ As in the above son, most patients require the use of a walker after approximately 15 years, but the course is variable.²

In addition to the later age of onset, additional clinical features of SCA6 include a relatively pure cerebellar syndrome and distinctive ocular motor signs,
although the latter are not unique to SCA6. These include horizontal gaze-evoked nystagmus, vertical nystagmus – typically downbeating, which is an important clue but often subtle – horizontal saccadic intrusions (square wave jerks), overshoot dysmetria, impaired suppression of the VOR, and normal velocity saccades.1,2 Extracerebellar signs occur infrequently and are typically mild, and may include decreased vibratory sense, ophthalmoplegia, neuropathy, and extrapyramidal signs.1,2 In keeping with the molecular relationship between SCA6 and episodic ataxia type 2, some patients with SCA6 have been observed to have episodic symptoms especially early in the course, including motion sickness and ataxia,1 but in the majority SCA6 is slowly and continuously progressive.

This case is instructive because it demonstrates the characteristic features of SCA6, one of the more common autosomal dominant ataxias: onset in middle age, slow progression, a relatively pure cerebellar syndrome, with downbeating nystagmus.

REFERENCES


**Legend to video**

**Case 88** The proband demonstrates scanning dysarthria, a broad-based, ataxic gait, past pointing, dysdiadokokinesia, downbeating nystagmus with horizontal saccadic intrusions, and ocular overshoot dysmetria. His mother, in a wheelchair, demonstrates an intention tremor, dysdiadokokinesia, inappropriate jocularity, and downbeating nystagmus.
CASE PRESENTATION

Three years prior to presentation, a 55-year-old right-handed judge noticed slowness of the left hand and discomfort of the left shoulder. He dragged the left foot while walking. He had no difficulty with his right hand, including writing, and was working full-time without any difficulty performing his duties. His speech was unaffected and there was no difficulty swallowing, but he did notice increased drooling while asleep. He was slightly slower in dressing and performing personal hygiene but had no difficulty handling eating utensils or turning in bed. He noticed an intermittent tremor of the left hand which was not very bothersome, and became more pronounced with emotional stress. There was slowness when reaching for his wallet. While walking on the treadmill he developed a painful cramp of the left foot with curling of the toes.

Over the last 3 years, he had also experienced mild softening of his voice, a feeling of being off balance with occasional stumbling, some difficulty buttoning, and washing his hair, and some trouble tying a necktie. His wife reported that friends and relatives would ask her: ‘What is wrong with his walking?’ The patient was initially diagnosed as having essential tremor. He was also seen by a podiatrist because of the foot cramping.

The examination at referral (see video, Case 89), 3 years after the onset of symptoms, revealed normal speech, slight facial masking, and a resting tremor in the left upper extremity. There was a mild kinetic tremor in the left upper extremity, moderate cogwheel rigidity at the neck and the left upper and lower extremity, and mildly increased tone on the right side. Finger tapping and all other repetitive movements were slow and irregular on the left and mildly decreased on the right. He was able to rise from a chair without difficulty. The gait was normal except for a mildly flexed posture and lack of left arm swing. There was no postural reflex instability.

The patient had had a magnetic resonance imaging (MRI) scan of the brain which was normal, and he was on no medication.

DISCUSSION

The subtle onset of resting tremor, cogwheel rigidity, bradykinesia, and mild gait alterations easily suggest parkinsonism. Particular historical clues include
slowness and clumsiness of one hand, cramps or dystonic postures, slight dragging of one leg, and tremor. Parkinsonism is not a difficult diagnosis to make, but remains strictly a clinical diagnosis. There is no blood test or imaging finding that confirms the diagnosis or can even screen for this diagnosis. Once the diagnosis of parkinsonism is made, the differential diagnosis includes Parkinson’s disease (the most common cause of parkinsonism), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), Lewy body disease, Alzheimer’s disease, drug-induced parkinsonism, and vascular parkinsonism, among many others.1

Are there important historical and examination findings that distinguish Parkinson’s disease from all of these others?2 The answer is both ‘yes’ and ‘no’. The important clues that this patient’s parkinsonism is due to Parkinson’s disease include the unilateral, insidious onset of his symptoms, and particularly the resting tremor. Although the most common age of onset for Parkinson’s disease is approximately 60 years, his symptom onset at age 52, while slightly early, is not atypical. Some argue that the diagnosis of Parkinson’s disease cannot be made until there is a demonstrated response to dopaminergic therapy. But, this rule is hardly applicable to patients presenting with parkinsonism who have yet to be treated, and many will be able to go several years before dopaminergic therapy is warranted.

There are other features of this patient’s presentation that are worth noting. The discomfort and pain in the shoulder on the side of the symptoms is an initial presentation in approximately 8% of patients with Parkinson’s disease (PD), and as many as 43% of patients give a history of such complaints.3 The history of a ‘frozen shoulder’ is valuable, and is most likely related to lack of normal spontaneous movements associated with the onset of bradykinesia and rigidity.3 The other feature that suggests Parkinson’s disease is the history of unilateral foot cramps. These cramps are, in reality, dystonic episodes, which may or may not be painful. Dystonia, as an early feature of PD, is more commonly seen in younger patients, and may appear spontaneously, particularly in the morning, or be precipitated by activity such as walking, as in this patient. The foot may assume a plantar flexed or inverted posture along with curling of all the toes, although sometimes the great toe will extend. Rarely, one hand may intermittently have cramps or dystonic postures.4,5

Approximately 20% of patients diagnosed as having PD during life will prove to have an alternative pathologic diagnosis, emphasizing the challenge in distinguishing PD from mimickers.5 Of the mimickers, one of the most important to recognize is drug-induced parkinsonism,7 and all patients should be queried about exposure to drugs known to cause parkinsonism. From there, it is essential to look for clinical features that are atypical for PD and raise the possibility of a parkinsonian syndrome, such as MSA or PSP.8

Of these atypical features, often referred to as ‘red flags’,8 lack of response to an adequate dose of levodopa is probably the most reliable indication that parkinsonism is not due to PD.2 Dementia appearing prior to or in conjunction with parkinsonism is another very clear indication that the patient probably does not have Parkinson’s disease, but instead, Lewy body dementia (particularly if there are hallucinations), Alzheimer’s disease, or frontotemporal dementia. Other red flags include the early appearance of autonomic dysfunction including
erectile dysfunction, urinary frequency and incontinence, constipation, and orthostatic hypotension, which suggest multiple system atrophy. Early and significant balance difficulties with falls suggest PSP, as does supranuclear vertical gaze palsy. Although approximately one-third of patients with PD do not have tremor, its absence, or a symmetrical onset of parkinsonism are additional clues that the patient may not have PD. Vascular parkinsonism and normal pressure hydrocephalus (NPH) are suggested by the prominence of ‘lower half’ parkinsonian signs, with little or no involvement above the waist.

This patient’s MRI scan of the brain was normal. The question often arises as to whether a patient who appears to have typical PD, with unilateral resting tremor, bradykinesia, and rigidity, and no red flags, requires brain imaging. In ‘typical’ cases, there is no need for brain imaging. However, if there are any red flags present or a question about the diagnosis, then imaging of the brain is suggested, on at least one occasion. It is important to note that red flags may not be apparent at presentation, and during each follow-up visit, the diagnosis of PD should be reconsidered, looking for the emergence of atypical features.

Initially, this patient was diagnosed with essential tremor. Although there should be little confusion between essential tremor and parkinsonism, this is a very common early diagnostic error. Parkinsonism includes not only a resting tremor, which is typically unilateral or asymmetrical at onset, but additional features such as micrographia, hypomimia, cogwheel rigidity, and bradykinesia. Essential tremor (ET), a ‘monosymptomatic disorder’, is characterized by only a postural and kinetic tremor which usually has a symmetrical onset and no associated features. One potential source of confusion with ET is that in addition to a rest tremor, early PD may also have a mild kinetic tremor which is asymmetric and more prominent on the side of the resting tremor. However, the presence of cogwheel rigidity, mild bradykinesia, and other parkinsonian features should aid in making the distinction. Other historical clues that help distinguish ET from PD include a strong family history (autosomal dominant) present in approximately half the families with essential tremor, and alcohol responsiveness, which is usually not a feature of the resting tremor or kinetic tremor of parkinsonism.

Finally, it is worth noting that this patient had been symptomatic for 3 years at the time of presentation. Yet, he was completely functional and continuing to work full-time at a demanding profession without any medication. This serves to underscore the point that early Parkinson’s disease should be treated with pharmacologic agents only when there is functional impairment.

This case is instructive because it demonstrates the early findings that characterize Parkinson’s disease. The insidious onset, marked asymmetry of the resting tremor, bradykinesia and decreased arm swing, and lack of atypical features lead the examiner to the diagnosis of Parkinson’s disease without the need for additional brain imaging. Additional important features of PD to recognize in this patient include a frozen shoulder on the same side as the other signs and symptoms, as well as the painful foot dystonia triggered by exercise.
REFERENCES


Legend to video

Case 89 At the beginning of the video, the patient discusses his early symptoms. There is mild hypomimia with a decrease in blink rate and a mild stare. Formal testing demonstrates normal rapid repetitive movements on the right but slowing of the left upper and lower extremity. As he walks there is no left arm swing and the left shoe can be heard to scuff the floor. While standing, there is a typical resting tremor of the left fingers, mostly the thumb.
Changing tremor in a 45-year-old woman

Alberto J Espay and Robert Chen

CASE PRESENTATION

This 45-year-old otherwise healthy woman developed tremor of the right hand 14 years prior to presentation. The tremor subsequently spread to the left leg, right leg, and left hand. The right hand tremor was worse with action whereas the left hand tremor was prominent at rest and while holding the arm outstretched. The left leg tremor improved with levodopa but she continued to have significant impairment from the tremor in the upper limbs. When she came to our attention, the patient also complained of occasional light-headedness and visual impairment (‘goes gray’). Walking was reported as ‘less balanced’ in the evenings and she occasionally fell when getting dressed. Walking downstairs was impaired, but not going upstairs.

On examination the abnormal neurological findings were restricted to the abnormalities of movement. The tremor frequency increased upon light touch and demonstrated marked variability in amplitude and axis of movement (see video, Case 90). Holding the left arm in different positions changed the tremor from forearm pronation–supination to wrist flexion–extension to wrist abduction–adduction, and its distribution changed from predominantly distal to predominantly proximal. This variation in the distribution of the tremor was also present when extending the left leg.

Two important aspects of the tremor were documented with electrophysiological testing, using an electromyograph (EMG) with surface electrodes and accelerometers (Figure 90.1). Entrainment was demonstrated when the patient was requested to tap the foot at 1Hz frequency paced by a metronome, which changed the tremor frequency of the affected arm from 6 to 1 Hz. The coactivation sign was also present, with simultaneous contraction of antagonistic tremor-generating muscles during a tremorless period, shortly prior to the resumption of clinical tremor (Figure 90.1B). In addition, the 6-Hz tremor in the left arm and leg at rest decreased to 2Hz when the left leg was held outstretched. There was also loss of a defined tremor frequency during distracting maneuvers and increased tremor amplitude during weight loading of the wrist (not shown). The tremor disappeared upon standing and walking.
DISCUSSION

This patient’s tremor had a number of features to suggest that it was psychogenic, including: (1) unusual evolution with spread from the upper limb to the contralateral lower limb; (2) tremor amplitude of relatively equal magnitude at rest, with action, and during maintenance of posture, yet not present when standing or walking; (3) tremor axis change with passively induced positional changes; (4) entrainment and the coactivation sign; and (5) its variability. The selective, inconsistent impairment of gait limited to walking downstairs but not upstairs was an additional element favoring a psychogenic etiology for the tremor.

Figure 90.1 (A) Entrainment. The patient was instructed to maintain both arms outstretched and start tapping with the left foot at 1 Hz with metronome guidance. The left arm tremor frequency clearly changed to that imposed by the task (arrow). The right arm developed a similar oscillating activity despite its previous absence. (B) Coactivation sign. Prior to the resumption of tremor, as measured by accelerometer (arrow), sets of antagonistic tremor-generating muscles cocontracted, recorded by EMG surface electrodes (double-headed arrow).
Electrophysiology is useful in establishing the two confirmatory features of psychogenic tremor: coactivation sign (increased electromyographic activity in a set of tremor-generating agonist-antagonist muscles prior to the onset of clinical tremor) and entrainment (change of the baseline tremor frequency to the frequency of voluntary rhythmic movement of a non-affected limb). The ‘coactivation sign of psychogenic tremor’ can be clinically palpated as increased tone during testing of limb muscle tone. When the ‘rigidity’ disappears, so does this tremor, which requires cocontraction of antagonistic muscles. The presence of this sign has prompted Deuschl et al to suggest that psychogenic tremor depends on the elicitation of a clonus mechanism, and may therefore be mediated by reflex mechanisms.

Psychogenic tremor is not just a diagnosis of exclusion but instead hinges on the presence of specific clinical features. Extensive investigations need not be done when the characteristic features of psychogenic tremor are recognized. Available clinical criteria help establish the diagnosis as ‘clinically definite’ when the abnormal movement disappears with suggestion, placebo, or psychotherapy and it is inconsistent over time or incongruent with a recognized movement disorder. The entrainment of tremor, presence of coactivation sign, and increase in amplitude with weight loading, ideally confirmed electrophysiologically, are never present in organic tremor, and therefore strongly support the psychogenic origin of the tremor. Variability in tremor frequency, decrease of tremor amplitude during distraction, sudden onset with paroxysmal occurrence, and multiple somatizations are frequent accompaniments of psychogenic tremor, but their presence does not preclude the coexistence of an organic disorder.

It is important to emphasize that an ‘obvious emotional disturbance’, a Fahn and Williams criterion for possible psychogenic dystonia, is rarely overt in psychogenic tremor, and referrals for psychotherapy can only succeed when the expertise on the pseudoneurologic effects of conversion, somatoform disorder, and malingering is provided by a motivated treating psychiatrist. Unfortunately, the prognosis of long-standing psychogenic tremor is poor. Loss of employment and progression of tremor severity and distribution, often in a fluctuating pattern, are common. Anecdotal evidence suggests that prompt recognition and early treatment of psychogenic tremor are crucial in curbing its potentially disabling consequences.

This case is instructive because it demonstrates the characteristic features of a psychogenic tremor and emphasizes that the diagnosis of a psychogenic tremor, like other psychogenic movement disorders, is based not just on ‘ruling out’ an organic disorder, but instead, recognizing features from the examination that are inconsistent and incongruous with an organic movement disorder. Specific features helpful in the diagnosis of a psychogenic tremor include abrupt onset, variability in frequency and distribution, entrainment, and the coactivation sign. This case also demonstrates the utility of electrophysiologic testing to support the diagnosis of a psychogenic tremor.
REFERENCES


Legend to video

Case 90 The video demonstrates several consecutive changes in axes in response to passive manipulation by the examiner in the left arm and leg. The left arm tremor showed ‘stimulus-sensitive’ exacerbation of rate and amplitude. Unusual gait is present when descending on the stairwell, when tremor is absent.
Is tremor essential?

Stephen G Reich

CASE PRESENTATION
A 64-year-old woman was seen for tremor of the upper limbs, jaw, and, when anxious, ‘the entire body’. The tremor had begun at age 14, with slow worsening over the ensuing years. Her father had tremor, eventually becoming so severe that he was not able to feed himself. Many of his relatives also had tremor. Two of the patient’s siblings have tremor, but it had not been observed in her children or grandchildren. The tremor interfered with many dexterous activities such as using eating utensils, including for eating soup, writing, and her hobby of oil painting, and she used two hands to hold a cup of coffee. The tremor made her self-conscious. She had not noticed alcohol to have an effect on the tremor. At presentation she was taking primidone 250mg twice a day, which had been helpful.

On examination, mental status was normal. There was no tremor of the voice. There was a slight tremor of the left hand at rest, with the more prominent tremor being a bilateral postural and kinetic tremor of the upper limbs without dysmetria (see video, Case 91). The limb tremor was apparent when she drew a spiral. There was a slight horizontal tremor of the head and an occasional perioral tremor.

I agreed with the prior diagnosis of familial essential tremor and added propranolol, eventually reaching 20mg three times a day, to the primidone, with improvement.

DISCUSSION
Tremor is a rhythmical oscillation of a body part, and this rhythmicity differentiates it from almost all other hyperkinetic movement disorders. It is classified on clinical grounds based on the activity of the limb during maximal activation of tremor: either at rest, with maintenance of posture, or during movement (kinetic tremor). The latter is further divided into simple kinetic tremor and intention tremor. The former is present either during non-Visually guided movements (e.g., wrist flexion-extension) or during a visually directed movement without an increase in amplitude as the limb approaches the target. Intention tremor is also present with movement, but the amplitude of the
tremor increases as the target is approached, usually accompanied by dysmetria, indicating a cerebellar or cerebellar-pathway localization.\(^1\)

This patient has the typical features of essential tremor (ET), one of the most common movement disorders. It has an estimated prevalence of 0.4–5%,\(^1\)–\(^4\) and both the prevalence and incidence increase with age, but ET\(^2\) affects all ages, including children. ET is diagnosed on clinical criteria, which include a bilateral (may be asymmetrical but not unilateral) postural and kinetic tremor of the upper limbs, unassociated with other neurological signs (aside from possibly tremor of the head or voice), with no evidence of an enhanced physiologic tremor or features to suggest an alternative diagnosis such as Wilson’s disease, dystonic tremor, or a psychogenic tremor.\(^1\)\(^,\)\(^2\) The frequency of ET is 4–10Hz, and since this overlaps with almost all other physiologic and pathologic tremors, frequency alone is not helpful diagnostically. Upper limb ET is often accompanied by tremor of the head, which may also occur in isolation, or tremor of the voice.\(^1\)

Despite being such a common disorder, ET is also commonly misdiagnosed. Jain et al reported that of 71 consecutive patients seen at a tertiary care center with a prior diagnosis of ET, 26 (37%) were found to have an alternative diagnosis, with Parkinson’s disease (PD) being most common.\(^5\) PD and ET can often be distinguished from the history: whereas most patients with PD who have a tremor seek medical attention within 6 months of onset, patients with ET, or their family, typically report that the tremor has been present for at least several years, sometimes many years or even decades, before seeing a physician. Most, but not all, patients with ET have an affected first degree relative, whereas PD is more likely to be sporadic. Finally, ET often improves transiently after a small amount of alcohol, which has little if any effect on the tremor of PD.

The examination further distinguishes PD from ET. As mentioned, the latter is almost always bilateral and present with posture and movement, whereas the tremor of PD begins unilaterally and is maximally activated at rest. Although the frequencies overlap, PD is slower than ET. Handwriting in PD is small but atremulous, and in ET it is of normal size but demonstrates tremor, including when drawing a spiral. In PD, in addition to the tremor, there will be associated signs such as bradykinesia, rigidity, shuffling, decreased arm swing, and hypomimia, in contrast to ET, which is largely a monosymptomatic disorder, although cogwheeling may be felt in both conditions. Distinguishing PD and ET is usually straightforward, but there are exceptions due to overlapping features such as the occasional appearance of a resting tremor in ET and the presence of a postural and kinetic tremor in PD.\(^1\)\(^,\)\(^2\)

The etiology of ET is not known. Even in familial cases, no gene has so far been isolated; there is some evidence that environmental factors may contribute.\(^2\)\(^,\)\(^3\) The pathophysiology of ET has largely centered on the cerebellum and its connections, especially the inferior olive.\(^2\)\(^,\)\(^3\) While ET has traditionally been considered free of any neuropathological changes, recent investigations have demonstrated brain-stem Lewy bodies in about 25% of older patients with ET, and in those without Lewy bodies, there were findings within the cerebellum (i.e. reduced number of Purkinje cells), raising the possibility that ET may in
Is tremor essential? 375

fact be a degenerative disorder.\textsuperscript{6} Contributing further to a broader view of ET as more than a monosymptomatic disorder are recent studies demonstrating that patients with ET may have subtle cognitive dysfunction, distinctive personality traits, and mild cerebellar signs.\textsuperscript{2,3}

In contrast to the historical moniker ‘benign’ ET, most patients experience impairment ranging from it being a mild nuisance to a disabling condition. The tremor interferes with most dexterous activities such as writing, pouring, holding a cup, using eating utensils and tools, putting on jewelry, and applying make-up. Furthermore, many patients are embarrassed particularly when tremor involves the head or voice, even when there is no actual physical limitation. Fortunately, most patients with ET can be helped. An evidence-based practice parameter by the American Academy of Neurology\textsuperscript{4} found convincing equal support for the first-line therapies of propranolol (60–320 mg per day), propranolol long-acting, and primidone (50–1000 mg per day) as well as evidence that they are synergistic. Second- and third-line drugs to be considered include gabapentin, topiramate, and clonazepam, among others. It was concluded that botulinum toxin ‘may be considered for limb, head, and voice tremor’, with the first limited by weakness. For medically refractory cases, thalamic deep brain stimulation should be considered; this has largely replaced thalamotomy because of its improved safety, especially when performed bilaterally. Patients with ET also benefit from learning more about the condition, including the support of others, and it is recommended that all be referred to the International Essential Tremor Foundation.\textsuperscript{7}

This case is instructive for two reasons. First, it demonstrates the typical historical and clinical features of essential tremor, including a long duration of tremor prior to seeking medical attention and usually a positive family history suggesting autosomal dominant inheritance. The examination in ET demonstrates a bilateral postural and kinetic tremor of the upper limbs. And, second, this case illustrates the available medical and surgical treatment options for ET.

REFERENCES
Legend to video

Case 91  After discussion of the patient’s history, the video demonstrates that there is no tremor at rest, although as mentioned in the case report, at times there was a mild rest tremor of the left hand. There is a bilateral postural tremor best demonstrated when she assumes a ‘wing-beating’ position. The tremor persists with finger-to-nose, but there is no terminal accentuation. Drawing a spiral further demonstrates a rhythmical oscillation.
Low cholesterol can be bad for your health

Elizabeth L Peckham and Barbara Illowsky Karp

CASE PRESENTATION

This 32-year-old man had had intolerance of formula during infancy and of fatty foods during early childhood. His early neurologic development appeared normal, although his parents recalled that he had had mild clumsiness and difficulty learning to ride a tricycle. By age 14 years he was having problems in school and had developed hand tremor, difficulty writing, an awkward gait, and poor coordination. Neurologic evaluation at that time demonstrated poor fine motor control and difficulty with tandem gait. The evaluation was remarkable only for a serum cholesterol of 50 mg/dl (normal 150–240 mg/dl), triglycerides 5 mg/dl (normal 70–150 mg/dl), and there was mild elevation of liver enzymes. No diagnosis was reached. He was referred for occupational and physical therapy.

Over the next few years, he was evaluated by several neurologists who documented worsening gait, slurred speech, tremor of the head and hands, poor vibratory and proprioceptive sensation, and absent deep tendon reflexes. Mild pes cavus and thoracic scoliosis were also noted. Testing for lysosomal storage diseases was negative. Brain-stem auditory evoked potentials were normal, and median nerve somatosensory evoked potentials showed abnormality of the ‘large fast-conducting sensory system’. Visual evoked potentials were abnormal bilaterally. Electromyography showed a mild sensorimotor neuropathy. He was given a diagnosis of Friedreich’s ataxia. He was followed without specific treatment, seeing several neurologists over the next 3 years.

DISCUSSION

At age 17, the constellation of tremor, ataxia, peripheral neuropathy, and retinal dysfunction was recognized in the context of low lipid levels as indicative of abetalipoproteinemia. The diagnosis was confirmed by finding acanthocytes on peripheral blood smear, marked fat malabsorption, and a low vitamin E level. High dose vitamin E and vitamin A supplementation was initiated along with a low fat diet. His neurological symptoms then stabilized. Examination at age 36 (see video, Case 92) shows truncal and appendicular ataxia with a postural and
intention tremor of his hands as well as titubation of the head. Marked dysarthria is also present. He has absent reflexes and poor vibratory sense in the lower extremities. He considers head tremor to be the most bothersome symptom.

Abetalipoproteinemia (Bassen–Kornzweig disease) was first described in 1950 in an 18-year-old Jewish woman. Her symptoms resembled Friedreich's ataxia with additional features of retinitis pigmentosa, bizarrely shaped red blood cells, and steatorrhea beginning in childhood. By the 1960s, the association of abetalipoproteinemia with the absence of low-density lipoproteins (beta protein) and of apolipoprotein B was reported. Initially this was considered a neurodegenerative disease of unknown etiology. However, in 1965, Kayden and Silber proposed that the neurological symptoms of Bassen–Kornzweig disease could be due to vitamin E deficiency resulting from malabsorption of this fat-soluble vitamin. Subsequent studies confirmed this, and showed that neurological deterioration could be slowed or prevented by early initiation of high dose vitamin E supplementation. Yet, once signs have progressed, they do not resolve with vitamin E repletion. Alternative causes of low levels of vitamin E, such as other malabsorption syndromes, can reproduce a similar spectrum of signs to abetalipoproteinemia.

Abetalipoproteinemia is autosomal recessive. The genetic defect has been mapped to chromosome 4q22–q24. The disease occurs in both sexes, but is more common in men. Hypobetalipoproteinemia, a dominantly inherited condition, can cause similar but less severe manifestations that may present later in life. The disorder is due to mutated apolipoprotein B resulting from defective aposecretion by enterocytes and hepatocytes. As in this case, symptoms of abetalipoproteinemia typically present in infancy with feeding intolerance and steatorrhea. The neurologic signs begin in childhood with progressive gait unsteadiness, tremor, and visual loss, especially night blindness, which can progress to loss of central vision. Ataxia, areflexia, sensory loss, and intention tremor are found on examination, along with kyphoscoliosis, Babinski signs, and pes cavus in some patients. Electromyography (EMG) may show a large fiber polyneuropathy. The prognosis depends on whether the condition is recognized and treated early. Untreated patients are usually bedridden by the third decade, and death due to progressive neurological decline is likely by the fourth decade.

Other neurological disorders causing a similar clinical presentation, such as Friedreich's ataxia, ataxia–telangiectasia, and spinocerebellar degeneration, can be differentiated by the absence of fat malabsorption, normal lipoprotein and vitamin E levels, and normal red blood cell morphology. The diagnosis of abetalipoproteinemia relies on recognition of the clinical findings, acanthocytes on peripheral blood smear, and very low total cholesterol and triglyceride levels. In addition, plasma apolipoprotein B is absent along with the individual fractions containing it, including chylomicrons, very-low-density lipoproteins, and low-density lipoproteins. Levels of fat-soluble vitamins, including vitamin E and vitamin A, are low. A prolonged prothrombin time identifies vitamin K deficiency in some patients. Vitamin D is normal due to alternative pathways of absorption. Fecal fat measurement with a 72-hour high fat challenge will demonstrate fat malabsorption. Intestinal biopsy reveals the diagnostic engorgement of mucosal cells with lipid droplets. However, patients can rarely tolerate the amount of fat required to perform such a test. Ophthalmologic examination
may reveal atypical retinitis pigmentosa. Management should focus on early recognition and treatment, as neurologic and ophthalmologic degeneration can largely be prevented by through supplementation with high doses of the fat-soluble vitamins. In addition, the patient should be maintained on a low fat diet.

This case is instructive because it demonstrates the classical presentation of Bassen–Kornzweig disease along with confirmatory laboratory findings. It also demonstrates the consequences of delayed treatment of abetalipoproteinemia. Even though Bassen–Kornzweig disease is rare, it is important to recognize the clinical and laboratory findings to make the diagnosis and initiate early, preventive treatment with supplementation of fat-soluble vitamins.

REFERENCES


Legend to video

Case 92 The video demonstrates a postural and kinetic tremor of the arms with dysmetria as well as titubation of the head and trunk.
A man with a jerky, useless arm

Ana Sanchez and Stephen G Reich

CASE PRESENTATION

A 66-year-old man presented with the gradual onset of a ‘left hand cramp’ and progressive inability to use the left hand. The patient described a loss of dexterity most apparent when using a key or buttoning with the left hand. He also complained of stiffness and irregular jerking confined to the left upper extremity. Over the next year, he developed numbness in the left hand, an unsteady gait, and the gradual onset of stiffness in the right upper extremity.

On examination at the initial visit (see video, Case 93), he was alert and attentive with no memory impairment. He was able to comprehend, name, and repeat, but there was decreased fluency. He had difficulty doing subtraction. Tests of ideomotor apraxia demonstrated primarily spatial errors and there was also constructional apraxia. A clock drawing suggested mild left-sided neglect. The cranial nerves were normal, including vertical gaze. The reflexes were 2+ and symmetrical with down toes. Limb strength was normal, but tone was increased in the left upper extremity. The left hand was claw-like with flexion of the fingers at the metacarpophalangeal (MCP) joint and the arm was flexed and adducted at the shoulder. There was poor voluntary control of the left upper extremity. There was both spontaneous and stimulus-sensitive myoclonus in the left arm. There was no tremor. Sensory testing demonstrated agraphesthesia in the right upper extremity. The gait was normal with the exception of decreased left arm swing.

Magnetic resonance imaging (MRI) demonstrated only asymmetrical atrophy involving primarily the right precentral gyrus.

DISCUSSION

The findings in this patient localize to the cortex as well as the basal ganglia, and this unique combination, especially with a unilateral presentation, is characteristic of corticobasal degeneration (CBD). With time, the patient developed bilateral rigidity and difficulty walking. The rigidity and dystonia were treated with botulinum, with mild benefit, and the myoclonus improved with clonazepam. Corticobasal degeneration, as it is now known, was originally described in 1968 by Rebiez, Kolodny, and Richardson under the name ‘corticodentatonigral degeneration with neuronal achromasia’. Referred to as ‘this strange disorder’, they presented three cases, two women and a man, all of Irish ancestry, of a progressive neurologic disorder ‘... characterized by severe impairment in the
control of muscular movements, by abnormalities in posture and by involuntary motor activity.' In all cases, the symptoms had begun unilaterally with clumsiness and slowness. The pathologic changes included asymmetrical atrophy of the frontoparietal cortex with neuronal loss, gliosis, and swollen neurons resistant to staining, hence the designation 'neuronal achromasia'. In addition to the cortical changes, there was also depigmentation of the substantia nigra and degeneration of the dentatorubrothalamic system.

Following the report by Rebiez et al, little attention was paid to CBD until it was 'reintroduced' in 1990 by Riley et al with a report of 15 cases. This paper made two prophetic statements that have subsequently been confirmed: first, that CBD was more prevalent than the few case reports prior to 1990 suggested, and second, that the clinical features made CBD 'readily recognizable on a clinical basis'. CBD is one of the most uncommon of the parkinsonian syndromes, typically presenting in the 60s, and is almost always sporadic. Exact data on the epidemiology of CBD are lacking but, estimating that CBD accounts for 4–6% of all cases of parkinsonism, Togasaki and Tanner calculated an incidence of 0.62–0.92/100,000 per year and a prevalence of 4.9–7.3/100,000, suggesting up to 20,000 cases in the United States in 2000.

The hallmark clinical features of CBD are unilateral extrapyramidal and cortical signs. These include limb clumsiness or uselessness, bradykinesia, rigidity, dystonia, myoclonus, apraxia, and cortical sensory loss. An alien limb, characterized by a limb that seems to have 'a mind of its own', is another distinctive feature of CBD. Although the original report stated that 'intelligence was relatively preserved until the end', it is now well appreciated that dementia and other neuropsychiatric abnormalities are common in CBD and may be the presenting features. As reviewed by Graham et al, these include constructional apraxia, impaired spelling, frontal lobe dysfunction, acalculia, visuospatial skills, and behavioral changes, with relative sparing of memory. Language impairment includes non-fluent aphasia and apraxia of speech.

When the presentation of CBD is 'typical', as in the above case, the diagnosis, to one familiar with the disorder, is relatively straightforward and can be made with a high degree of specificity. Yet, either because the full-blown clinical picture may not be present initially, or due to less typical features at onset, such as dementia, behavioral changes, and aphasia, CBD is often difficult to diagnose, with a relatively low rate of sensitivity. The broad spectrum of abnormalities in CBD overlap with many other disorders, leading to a broad differential diagnosis ranging from other parkinsonian syndromes such as progressive supranuclear palsy (PSP), Parkinson’s disease (PD), and multiple system atrophy (MSA) to primary dementing illnesses such as frontotemporal dementia (FTD), Alzheimer’s disease (AD), and dementia with Lewy bodies, to primary progressive aphasia, among others. At present, there are no paraclinical diagnostic markers that can confirm the clinical diagnosis of CBD, but asymmetrical cortical atrophy on MRI or computed tomography (CT) can be supportive, and functional imaging, while not specific for CBD, may help to separate it from other disorders such as PD or AD.

A definite diagnosis of CBD cannot be made except at autopsy. As demonstrated by Rebiez et al, the gross features include asymmetrical or focal cortical atrophy with depigmentation of the nigra, and histologically, there is neuronal...
loss. The most important pathological advance has been recognition that CBD is associated with an accumulation of hyperphosphorylated tau, and current criteria require the presence of tau immunostaining of neural and glial elements in the cortex and basal ganglia, which has largely replaced the originally described ballooned, achromatic neurons as the most distinctive features of CBD.10

Despite significant advances in the clinical spectrum of CBD, the development of clinical and pathological diagnostic criteria, and the discovery that CBD is a tauopathy, little progress has been made in the treatment of this inexorably progressive disorder, usually leading to death in 7–10 years. Pharmacotherapy has a limited role but should be considered, for example levodopa for rigidity and bradykinesia, and clonazepam for myoclonus. Dystonia and rigidity may improve with botulinum toxin. Largely, though, care is supportive/palliative.1,9

This case is instructive because it demonstrates a typical presentation of corticobasal degeneration with the unilateral onset of a jerky, rigid, ‘useless’ limb with dystonia and myoclonus as well as cortical signs of agraphesthesia, dyscalculia, apraxia, and decreased fluency.

REFERENCES


Legend to video

Case 93 This video, made at presentation, demonstrates dystonia of the fingers of the left hand, poor use of the hand, and spontaneous and stimulus-sensitive myoclonic jerks.
Chorea in a septuagenarian

Stephen G Reich and Karen E Anderson

CASE PRESENTATION

A 76-year-old woman was seen for chorea and imbalance. On the background of good health, these problems were first noticed 6 years previously and had been slowly worsening. The patient had not noticed any significant cognitive symptoms nor had her family, but they did observe that she had more difficulty processing several mental tasks simultaneously. She had had several falls and was using a walker. She was not depressed. There was no history of drugs known to cause movement disorders, but one of the two neurologists she saw previously had started thioridazine for the chorea; in neither case was a diagnosis established. Magnetic resonance imaging (MRI) of the brain was interpreted as normal.

There was no known family history of chorea, dementia, psychiatric illness, or imbalance. Both of the patient’s parents had lived until their 70s, each dying of cancer without a known or observed neurologic psychiatric abnormality. A sister, age 70, was reported as healthy, and her only other sibling, a brother, had died of cardiac disease at age 70 without any neurologic problems. She had lost one son in an accident and her two other children, a son age 37 and a daughter age 49, were in good health, as were her four grandchildren.

The patient’s medical history included only hypertension, a hysterectomy, and surgery for rectal prolapse. Aside from thioridazine (75 mg at bedtime), her only other medications were valsartan and alendronate. On presentation, she scored 23/30 on the Mini Mental State Examination (MMSE). Speech was slightly slurred. Her gait was abnormal with imbalance and choreiform movements. There was mild chorea of all limbs with mild slowing and incoordination of rapid repetitive movements (see video, Case 94). Reflexes were normal as were the cranial nerves, with the exception of possible, mild slowing of saccades.

DISCUSSION

This 76-year-old woman presented with chorea and dementia beginning at age 70 without a known family history of chorea. Despite the advanced age and lack of family history, Huntington’s disease (HD) was still suspected and confirmed by genetic testing, demonstrating 40 CAG repeats. A review of the MRI originally interpreted as normal demonstrated caudate atrophy.
Huntington’s disease is an autosomal dominant disorder due to an expanded CAG trinucleotide repeat on chromosome 4, which encodes the protein huntingtin whose function remains unknown.\textsuperscript{1–3} Alleles with 40 or more CAG repeats cause HD; repeat lengths of 36 or fewer are not associated with disease, and 37–39 repeats represent an intermediate phase which may or may not manifest clinically but can be expanded and lead to HD in subsequent generations.

The main clinical features of HD include chorea, dementia, personality changes, and psychiatric disturbances,\textsuperscript{4} which vary in severity between patients and not all may be obvious at presentation. The usual age of onset is the fourth to fifth decade, but there is marked variability ranging from childhood to the elderly.\textsuperscript{3} Late-onset cases, defined as onset after age 50, account for 10–25\% of all patients,\textsuperscript{5,6} and are particularly susceptible to misdiagnosis as information about other family members may be sketchy, unknown, or incorrect. Furthermore, when HD begins late, parents may have passed away before manifesting signs of HD or may have received an incorrect diagnosis such as alcoholism, schizophrenia, or dementia in the years prior to genetic testing. Other reasons that late-onset HD may be misdiagnosed include minimal or no chorea, prominent behavioral or affective disorders leading to a psychiatric diagnosis, and inadequate appreciation that HD may begin in the elderly. Even George Huntington, who described the disorder, was unaware of this fact: ‘I do not know of a single case that has shown any marked signs of chorea before the age of thirty or forty years, while those who pass the fortieth year without symptoms of the disease are seldom attacked.’\textsuperscript{7}

In a series of 111 patients with clinically diagnosed HD, 25 became symptomatic (defined by the presence of chorea) after age 50 (average 57.5 years), with an average age of diagnosis of 63.1 years.\textsuperscript{5} Late-onset cases were more often of maternal inheritance and had a slower disease course,\textsuperscript{5} now understood to largely reflect a smaller expansion of the CAG repeat. But, repeat size alone cannot account for the heterogeneity in age at onset or trajectory of progression, and not all studies have shown that late-onset cases are most often of maternal inheritance.\textsuperscript{6} The average expansion of the CAG repeat was 42 (range 38–48) in a study of late onset HD by Kremer et al.\textsuperscript{6} While there was a negative correlation between repeat size and age of onset for the entire cohort, that correlation did not hold for those with age of onset after age 60 years, nor was there a preponderance of maternal transmission.

A particular challenge in families in whom HD is first discovered in an individual with a late age of onset is a potentially large number of subsequent generations at risk. In this patient, there were two generations. In another of our patients with late-onset HD, at the time of diagnosis, there were three susceptible generations with 64 individuals at risk.\textsuperscript{8}

While HD should be one of the first considerations in an elderly patient with chorea, there is a long list of other causes of chorea, including mimickers of HD. These can be divided into the broad categories of cerebrovascular, associated with medications or toxins, hereditary, autoimmune, metabolic, infectious, and others.\textsuperscript{9,10} It is beyond the scope of this chapter to review the entire differential diagnosis of chorea, but two deserve mention. The first includes other hereditary diseases that may mimic HD and need to be considered when a patient with a HD phenotype proves not to have an expanded trinucleotide repeat and other
sporadic causes of chorea are ruled out.\textsuperscript{11,12} In a series of 285 HD ‘phenocopies’, Wild and Tabrizi\textsuperscript{11} found a genetic cause in only eight, including five with spinocerebellar ataxia type 17 (SCA17), and one each with Huntington’s disease-like 2 (HDL2), familial prion disease, and Friedreich’s ataxia.

Phenocopies of HD include HDL1 (a familial prion disease), HDL2 (due to a trinucleotide expansion in the gene encoding junctiphilin-3), HDL3 (genotype not identified), and HDL4, now known to be SCA17, also due to an expanded trinucleotide repeat. Aside from SCA17, additional spinocerebellar ataxias that may mimic HD include SCA1, SCA2, SCA3, and dentatorubropallidoluysian atrophy (DRPLA). Disorders characterized by iron deposition in the basal ganglia may also mimic HD, including the autosomal dominant neurodegeneration with brain iron accumulation (NBIA) due to a mutation in the ferritin light chain, and neuroferritinopathy (NBIA2), a recessive disorder also known as PKAN (pantothenate kinase-associated neurodegeneration), both of which are associated with abnormal MRI. Two other recessive disorders to consider include neuroacanthocytosis and Wilson’s disease.\textsuperscript{11,12}

It is not too uncommon to encounter an older patient with sporadic chorea, normal imaging, and a completely negative work-up, including the disorders mentioned above, fitting the description of ‘senile chorea’.\textsuperscript{13–16} Prior to discovery of the HD gene, it was generally assumed that such cases were HD with an unknown family history, with questionable paternity, or due to spontaneous mutations. With the availability of gene testing, it is clear that while at least half of all patients with senile chorea have late-onset HD, there remain patients in whom the description ‘senile chorea’ still applies.\textsuperscript{13–16} But, we caution against applying this as a specific diagnosis, recognizing that the list of HD phenocopies continues to expand, with simultaneous shrinkage in the number of individuals with ‘senile chorea’.

This case is instructive because it demonstrates that Huntington’s disease can begin at any age from childhood through the elderly. It should always be considered in older patients with chorea, even when the family history is negative.

REFERENCES

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Legend to video

Case 94  There is mild slurring of speech. While sitting, there is chorea of the neck, lower face, and all limbs. The upper limb chorea exacerbates while maintaining posture demonstrating ‘piano playing movements’. The gait is unsteady and irregular due to a combination of chorea and imbalance.
Treatment of dyskinesias in Parkinson’s disease: new use of an old drug

Daniel Kremens and Howard I Hurtig

CASE PRESENTATION

In 1976, a 34-year-old man first noticed stiffness and decreased left arm swing. One year later a tremor emerged and he was diagnosed with Parkinson’s disease (PD). He started taking carbidopa/levodopa with marked improvement in all of his symptoms. Eventually, he developed levodopa-related motor fluctuations with dyskinesias in the ‘on’ state and tremor with bradykinesia in the ‘off’ state that responded to more frequent dosing of carbidopa/levodopa and benztropine mesylate. By age 48, the tremor had become worse, and he developed intermittent freezing of gait. He had episodes of the left arm curling behind his back and toe cramps. Bromocriptine, then pergolide, and controlled release levodopa were added with modest benefit.

At age 50, he was no longer able to work as a salesman and retired. By age 54, he had worsening dyskinesias on both sides of the body, rest tremor alternating with dystonia on the left side, and increasing postural instability with occasional falling. He underwent a right pallidotomy and initially had marked improvement in gait, tremor, and dyskinesias. However, over the next several years, symptoms worsened, especially left leg dystonia, despite the addition of pramipexole and entacapone. He also developed urinary urgency with incontinence and difficulty with speech. By age 60, the patient had to move into an assisted living facility.

In March 2004, at age 63, he was on a complicated regimen of regular and controlled release carbidopa/levodopa, carbidopa/levodopa/entacapone (Stalevo®), pramipexole, and proamantine with fludrocortisone for orthostatic hypotension. He was unable to walk without a walker and was falling up to 25 times daily because of marked dyskinesia/dystonia, especially in the left leg. He was started on amantadine 100mg twice daily in an effort to modulate the fluctuations and dyskinesias. Within 48 hours of starting amantadine, he improved dramatically. The tremor, dyskinesia/dystonia, and wearing-off were eliminated. He stopped freezing, and his gait improved to the point where he was able to jog. He was so enthusiastic that he wrote an editorial in his local
newspaper describing his experience with Parkinson’s disease. He noted, ‘[M]iracles do happen and [amantadine] is doing the impossible … amantadine has reversed my Parkinson’s.’ By August 2004, some mild dyskinesias had returned. When the patient was last seen, in November 2004, his gait had worsened slightly but he remained free of freezing, dyskinesia/dystonia, and tremor.

**DISCUSSION**

In 1969, Schwab et al described a serendipitous discovery that amantadine, taken for influenza A prophylaxis, abolished the rigidity, bradykinesia, and rest tremor of a patient with severe PD. This observation was followed by a series of clinical trials in the early 1970s that evaluated the efficacy of amantadine compared to levodopa and anticholinergics, either as monotherapy or adjunctive therapy. These trials confirmed that amantadine was effective in relieving symptoms in over 50% of PD patients. Moreover, the side-effects, including nausea, anxiety, dizziness, livedo reticularis, leg edema, psychosis, and confusion (generally in patients with cognitive impairment) were infrequent and relatively mild. These positive effects of amantadine, although satisfying, were considered modest at best, and with the development of levodopa and dopamine agonists, interest in amantadine waned.

This lack of enthusiasm was heightened by the fact that no one understood the mechanism by which amantadine relieved the symptoms and signs of PD. Early investigators hypothesized that amantadine directly inhibited dopamine reuptake at nigrostriatal receptors. However, a series of experiments in the early 1990s suggested that the dominant pharmacological basis of amantadine’s antiparkinson effect resulted from non-competitive antagonism of the N-methyl-D-aspartate (NMDA) receptor. Papa and Chase demonstrated that another potent NMDA receptor antagonist relieved levodopa-induced dyskinesias in primates with MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine) parkinsonism, and this insight led researchers to consider whether amantadine could relieve dyskinesias in humans.

In 1997, Adler et al published a retrospective chart review of four patients with advanced PD who had sustained relief (9 months to 2 years) from dyskinesias, dystonia, and motor fluctuations after starting amantadine. In 1998, Rajput et al described an open-label study in which 42 PD patients with dyskinesias were given amantadine. A subgroup of 27 patients remained on a stable drug regimen except for the addition of amantadine. In this subgroup, 19 (70%) had a 25% or greater reduction in dyskinesias, and at last follow-up 8–28 months later, 47% of patients had sustained dyskinesia relief. Around the same time, Verhagen Metman et al published the first placebo-controlled, double-blinded crossover study of amantadine, in which 14 out of 18 patients with advanced PD had a 60% reduction in dyskinesias compared with placebo. A follow-up study 1 year later found that the benefits persisted. At least six other double-blind placebo-controlled studies employing validated rating scales have also demonstrated that amantadine (200–600 mg orally, 200–400 mg intravenously) relieved levodopa-induced dyskinesias by up to 60%.

Although it is well accepted that amantadine ameliorates levodopa-induced dyskinesia, controversy remains regarding its long-term efficacy. As in our
Treatment of dyskinesias in Parkinson’s disease

Some dyskinesias may return, but most patients studied have maintained some benefit. Moreover, patients often worsen when amantadine is withdrawn. Finally, Uitti et al observed that amantadine use was an independent predictor of improved survival, and this may reflect a putative neuroprotective effect.

This case is instructive because it demonstrates that even a complicated patient with advanced Parkinson’s disease may have marked improvement with the addition of amantadine, particularly for treatment of levodopa-induced dyskinesias.

REFERENCES

Asymmetrical movement disorder and behavioral disturbance in a young man

Dzintra F Celmins and Eric S Molho

CASE PRESENTATION

A 24-year-old man from Hong Kong was evaluated for the gradual onset of a tremor affecting his right arm, of 6 months’ duration. The tremor was initially noticed when holding plates at his job in his father’s restaurant. Over time his handwriting had become difficult and his right arm felt slightly stiff and clumsy. He also complained of a decline in his short-term memory and the need to write things down to remember them. He was previously very bright. He held a bachelor’s degree in finance and accounting and had worked temporarily for a financial corporation in New York City, but left because of not being able to tolerate the high job stress. He reported mood lability, uncontrollable laughter during socially inappropriate times, and difficulty controlling sexual impulses.

He had no history of head injury, birth trauma, mental disorder, or exposure to toxins or neuroleptic medications. His medical history was relevant for kidney stones at age 16. At that time, he was found to have nephrolithiasis, microhematuria, and hypercalciuria with increased oxalate excretion. He denied liver disease. There was no family history of neurological disease.

The general examination was normal except for brown-pigmented rings in the periphery of his corneas that were difficult to distinguish from the brown color of his iris. On neurologic examination he was oriented but slightly slow in responding. He had trouble expressing himself and confining his thoughts to the subject. He had a mild, intermittent, horizontal tremor of his head and mild hypomimia. There was mild rigidity in his right arm. He had a coarse, slow tremor of his right arm present at rest, with posture and also with action. When performing finger tapping with the opposite hand, the tremor became quite prominent and proximal in its distribution. Repetitive tasks were bradykinetic on the right. Handwriting was micrographic and unsteady. There was a mild decrease in arm swing bilaterally and a tremor of his right hand as he walked.
DISCUSSION

The onset of a progressive, asymmetrical mixed movement disorder with cognitive and psychiatric symptoms at the age of 24 suggested the possibility of Wilson’s disease in this patient. Laboratory testing showed a normal blood count and comprehensive metabolic panel, including thyroid and liver function tests. Serum copper level was 36µg/dl (normal 70–155µ/dl). Serum ceruloplasmin was 2mg/dl (normal 26–63mg/dl). To calculate non-ceruloplasmin copper, multiply ceruloplasmin by 3 (each mg/dl of ceruloplasmin contains 3µg/dl of copper) and subtract from the total copper. Doing so in this patient yields a value of 30µg/dl (normal is 10–15µg/dl).² Twenty-four-hour urinary copper excretion was 870µg (normal 3–35µg/24 h). Slit lamp examination confirmed the presence of Kayser–Fleischer (KF) rings (Figure 96.1). Brain magnetic resonance imaging (MRI) showed abnormally increased T2 signal in the brainstem, deep cerebellum, and basal ganglia, decreased signal in the globus pallidus, and diffuse brain atrophy (Figure 96.2).

The diagnosis of Wilson’s disease was confirmed by the extremely low serum ceruloplasmin, high non-ceruloplasmin serum copper, high urinary copper, presence of KF rings, and characteristic brain MRI findings.²,³ The patient was started on D-penicillamine 250mg daily, increasing gradually to 1000mg daily. After 4 months he was on a maintenance dosage of 250mg three times a day, which he has been receiving for 10 years with no side-effects. His neurological symptoms gradually improved, and the tremor and rigidity disappeared within 1 year. The emotional lability, irritability, and impulsiveness gradually resolved over the next 2 years. However, his cognitive symptoms never recovered fully.

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Figure 96.1  Kayser-Fleischer rings are most apparent in the superior and inferior portions of the cornea in this patient.
He was not able to work at a job consistent with his high educational level. Repeat brain MRI 6 years later was normal other than moderate diffuse brain atrophy. His two younger siblings, a 20-year-old sister and a 23-year-old brother, were screened for Wilson’s disease and were normal.

**DISCUSSION**

Wilson’s disease is a rare, autosomal recessive disorder of hepatic copper metabolism caused by mutations in a gene encoding a copper-transporting P-type adenosine triphosphatase (ATPase) located on chromosome 13. More than 200 mutations in this gene have already been identified. These mutations result in insufficient copper excretion from the hepatocyte into the bile canaliculus. Excess copper accumulates and initially damages the liver. When liver storage becomes overwhelmed, copper spills into the plasma and ultimately damages other organs, causing the neurological, hematological, ophthalmological, orthopedic, dermatological, and renal manifestations of the disease. The mean age of onset is 17 years, and 80% of patients present with either hepatic or neurological symptoms. The main neurological signs are tremor, dysarthria, dystonia, dementia, and gait abnormalities. Psychiatric manifestations range from subtle personality changes to overt depression and psychosis. Currently, there is no single diagnostic test for Wilson’s disease, and the large number of mutations makes genetic testing impractical.

Lifetime therapy is required for patients with Wilson’s disease, which is uniformly fatal if left untreated. Historically, the goal of copper removal has been successfully achieved through the administration of potent chelating agents such as D-penicillamine. However, approximately 30% of patients do not tolerate this as long-term therapy because of side-effects, including allergic reactions, immunological disorders, and disfiguring skin reactions. Also of concern is the possibility that D-penicillamine can occasionally cause an initial worsening of neurological symptoms. This paradoxical deterioration has been attributed to the mobilization and redistribution of copper resulting in higher levels in the blood and subsequently in susceptible organs such as the brain. Trientine and
ammonium tetrathiomolybdate have been proposed as safer initial treatments for patients with neurological symptoms, but this remains controversial. Maintenance therapy is generally achieved with either lower doses of chelating agents or oral zinc therapy, which blocks intestinal absorption of copper.

**ACKNOWLEDGMENT**

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This case is instructive because it demonstrates the classical neurological presentation, laboratory abnormalities, and imaging findings of Wilson’s disease. It also serves as a reminder that any young patient (<40 years old) who presents with parkinsonism, dystonia, or an unusual tremor could have this rare disorder. Interestingly, this patient’s liver function tests had been normal, but he had had kidney stones 8 years prior to his neurological presentation, which were almost certainly the result of Wilson’s induced renal disease. The significance of his renal disease went unrecognized, and represents a tragically missed opportunity to have started definitive treatment prior to the onset of neuropsychiatric dysfunction. This case, again, emphasizes the need for early diagnosis of Wilson’s disease so that irreversible neurological deficits can be prevented.

**REFERENCES**

CASE PRESENTATION

A 51-year-old man presented with a 6-month history of progressive rigidity, slowness, and cognitive difficulties. At the age of 5, he had developed cramping in his legs, difficulty walking, tetany, and convulsions, and was diagnosed with primary (idiopathic) hypoparathyroidism. Despite treatment, he developed renal calcifications by age 13. His condition remained stable for many years with only one hospital admission 4 years ago due to a medication change leading to hypocalcemia. He maintained an active family, social, and professional life with no limitations.

Other symptoms at presentation included slowness of movement, difficulty writing, and an intermittent tremor of the left hand. Co-workers commented that his face had a ‘blank’ expression. He was becoming increasingly irritable and distractible. Difficulty concentrating and processing information led to problems at work. For example, if he did not immediately write down a record of a meeting, he would not recall its content. He also began experiencing slowness of gait with muscle cramping, clumsiness, difficulty swallowing, and trouble turning in bed. He reported a loss of taste and smell.

His family history was unremarkable. His medical history was, in addition to hypoparathyroidism, notable only for pericarditis, tonsillectomy, and lumbar surgery. He had previously been treated for anxiety with a benzodiazepine. His current medications included calcitriol and calcium.

On examination, he was alert and interactive. He followed all commands with a slow deliberateness. He was unable to perform serial subtractions despite prior proficiency in math, and had 3/3 immediate recall but 0/3 at 3-minute follow-up. He could name only five objects beginning with the letter ‘S’ in 1 minute. Speech was slow and monotonic. His strength and reflexes were normal. Sensory testing and coordination were normal. He had a masked face. He had a mild, intermittent resting tremor of the left hand with a mild bilateral action tremor. Muscle tone was increased throughout, with moderate, left-greater than right-sided bradykinesia. He had mild trouble arising from a chair. His gait was slow with diminished arm swing. On pull-testing, he required several steps to recover.

The most recent relevant laboratory results were: calcium 8.2 mg/dl (normal 8.5–10.4), phosphorus 5.8 mg/dl (2.5–4.5), magnesium 1.92 mg/dl (1.5–2.5), thyroid stimulating hormone (TSH) 2.12 mIU/l (0.4–5.5), tri-iodothyronine (T3)
148 ng/dl (60–181), thyroxine (T4) 9.4 µg/dl (4.5–12), ceruloplasmin 26 mg/dl (18–36). Parathyroid hormone (PTH) has been repeatedly undetectable. Magnetic resonance imaging (MRI) of the brain revealed hyperintense signal changes on T1 throughout the basal ganglia and the posterior thalamus (see video, Case 97). A follow-up computed tomography (CT) scan confirmed extensive abnormal calcification throughout the basal ganglia, thalami, dentate, and gray–white junction (Figure 97.1).

He was started on levodopa with mild improvement in the resting tremor but no change in rigidity or bradykinesia. Adjustments continue to be made to see whether there are any improvements on higher doses.

**DISCUSSION**

Cramping, tetany, and convulsions are common manifestations of hypocalcemia secondary to hypoparathyroidism. Chorea, paresthesias, and psychiatric issues such as personality changes can also occur. Only a minority of patients with hypoparathyroidism go on to develop parkinsonism. When it does occur it tends to be years – sometimes decades – after the initial diagnosis. It can occur as a result of primary (idiopathic) hypoparathyroidism or from secondary causes (such as post-thyroidectomy). The movement disorder can be heterogeneous, including ocular motor disturbances, an akinetic–rigid syndrome, resting tremor, stereotyped hand movements, ataxia, apraxia, and dementia. This variability may reflect the different areas of the brain that can be affected by hypercalcinosis. There is often calcification of the basal ganglia, thalami, and cerebellum (particularly the dentate) as well as scattered throughout the cortex and subcortex. The location and extent of calcification does not necessarily correlate with clinical severity. Indeed, there are cases of presumed hypoparathyroid-related parkinsonism with no apparent calcification and cases of extreme hypoparathyroid-induced basal-ganglionic calcification without evidence of parkinsonism. The reasons for the variability, latency, and pathogenesis of the parkinsonism remain unclear.

![Figure 97.1](image-url)  The CT scan shows extensive abnormal calcification throughout the basal ganglia, thalami, dentate, and gray–white junction.
How calcium deposition might lead to parkinsonism is not known and is complicated by the variability of both the symptoms and response to treatment. It has been postulated that low calcium and/or high phosphorus could, themselves, directly damage the nigrostriatal pathway. That some individuals have improved with levodopa suggests that the postsynaptic dopaminergic system may remain intact. Levodopa non-responders (who appear to be the majority) would, however, point to postsynaptic damage in other cases. The few reports of parkinsonism improving following therapy with calcium and vitamin D suggests, alternatively, that the etiology may be, at least in part, metabolic as opposed to purely structural. Unfortunately, many cases fail to improve significantly despite levodopa or calcium supplementation.

Calcification of the basal ganglia with hypoparathyroidism should be differentiated from Fahr’s disease. Fahr’s also leads to basal ganglionic calcification with variable neurological manifestations but is an inherited disorder (usually autosomal dominant) and is not associated with hypocalcemia. Additionally, it seldom responds to treatment with either levodopa or calcium supplementation.

This case is instructive because it underscores the need to differentiate between different etiologies of basal ganglionic calcification. Hypoparathyroidism is a potentially treatable cause of parkinsonism. Early vigilance of calcium levels in patients with the disorder may help to avoid the late and rare development of parkinsonism. When present, it may respond to treatment with vitamin D and calcium and/or with levodopa.

REFERENCES

Legend to video
Case 97 MRI reveals hyperintense signal changes on T1 throughout the basal ganglia and the posterior thalamus. The examination demonstrates hypomimia, increased neck tone, bradykinesia, absent arm swing, mild slowing of gait, and mild postural instability.
A 70-year-old man presented with his wife who reported that he was having frequent falls, cognitive impairment, urinary incontinence, and dysarthria. His problems had started several years previously with loss of balance and falls, which worsened progressively. A recent fall resulted in a fracture of the left humerus. He had also experienced a few episodes of ‘syncope’. After one episode, he was admitted to a hospital where work-up included electroencephalogram (EEG), carotid Doppler, echocardiogram, and Holter monitoring, but no significant abnormalities were found. Magnetic resonance imaging (MRI) of the head showed diffuse cerebral atrophy and signal changes in the deep white matter. A neurologist who had examined the patient previously diagnosed mild dementia (Mini Mental State Examination (MMSE) score 27/30) and autonomic dysfunction suggesting multiple system atrophy. However, autonomic nervous system studies failed to document dysautonomia.

Medical history included only hypertension. There was no similar condition in his family. His son, daughter, and two granddaughters were all healthy.

General physical examination was normal except for restricted movement at the left shoulder caused by the humeral fracture. There was no orthostatic hypotension.

Neurologic examination initially revealed mild dementia, which worsened considerably on follow-up. Ocular motility was normal, as were the fundi and remainder of the cranial nerves. Motor examination revealed mild bradykinesia and rigidity with no rest tremor. He had a slight kinetic tremor of the right upper extremity. Sensory examination was normal. Gait was wide-based. There was slight dysmetria with finger-to-nose and heel-to-shin tests, bilaterally. He had truncal ataxia with postural instability. The tendon reflexes were diffusely exaggerated. He had frontal release signs including palmomential, grasp, and snout.

Work-up revealed normal blood studies, including non-reactive Venereal Disease Research Laboratory (VDRL) testing. Spinal tap revealed an opening pressure of 140 mm. Red blood cells (RBCs) were $3 \times 10^6$ and white blood cells (WBCs) $2 \times 10^3/\mu l$; glucose 58 mg/dl; and protein 59 mg/dl. Head MRI revealed diffuse cerebral and cerebellar atrophy with scattered periventricular white matter hyperintensities. There were also hyperintensities in the middle cerebellar
peduncles best seen on FLAIR (fluid attenuated inversion recovery) sequences (Figure 98.1).

Based on the MRI findings, fragile X premutation was suspected. DNA analysis of the fragile X mental retardation gene (FMR1) revealed 84 CGG repeats (normal ≤ 40), diagnostic of fragile X tremor-ataxia syndrome (FXTAS).

In the four years of follow-up, the patient deteriorated gradually. He became more ataxic and fell almost daily. On several occasions, he has been found wandering in the neighborhood and the police have been called. On a visit about two years after diagnosis (see video, Case 98), he did not know the day, date, month, year, or his age. He could not remember any of three phrases after 3 minutes. His ability to explain proverbs was markedly impaired. He had truncal ataxia and a wide-based gait in addition to dysdiadochokinesia. He continued to deteriorate progressively until his wife could no longer cope because he could not be left unattended for even brief episodes. He spent his final two years in a nursing home. He died in September 2007, about four years after the diagnosis was established.

**DISCUSSION**

This patient presented with ataxia, frequent falls, dementia, and minimal action tremor, and was initially thought to have multiple system atrophy. The finding that made us consider FXTAS was the MRI showing the characteristic middle cerebellar peduncle abnormality (Figure 98.1). FXTAS was first described in 2001 in grandfathers of children with fragile X mental retardation syndrome.

**Figure 98.1** Magnetic resonance axial FLAIR images of the cerebellum (A) and cerebrum (B) demonstrating increased signal intensity in the middle cerebellar peduncles and in the periventricular cerebral white matter. They also show moderate ventriculomegaly and cerebral atrophy.
FXTAS is caused by excess CGG repeats in the FMR1 gene. It has protean clinical manifestations that overlap with several neurodegenerative disorders including essential tremor, multiple system atrophy, and other parkinsonian syndromes, as well as spinocerebellar degenerations. An attempt was made to improve patient detection by proposing diagnostic criteria.¹ The major clinical criteria are kinetic tremor and gait ataxia. Minor clinical criteria include: parkinsonism, short-term memory loss, and executive dysfunction. White matter lesions of the middle cerebellar peduncles were considered a major imaging criterion, while diffuse cerebral white matter disease and brain atrophy were considered minor imaging criteria. ‘Definite’ FXTAS diagnosis requires one major clinical and the major imaging criteria.¹ Our patient did not have tremor, which is a proposed major criterion. However, he did satisfy the requirements of ‘definite’ FXTAS diagnosis. Historically, a clue about FXTAS is to ask elderly men whether there is a history of mental retardation or autism in the children of their daughters.

What are the biological mechanisms that underlie FXTAS? The normal FMR1 gene has ≤40 CGG repeats. Patients with the fragile X mental retardation syndrome have >200 and often >1000 CGG repeats. This huge number of CGG repeats results in virtual absence of FMR1 protein. Patients with fragile X premutation have 55–200 CGG repeats. This relatively mild increase in CGG repeats does not considerably alter levels of FMR1 protein but it increases the formation of FMR1 mRNA.¹ It was proposed that FXTAS is caused by a gain of function that may be related to the increase in FMR1 mRNA. The exact pathophysiological mechanisms of this proposed process remain to be elucidated. Also unknown is why patients with FXTAS have only 55–100 CGG repeats and only a few instances of between 100 and 200 CGG repeats in their FMR1 gene.

The neurological syndrome of FXTAS is mostly restricted to middle-aged and elderly men. Thus far, about at least 70 patients have been reported. This is a relatively low number given that the incidence of the premutation, which varies amongst races and geographical regions, is about 1/800 men and 1/250 in women. We believe that this syndrome is more prevalent than is currently appreciated. Furthermore, we believe that FXTAS manifests only in a fraction of individuals with fragile X premutation. Whether the premutation requires other genetic concomitants or environmental factors to manifest its phenotype remains to be elucidated. Women with fragile X premutation have premature ovarian failure, but some were also noted to have subtle behavioral abnormalities. Of all reported adults with FXTAS, about 10% are women. The gender difference could be explained by the presence of two X chromosomes in women.³

The MRI abnormalities in the middle cerebellar peduncles, best seen in FLAIR sequences, are the most striking imaging feature of this disease, and are present in about 80% of patients with FXTAS.⁴ The biological basis for the MRI findings remains unknown. The pathology of FXTAS revealed intranuclear inclusion bodies in neurons and glia. These inclusions do not stain for antibodies to tau or α-synuclein. Thus, FXTAS is not a tauopathy.⁵ The inclusions immunostain with ubiquitin antibodies, but this is not a specific feature.

At present, there is no specific treatment for FXTAS and therapy is symptomatic and supportive, including treatment of tremor, dementia, and
incontinence of bowel and bladder, in addition to physical therapy. Even though effective treatment is lacking, it is important to make the proper diagnosis because it allows families and physicians to prognosticate and patients and their families to stop searching for a diagnosis. Proper diagnosis also allows for genetic counseling for families.

This case is instructive because it demonstrates the clinical and radiographic features of FXTAS. Confirming the genetic diagnosis, suspected on the basis of the clinical features of ataxia and dementia, and especially the signal changes of the middle cerebellar peduncle, provided a definitive diagnosis to a patient who was previously thought to have multiple system atrophy.

REFERENCES


Legend to video

Case 98 There is cognitive impairment with disorientation to date and age as well as inability to interpret a proverb. He is unable to copy interlocking pentagons. The gait demonstrates mild ataxia with a tendency to veer.
Patient selection for deep brain stimulation for idiopathic Parkinson’s disease

Suketu M Khandhar and William J Marks Jr

CASE PRESENTATION

A 63-year-old, left-handed man developed an intermittent, unilateral rest tremor of his left hand 15 years ago. He then experienced slowness of gait and reduced dexterity and was diagnosed as having Parkinson’s disease. Several years later, he began taking carbidopa/levodopa, with an excellent response. His condition continued to worsen, with spread of tremor to other limbs and increasing rigidity. Despite escalating doses of levodopa taken every 3 hours in conjunction with dopamine agonists, anticholinergic medication, amantadine, and a catechol-O-methyltransferase (COMT) inhibitor, the patient developed increasing difficulty with mobility. He began to fall frequently, but only when the effect of levodopa abruptly and often unpredictably wore off.

Twelve years following the diagnosis, he started to use a walker and eventually a motorized wheelchair. After taking his medication, he would enjoy a brief period of excellent, independent mobility, followed by severe choreoathetotic dyskinesia. Higher doses of the dopamine agonist were poorly tolerated. He experienced mild dysarthria but no cognitive difficulty, depression, or dysphagia. He had mild chronic obstructive pulmonary disease but no other significant medical history.

Examination ‘off’ medication revealed a masked face, mild hypophonic dysarthria, and full extraocular motility. There was severe rigidity affecting all limbs, left greater than right; moderate to severe bradykinesia; intermittent but severe tremor of both arms; inability to arise without assistance; and severe hesitancy of gait initiation. Following his usual morning dose of antiparkinsonian medication, his face became animated, rigidity and bradykinesia improved, and the patient arose and walked without assistance. The patient then sought advice regarding additional treatment options.

DISCUSSION

This patient’s history, clinical course, and examination are consistent with idiopathic Parkinson’s disease (PD). At this stage in the patient’s disease, the only
treatment option likely to provide substantial improvement in function is deep brain stimulation (DBS). Treatment for PD initially consists of pharmacological treatment, but with disease progression escalating doses of medication fail to provide consistent and sustained control of motor symptoms. For such patients, surgical intervention with DBS is a reversible, relatively non-destructive, and adjustable treatment that can suppress cardinal parkinsonian motor symptoms (see video, Case 99).

Deep brain stimulation of either the subthalamic nucleus (STN) or globus pallidus interna (GPI) is effective for patients with idiopathic Parkinson’s disease, but not for those with atypical parkinsonian syndromes. Thus, in determining candidacy for treatment with DBS, the most important issue is to confirm the diagnosis of idiopathic PD. A careful history and examination looking for typical and atypical features is critical. Features that suggest atypical disorders include rapid disease progression (most patients with disabling PD in whom DBS therapy is being considered have disease duration of greater than 5 years and typically 10 or more years), pyramidal or cerebellar findings, prominent dysautonomia, prominent cognitive impairment, supranuclear vertical gaze palsy, or lack of robust response to levodopa. The patient in this case developed progressive worsening of the cardinal signs of PD, had no unusual features, exhibited a brisk response to levodopa, and carried the diagnosis for more than 10 years.

Once the clinical diagnosis of PD is certain, the examiner should assess which symptoms are most troublesome to the patient. DBS is most effective for treatment of bradykinesia, rigidity, tremor, associated motor fluctuation, some disturbances of gait, and dyskinesia. Dyskinesia, a result of long-term use of dopaminergic medication (especially levodopa), did occur in this patient. GPI stimulation usually decreases dyskinesia directly, whereas STN stimulation can improve dyskinesia either by associated reduction in medication requirements or by direct effects. Symptoms less responsive to treatment with DBS include freezing of gait (particularly when persistent in patients’ best ‘on’ periods of function), postural instability, speech disturbances, and non-motor symptoms.

Assessment of disability should be individualized for each patient. DBS is considered when the patient reaches a point where it becomes increasingly difficult to carry out usual daily activities due to inadequate quantity or quality of ‘on’ time. Because of the potential risk of serious complications, although relatively small, DBS is reserved for patients who experience troubling symptoms despite optimization of pharmacotherapy. Yet, it is important not to persist with futile attempts at medication adjustment, since the ideal time to intervene with DBS seems to be prior to the onset of substantial disability whenever possible.

Comorbid conditions, such as diabetes, coronary artery disease, or hypertension, if treated and stable, should not deter consideration of DBS. Patients with PD complicated by dementia are generally poor candidates for DBS, as they seem less likely to obtain robust motor benefit and may sustain surgery-related cognitive decline. For patients with questionable mental status, formal cognitive testing is imperative. Since depression, anxiety, and psychosis are common in PD, identification and treatment of these comorbidities prior to surgery is important. It is crucial to discuss all aspects, potential risks, and expected benefits of surgery with the patient and their family – emphasizing realistic expectations
and goals. Patients need to be aware that maximal benefit may not be realized until several months after DBS surgery, due to the need for optimization of stimulation parameters and the concomitant medication regimen.

This patient underwent DBS 2 years ago and continues to experience persistent substantial benefit. His off-medication Unified Parkinson’s Disease Rating Scale motor score has improved by 60% compared to his pre-surgery score. He experiences consistent control of his cardinal parkinsonian symptoms without motor fluctuations or dyskinesia throughout the entire day, is ambulatory, and no longer falls. His medication requirements have been reduced by 75%.

This case is instructive because it illustrates appropriate and generally established clinical criteria in selecting patients for DBS to treat Parkinson’s disease. It also demonstrates the improvement possible with DBS.

Legend to video

Case 99  In the first segment, the patient is pre-deep brain stimulation (DBS) in the ‘off’ state. He has a shuffling gait, eventually progressing to akinesia. In the second segment, also pre-DBS, his is seen in the ‘on’ state. He is much more mobile but has moderate dyskinesia. In the final segment, the patient is seen ‘off’ medication but with DBS activated. The significant improvement is very dramatic as he looks essentially normal with no difficulty walking, including normal stride length and velocity.
CASE PRESENTATION

A 56-year-old professional guitarist presented for evaluation of a progressive decline in his ability to play. Nine years previously he had noticed a decrease in the speed of his dominant right hand while playing, and over time his ability had gradually declined, especially during the year before being seen. Classical playing, requiring all five fingers to strum, was described as ‘90% off’, whereas jazz pieces were only ‘2% off’ as they were done with a pick. While playing classical music, digits 3, 4, and 5 would flex involuntarily. When he attempted to increase his finger speed, the fingers would ‘lock’. He tended to miss notes. The involuntary movements also interfered with demonstrations to his students. About 4 years after the onset of difficulty playing guitar, he noticed a similar decline in his handwriting, but all other tasks were performed normally. There was no family history of a movement disorder.

On examination, while at rest and with maintenance of posture, there were no involuntary movements of the right hand. Strength, coordination, sensation, and deep tendon reflexes were normal. While playing guitar (see video, Case 100) he developed progressively worse flexion of digits 3, 4, and 5, less ability to use the thumb and index finger, and a gradual decline in speed and dexterity of the fingers. While writing, he exhibited involuntary flexion of the wrist and difficulty moving the pen, with an irregular tremor of the hand. There were no other involuntary movements on examination.

Case 100.2

A 45-year-old amateur guitarist was self-referred for a decline in his playing with the non-dominant left hand, which had begun about 4 months prior to presentation. Based on his internet research, he diagnosed dystonia. He related that he was ‘constantly playing’ and often the same pieces or exercises repetitively. He noticed ‘loss of control’ over the left 3rd, 4th, and 5th digits. While playing, the 3rd digit would extend, the 4th digit would ‘quiver’, and the 5th digit would flex. He still had good control over the 1st and 2nd digits. He did not experience involuntary movements during other tasks with the left hand, but wondered whether it was a bit clumsier when using the computer keyboard.
There was no associated pain or weakness. Occasionally, while running, he would experience numbness in the hands, and 1 year earlier he had been diagnosed as having carpal tunnel syndrome for which he wore wrist splints at night. There was no family history of a movement disorder.

On examination, strength, coordination, sensation, and deep tendon reflexes were normal. While playing guitar (see video), there was extension of the left 3rd digit, both proximally and distally, and simultaneously, flexion of the distal 4th and 5th digits.

**DISCUSSION**

Both of these patients have dystonia, characterized by sustained muscle contractions causing stereotyped twisting or turning movements or abnormal postures. The unique feature is that dystonia occurs only during specific tasks — while playing the guitar — although the first patient also demonstrates dystonic writer’s cramp. These are examples of ‘musician’s dystonia’, a focal task-specific dystonia.

As pointed out by Lederman, musician’s dystonia (‘cramp’) has been recognized since the early 18th century, but only during the past several decades, with the emergence of clinics specifically devoted to medical problems of musicians and other performers, has the extent of musician’s dystonia been more fully appreciated, along with greater recognition. It has been estimated that 1 in 200 professional musicians experience task-specific dystonia. Of musicians seeking neurologic care for performance-related symptoms, approximately 10% are diagnosed with dystonia. In Lederman’s series, and others, men are more frequently affected, with an average age of onset of 32 years, and 38 years for women. The average duration of symptoms at presentation was 5 years, with a range of 1 month to 27 years, suggesting that the diagnosis is often delayed, and that musicians themselves do not seek prompt attention.

All varieties of instruments have been associated with focal dystonia, including string (bowed and plucked), keyboard, woodwind, brass, and percussion. While the hands are most often affected, dystonia may also affect the lips, tongue, and face. Playing brass and woodwind instruments requires a fine-tuned pattern of lip, tongue, jaw, face, and respiratory control. This pattern, referred to as the embouchure, can be affected by dystonia as well. Embouchure dystonia typically manifests as lip tremor, involuntary twisting, puckering or closure (‘locking’) of the lips, or jaw closure or tremor movements when playing woodwind and brass instruments.

This diagnosis of musician’s dystonia rests on observing the characteristic movement while the patient is playing, yet only one-third of patients present with the symptoms of an involuntary movement. The most common presenting symptom in Lederman’s series was impaired control in over half of patients, followed by stiffness or cramping in an almost equal number. Ten to 20% presented with pain, fatigue, tremor, or jerking, whereas only 7% complained of weakness. As neither weakness nor sensory loss are features of dystonia, their presence suggests that electrodiagnostic studies should be performed, searching for a focal neuropathy or radiculopathy which can either coexist with dystonia or cause compensatory postures mimicking dystonia.
Dystonia results from cocontraction of agonist and antagonist muscle groups, as well as overflow of contractions to adjacent or remote muscles. It is increasingly recognized that dystonia results from abnormal cortical processing and integration of sensorimotor information. Primate models show that repetitive movements of a limb can modify the cortical sensory representation of that limb, causing reorganization of sensorimotor cortex. Brain mapping studies in musicians with focal dystonia have confirmed this plasticity in motor, pre-motor, and sensory cortices. Electrophysiologic studies have also demonstrated that ‘beneficial’ or adaptive changes in sensory–motor organization in healthy musicians ‘goes awry’ in musician’s dystonia, resulting in a maladaptive response to sensory input. The resulting motor output is then abnormal, causing an involuntary movement or posture in the affected body part. Task-specific dystonia, and particularly musician’s dystonia, likely reflects impaired central integration and, as summarized by Abbruzzese and Berardelli, such impaired integration affects motor programs which may be restricted to specific body parts and specific tasks.

Treatment of focal dystonia is challenging, and musician’s dystonia has unique features that make management even more difficult, since playing music professionally requires very fine, well-honed control, and therefore even slight deficits can cause significant impairment in the ability to play, which can be career threatening. Oral medications for focal dystonia may be beneficial, including anticholinergics and muscle relaxants. Some patients are able to employ sensory tricks to suppress dystonia, such as the use of dental prostheses for embouchure dystonia. As such, all patients with musician’s dystonia should be queried about sensory tricks, as well as tested for such tricks while being examined. Other options include retraining in technique, possibly under a new teacher, rest, physical therapy, and local injection of botulinum toxin. With treatment(s), some musicians have been able to continue their professional careers; however, many have been significantly impaired, despite aggressive therapy. Finally, when caring for professionals with musician’s dystonia it is also important to focus on its psychological effects, as dystonia can be associated with significant stress and depression when a career and lifetime devotion to music are threatened.

These cases are instructive because they demonstrate the features of guitarist’s dystonia, a task-specific form of dystonia, usually encountered in professional musicians. They also serve as a reminder that musicians and others who perform repetitive tasks may be at risk for the development of focal dystonia.

REFERENCES

**Legend to video**

**Case 100.1** While playing guitar he develops progressively worse flexion of digits 3, 4, and 5, with less ability to use the thumb and index finger, and a gradual decline in speed and dexterity of the fingers.

**Case 100.2** While playing guitar there is extension of the left 3rd digit, both proximally and distally, and simultaneously, flexion of the distal 4th and 5th digits.
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