Current Clinical Neurology
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Stephen G. Reich
Stewart A. Factor *Editors*

Therapy of Movement Disorders

A Case-Based Approach

Humana Press

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A Case-Based Approach

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Series Editor Introduction

It is a pleasure and a privilege to welcome *Therapy of Movement Disorders: A Case-Based Approach* to the *Current Clinical Neurology* series by Springer/Humana Press. Dr. Stephen Reich and Dr. Stewart Factor are very distinguished figures in the field of movement disorders who have devoted their careers to explaining and teaching all they have come to know about their field. Both have previously written and edited several volumes on the subject. In this volume, they have invited more than 80 clinical experts to contribute 77 chapters on their respective fields of expertise within what has become an increasingly broad neurological specialty. It is very appropriate that, as stated by Drs. Reich and Factor and Dr. Lisa Shulman in their dedication and foreword, the book is dedicated to Dr. William J. Weiner, their mentor and role model, who was a master clinician and very generous teacher in the field.

The field of movement disorders has always been a clinical specialty in which accurate diagnosis rests on very careful history taking, keen observation, and a meticulous neurological examination. Although recent advances in genetics, biomarkers, and brain imaging have come into play in the field, correct diagnosis and appropriate treatment continue to be based on broad knowledge and extensive personal clinical experience concerning how best to evaluate and treat patients suffering from these disorders. It is notable that the majority of chapters in this book were written by a single highly experienced clinician. As the editors state in their foreword, although in this rapidly expanding information era much of what is written here may be available elsewhere, reading this clinical case-based approach will simply make the reader a better clinician. The broad topics covered include the traditional fields of Parkinson's disease-motor, Parkinson's disease-non-motor, tremor, dystonia, tics, myoclonus, tardive drug-induced movement disorders, and other miscellaneous disorders. Although the focus of the book is on the therapy of these disorders, much will also be learned about the clinical phenomenology and diagnosis of these conditions. This book should be required reading for all of our younger colleagues who are beginning to grow up in this field.

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William J. Weiner, M.D. (1946–2012)

For both of us, Bill Weiner was a special friend, colleague, mentor, and role model as he was for many contributors to this book as well as the worldwide neurologic community and particularly among movement disorder specialists. His generosity had a great impact on our lives and careers, and his loss continues to leave a significant void. I (SAF) first met Bill as a fellow at the University of Miami (1986–1988) where he was professor and director of movement disorders. The two years I spent with Bill were extraordinarily influential and fun years. During this time he taught me how to write and edit and made it fun, how to read critically, and to question dogma. I remember some years later when we met in Washington DC to put the finishing touches on the first edition of our PD text he insisted we stop and go to the Smithsonian to see the Terracotta Army exhibit. That was vintage Bill. I learned so much from his remarkable clinical diagnostic ability. He had a great bedside manner. Fellowship was also my first step in studying therapeutics. He helped to get me more involved in our specialty, MDS and AAN. That was the beginning a long close cherished friendship.

I (SGR) did not know Bill well when he approached me about joining him at the University of Maryland where he moved in 2000 and became chairman in 2001. It took just a few meetings before I was hooked by his enthusiasm and sense of purpose. Just before I started in 2002, Bill and Stewart's book, Parkinson's Disease: Diagnosis and Clinical Management *was published, and Bill inscribed it saying that he looked forward to me joining the faculty: "It will be fun." I soon learned that Bill approached much of his work as fun,*

and I found this both infectious and inspiring. It is for his ability to inspire, his eagerness to push the field of movement disorders forward, his questioning of dogma, his devotion to patient care, and his commitment to our careers, all the while having fun, that we dedicate this book to Bill.

Bill had many achievements in his career, but beyond that, he was a person of varied interests, including history, politics, baseball, traveling, the outdoors, and cooking, and he loved to partake in adventurous dining and drinking. Among his passions was collecting books, especially classics of neurology. Bill also enjoyed writing and editing and was a prolific author with over 300 peer-reviewed publications, over 100 chapters, and he wrote or edited 24 books. He is perhaps best known for Movement Disorders: A Comprehensive Survey *published in 1989. This book was written in its entirety by Bill and Dr. Tony Lang and is now considered a classic in movement disorders. Bill's* Neurology for the Non-Neurologist*, coedited with Dr. Chris Goetz, was first published in 1981 and is now in its sixth edition. Equally successful is Bill's book for patients with Parkinson's disease, cowritten with Drs. Lisa Shulman and Tony Lang:* Parkinson's Disease: A Complete Guide for Patients and Families*. Although Bill's career was very much devoted to research, he was at the same time a devoted, astute clinician who cared deeply for his patients, and as such, we believe Bill would have liked this book, its scope, and innovative approach, focusing on the patient.*

Stephen G. Reich, MD
Stewart A. Factor, DO

Foreword

Two consummate movement disorder clinicians, Drs. Stephen Reich and Stewart Factor, bring more than 50 years of combined experience caring for people with movement disorders to a book that is as comprehensive as it is practical. You may ask – *why do we need a new book when vast information is at our fingertips online?* An online search gives quick answers to questions, but reading *Therapy of Movement Disorders: A Case-Based Approach* will make you a better clinician.

It is fitting that this book is dedicated to Dr. William J. Weiner. Stewart and Stephen were close friends and colleagues and share Bill's passion for books. Bill believed nothing would surpass reading a book from cover to cover to make a true impact on your clinical skills. He acquired books by the armful, building an immense personal library to dive into at will.

It is remarkable to look back at the classic text *Movement Disorders: A Comprehensive Survey* written by Drs. William Weiner and Anthony Lang, 30 years ago. The "red book," measuring nine by six inches, could be easily held in one hand. While *Therapy of Movement Disorders: A Case-Based Approach* comprises nearly 80 chapters, half on Parkinson's disease and parkinsonism alone, the red book comprised 13 chapters with a single chapter on Parkinson's disease and second describing other forms of parkinsonism. The field of movement disorders has witnessed a remarkable expansion of knowledge over the last three decades. Using a practical case-based approach, this new book will fundamentally advance your understanding and management of a diverse range of movement disorders, from everyday clinical problems to challenging less common presentations.

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Preface

From 2013 to 2016, we presented a course entitled *Therapy of Movement Disorders: A Case-Based Approach* at the annual meeting of the American Academy of Neurology. The purpose of the course was to provide an approach to treating a wide variety of motor and non-motor problems in Parkinson's disease and selected other movement disorders. Our goal of using the case-based method, with actual patients we encountered, was to give attendees a pragmatic real-world view of how to manage Parkinson's disease and other movement disorders.

After Greg Sutorius from Springer contacted us about developing a book by the same title, the content morphed from covering 21 topics in our course to 77 in this book, covering a broad spectrum of movement disorders. Further, we drafted 68 world experts to write additional chapters. The intent of this book is to be a very practical and quick guide to help physicians care for patients with a wide spectrum of movement disorder-related problems. We wanted to have the reader, in essence, "listen" to experts discuss specific cases as if they were in the clinic with them.

All chapters begin with an actual case that is followed by a free-style discussion on approaching the problem, balancing evidence from the literature with the author's own experience emphasizing practical suggestions. Instead of being heavily referenced, in keeping with our goal of providing "advice" rather than an exhaustive review of the literature, each chapter includes a short list of suggested readings. Most of the authors have provided helpful figures and tables and, in some cases, videos of the movement disorder. The chapters are short in order to provide a quick reference to the subjects. We asked authors to write as though the reader was seeing a patient in the clinic with a particular problem and needed handy, quick, practical advice about management. Our goal was to make this text the "go to" source for the management of movement disorders. This book should be useful to general neurologists, neurology residents and fellows in movement disorders, gerontologists, psychiatrists, neuropsychologists as well as nurses, and other allied health specialists.

This book includes chapters on all of the common movement disorders and many uncommon disorders, but due to inadequate space, we could not cover the entirety of this rapidly growing field. Nearly half of the chapters are devoted to the wide spectrum of motor and non-motor problems encountered in caring for people with Parkinson's disease as well as parkinsonian syndromes. Next are chapters addressing essential and other tremor disorders followed by management of the various dystonic syndromes and other hyperkinetic disorders including chorea, tics, and myoclonus. Other disorders covered are drug-induced movement disorders, psychogenic movement disorders, Wilson's disease, hemifacial spasm, and more.

We want to thank our coauthors for their contributions and, especially, acknowledge the patients we have the privilege to care for and learn from and who motivate us to come up with better therapies. We hope that as you encounter patients with Parkinson's disease and other movement disorders in your practice that you will turn frequently to this book, in print or online, to assist in their care.

Baltimore, MD, USA — Stephen G. Reich, MD
Atlanta, GA, USA — Stewart A. Factor, DO

Acknowledgments

From Stephen and Stewart

We thank Greg Sutorius for suggesting that we turn our AAN course into a book. Lorraine Coffey served as developmental editor, and we appreciate her diligence, patience, and support. We would also like to thank the many patients over our 30 years each of practicing who have put their trust in us and allowed us to learn from and be inspired by them.

From Stephen

My work has been generously supported by Diana and the late Frederick Henry Prince, IV, as well as Frank and Marcia Carlucci, among many others. I have been fortunate to have many wonderful mentors, role models, and colleagues who have enriched my career, too many to thank individually, but a few deserve mention: Robert Daroff, Mahlon DeLong, David Zee, John Leigh, Mark Hallett, Richard Johnson, Steve Grill, Lisa Shulman, and, especially my coauthor and friend, Stewart Factor. While a resident, a rotation with David Marsden and Niall Quinn, then at King's College, was instrumental in my choosing to specialize in movement disorders (I think it chose me). My dear friend, Dr. Gerson Paull, has been a great source of support for which I am grateful. My parents, Henry and Edith Reich, are simply *perfect* parents and grandparents. If my wonderful wife, Dr. Dana Boatman, and my great kids, Daniel and Si Yan, were not so much fun to be with, I could have finished this book a lot sooner.

From Stewart

I would like to thank my friend and fellow baseball fan Stephen Reich for inviting me to be faculty in our AAN course *Therapy of Movement Disorders: A Case-Based Approach* which ultimately led to the development of our book and our cold night at Camden yards. My work and programs at Albany Medical Center and Emory University have been generously supported by Marilyn and Victor Riley, Julie Lanier Balloun and the trustees of the Sartain Lanier Family Foundation, Jean and Paul Amos, Mary Louise Brown Jewell, Merrie and Daniel Boone and family, and Dana and Thomas Curtis and family, among many others. Thanks to my movement disorder colleagues at Emory for making the last decade plus fun. Special thanks to the women in my life, my wife, Ann Marie, the love of my life, and my wonderful daughters, Katie and Rachel, for all their love and support and for enduring hours with me at Mets games. And finally, thanks to Jeff for all the memories. I miss you.

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Part X Other

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Part I

PD: Motor

Diagnosing Parkinson's Disease

1

Stephen G. Reich

Case

A 59-year-old attorney noticed a subtle change in his handwriting 2 years before presentation which worsened gradually. He reported that when taking notes, "the hand cannot keep up … grinds to a halt" with micrographia. He also noticed that performing other tasks with the dominant right hand was more difficult including brushing his teeth and buttoning the left cuff button. Several years before the change in his handwriting, he started "flailing" during sleep. He reported that the flailing seemed to be connected to dreams of being chased and trying to get away. His wife reported that the flailing occurred 3 or 4 nights per week, typically several hours after falling asleep. Although he had never struck her during a dream, she avoided sleeping next to him. In addition, for many years, he had noticed a "terrible sense of smell." He had no symptoms to suggest orthostatic hypotension or any change in bowel, bladder, or sexual functioning. Although he was frustrated by the difficulty of writing and worried about the diagnosis, he was not depressed or anxious. There was no family history of PD or exposure to dopamine-blocking medications.

On examination, there was mildly diminished voice volume and facial expression. He arose easily from a chair and walked well with the exception of absent right arm swing and a tendency to scuff the right shoe. Finger, heel, and toe tapping on the right were all mildly slow with a decrement, meaning that the longer he did the task, the smaller the amplitude of the movement became, with some brief arrests of movement. There was also subtle slowness of the left limbs and mild cogwheel rigidity of the right greater than left limbs. Handwriting was micrographic. There was no resting tremor. Reflexes were normal as were eye movements with no slowing of saccades.

I informed the patient that he had early Parkinson's disease and explained how I came to the diagnosis. I did not think that imaging was needed as the history and examination were typical for PD with no symptoms or signs to suggest an alternative cause of parkinsonism. I spent time educating the patient and his wife about PD, emphasizing the availability of medication to improve his symptoms and discussed its slowly progressive course. Because handwriting was such an important part of his occupation, I started treatment with carbidopa/levodopa 25/100 beginning with one-half tablet three times per day, around 7 am, noon, and 5 pm for 1 week and then a full tablet.

Discussion

Parkinson's disease is often assumed to be a straightforward "waiting room" diagnosis. In support of this, consider that in his description of *The Shaking Palsy* (1817), James Parkinson reported the details of six people but had seen only three of them as patients—the others were encountered in the streets of London, as Parkinson's recognized their distinctive physical features. In contrast to a generally held belief that diagnosing PD is easy, autopsy studies have shown that up to 20% of patients diagnosed as having PD during life prove to have an alternative diagnosis—usually a parkinsonian syndrome; the misdiagnosis rate is even higher (over 1/3) if only the initial diagnosis is considered. Making an early diagnosis of PD is not just a challenge for the general neurologist but also for specialists in movement disorders. Clinical trials conducted by specialists, using dopamine transporter imaging as the "gold standard" (admittedly it is not perfect), have demonstrated a misdiagnosis rate ranging from 3.6% to almost 20% for early cases, typically symptomatic for less than 2 years. In contrast, when a patient is followed long-term by a movement disorder specialist, the positive

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predictive value of the last clinical diagnosis prior to death, compared to the autopsy, is nearly 100%. This demonstrates that diagnostic accuracy hinges on having familiarity with the characteristic features of PD, as well as recognizing symptoms and signs at onset and especially during follow-up that cast doubt on the diagnosis ("red flags") of PD. Since red flags and other atypical features may not be present when PD is diagnosed initially, the quality measure set of the American Academy of Neurology recommends an annual review of the diagnosis.

Why a disease as common as PD is so frequently misdiagnosed? Consider the following five reasons. First, since PD is largely an outpatient condition, residents get relatively little exposure to it during training and especially early PD. In fact, many residents graduate without ever having had the opportunity to make the diagnosis of PD. Second, the earliest symptoms and signs of PD are subtle, and unless one suspects it, they are often overlooked—decreased arm swing on one side, a little slowing of finger or toe tapping, a slightly decreased blink rate, and a soft voice. It can take time for the disease to "blossom" to the point where the disease is recognized and the diagnosis is considered. But, like most of medicine, one's ability to make a diagnosis requires a "prepared mind," and this means familiarity with the early symptoms and signs of PD.

The third reason I have observed for misdiagnoses is inadequate history and examination. This leads to two types of errors. First, false positives: the patient is diagnosed with PD when in fact they have an alternative diagnosis. This includes failure to take a careful drug history and even inadequate recognition of drugs which cause parkinsonism and therefore missing drug-induced parkinsonism. Another example is lack of familiarity with or failure to look for "red flags" casting doubt on the diagnosis of PD and pointing instead toward an atypical parkinsonian syndrome such as multiple system atrophy-parkinsonism (MSA-P), progressive supranuclear palsy (PSP), corticobasal syndrome (CBS), or dementia with Lewy bodies (DLB). For instance, not screening for dysautonomia relating to MSA or paying enough attention to eye movements relevant to PSP.

In addition to false-positive diagnoses of PD are false negatives: in this case, the patient *has* PD, but because it may be a bit atypical, the diagnosis is not considered. Pitfalls include young-onset PD, a sensory presentation of PD such as shoulder pain, a tremulous PD, or PD beginning in one lower extremity (foot tremor), among others. In these circumstances, patients are often diagnosed as having had a stroke, spinal cord or neuromuscular problem, or a rheumatologic condition and end up undergoing unnecessary testing before it becomes clear that the problem is PD.

The fourth reason for diagnostic errors is the lack of a specific biomarker for PD (note: dopamine transporter imaging cannot distinguish PD from a parkinsonian syndrome). We have become very reliant on imaging and other objective tests to make neurologic diagnoses, and as such, there seems to be less confidence in making a clinical diagnosis, which is the basis for diagnosing PD. And lastly, diagnostic errors can be the result of failing to reconsider the diagnosis of PD at each visit. Early on, parkinsonian syndromes may look like PD, but with time, their distinctive features become more obvious, and the natural history deviates from that expected with PD.

The diagnosis of PD remains clinical relying on recognizing characteristic features of PD and taking into consideration alternative diagnoses, such as drug-induced parkinsonism or essential tremor (see chapter 37, Essential Tremor for distinguishing PD from ET), and looking for atypical features (red flags) which cast doubt on the diagnosis of PD. My approach to the diagnosis largely parallels the Movement Disorder Society's clinical diagnostic criteria for PD published in 2015 (see Postuma et al.). Although yet to be validated (the gold standard to be used is the clinical diagnosis by experts), these represent an important update of the UK Brain Bank Criteria proposed in 1988. In the MDS criteria, there are two levels of diagnostic certainty: clinically established and probable PD distinguished by the degree to which certain features are present or absent (e.g., number of "red flags"). There are four basic steps in the diagnostic criteria. First is to establish that the patient in fact has parkinsonism defined as bradykinesia (the defining feature of parkinsonism) accompanied by either rigidity or resting tremor. It should be noted that 20–30% of PD patients never develop tremor. The second step is the presence of supportive criteria including a "clear and dramatic beneficial response to dopaminergic therapy." Other supportive features include the eventual appearance of levodopa-induced dyskinesias, the presence of a rest tremor, unilateral or asymmetrical onset, and positive results from at least one ancillary test such as olfaction or cardiac MIBG scintigraphy (note: only two supportive criteria are needed for clinically established PD, so additional testing is not necessary).

The third diagnostic criterion is the lack of "absolute exclusionary criteria," that is, a feature which is not expected with PD such as cerebellar signs, supranuclear ophthalmoplegia, or cortical sensory loss, and their presence rules out PD. Additional exclusionary criteria include exposure to a dopamine-blocking agent in a time course that could explain the findings, absent response to high-dose levodopa, and normal functional imaging of the presynaptic dopamine system. Regarding imaging, it is important to note that the criteria *do not necessitate* the performance of imaging, but if such imaging is done, and if normal, then that "rules out" PD, but there are some caveats about DA transporter imaging discussed below.

The fourth and final criterion concerns "red flags." These are clinical features that cast doubt on the diagnosis of PD

and usually point toward a parkinsonian syndrome. In contrast to the *absolute* exclusion criteria above, some of the red flags may be seen with PD, but it is usually their timing in the course of the disease or severity that makes them atypical features and calls the diagnosis of PD into doubt. These include rapid progression (faster than expected with PD—evolution to Hoehn-Yahr stage 3 within 3 years), *early* falls, *early* autonomic failure, *early* bulbar dysfunction, symmetrical onset of parkinsonism, and others (see Table 1.1). Although red flags indicate the *presence* of an atypical sign, the MDS criteria also specify that the *absence* of the expected non-motor features of PD is also as a red flag. For instance, the lack of hyposmia, a REM behavioral disorder, autonomic dysfunction, or neuropsychiatric features (depression, anxiety) should also call into question the diagnosis of PD or at least a synucleinopathy.

One area of controversy with the MDS criteria concerns the timing of dementia. Traditionally, early dementia was considered a red flag pointing away from PD suggesting instead dementia with Lewy bodies (DLB), frontotemporal dementia (FTD) with parkinsonism, vascular parkinsonism, or Alzheimer's disease with parkinsonism, but in the new criteria, dementia, regardless of when it occurs, is no longer an exclusionary feature. To a large degree, this reflects the somewhat arbitrariness of setting a 1-year limit between the onset of parkinsonism and dementia for the diagnosis of DLB and, second, recent recognition that cognitive impairment can be seen early in the course of PD. The MDS criteria notwithstanding, I am skeptical about diagnosing PD if there is dementia early in the course. Having voiced this reservation, the way the criteria are constructed, most causes of concurrent parkinsonism and dementia, which are not due to PD, will likely fail to fulfill other criteria necessary for the diagnosis of PD so this may prove to be a moot point.

Although imaging of the presynaptic dopamine transporter is not required for the diagnosis of PD, if performed and normal, according to the MDS criteria, that rules out PD, yet no test is foolproof, and there can be exceptions to this part of the MDS criteria. In the United States, DaTSCAN™ is approved for differentiating PD from ET, but this is rarely a clinical conundrum, and the two can almost always be distinguished on clinical grounds, with rare exceptions. There are some off-label situations where a DaTSCAN™ can be useful such as distinguishing PD from drug-induced parkinsonism or distinguishing "parkinsonism" due to NPH or vascular disease from parkinsonism associated with nigrostriatal degeneration. In my view, a DaTSCAN™ should be considered if (1) there is *legitimate* confusion over the diagnosis, (2) if the result will change management, and (3) if the information cannot be obtained in another more convenient and less expensive way such as the "test of time" or consultation with a movement disorders specialist. It is important to note that a DaTSCAN™ cannot distinguish PD from other causes of parkinsonian associated with nigrostriatal degeneration including MSA, PSP, and CBS. In most cases when the cause of parkinsonism is not clear, the main question is whether it is PD or a parkinsonian syndrome, and the DaTSCAN™ will not give the answer.

Table 1.1 Red flags casting doubt on the diagnosis of PD

Lack of response to levodopa
Early falls
Rapid progression
Early bulbar signs
Early dementia
Early hallucinations or delusions
Early and prominent dysautonomia
Signs not expected with PD: apraxia, ataxia, pyramidal, cerebella, aphasia
Slow vertical saccades/supranuclear vertical ophthalmoplegia
Movement disorders usually not seen with PD: blepharospasm, eyelid opening apraxia, anterocollis or retrocollis, myoclonus, fixed dystonia
Lower-half parkinsonism (bilateral parkinsonian signs exclusively below the waist)

A few caveats to consider regarding the diagnosis of PD:

- Drug-induced parkinsonism (DIP) is under-recognized. The main reason is failure to take a careful drug history or recognize which drugs cause parkinsonism. Since DIP may persist for up to 1 year after the offending medication is stopped, the patient may not be on it at the time of the visit. The most common medications causing DIP include atypical antipsychotics and metoclopramide.
- Even though a "robust" response to levodopa is required for the diagnosis of PD, and lack of such response is an exclusion criterion, there are a few exceptions. Patients with tremor-predominant PD, especially those with large amplitude tremors, may not respond well to levodopa. Second, if levodopa is started at a point where symptoms are mild and there is little impairment of functioning (in which case levodopa was probably not needed), no improvement will be appreciated since there is not much to improve on even though the patient has PD. neither of these circumstances should be considered a levodopa failure automatically casting doubt on the diagnosis. Conversely, some patients with parkinsonian syndrome (especially MSA) will respond to levodopa early on, even in a significant way, but the benefit is usually not sustained, and motor fluctuations typically do not appear as they do in PD.
- An adequate trial of levodopa is at least 1000 mg per day of immediate release, not controlled release. It should be taken during the active part of the day (not before bed) and ideally on an empty stomach.

- Reconsider the diagnosis of PD at each visit. Early on, several of the parkinsonian syndromes, particularly the Parkinson's-like presentation of PSP or MSA-P can look like PD, but within the next few years, the natural course deviates from that expected with PD (faster progression), and red flags are added.

Back to the patient. He had typical symptoms and signs of PD including bradykinesia, cogwheel rigidity, hypomimia, hypophonia, micrographia, and a unilateral onset without any atypical features. The diagnosis of PD was further supported by the presence of non-motor features including a REM sleep behavioral disorder and hyposmia. On 300 mg of levodopa, both he and his wife noticed significant improvement in his symptoms and functioning, especially handwriting. To be more confident of the diagnosis, he will need to be followed over time, but for now, he has PD.

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Initiating Treatment for Parkinson's Disease

2

Stephen G. Reich

Case

A 61-year-old attorney was seen for a second opinion after the recent diagnosis of Parkinson's disease. About 1 year previously, he noticed "weakness" of the dominant right hand in that it was harder to perform fine motor tasks such as buttoning the left cuff button, texting, turning pages, stirring coffee, and brushing his teeth. His wife noticed that he did not swing the right arm while walking. While walking the right leg seemed stiff, and he had difficulty sliding his right foot into a loafer. It was more difficult to arise from a soft or low chair. He often was asked to repeat himself as his voice had become softer. Although he was still functioning at a nearly normal level, all tasks took a more time such as getting dressed. His most significant limitation was handwriting which had become laborious and small making it very difficult to take notes while talking on the phone, in depositions, and at trial, and this was affecting his work performance. The difficulty writing was also a source of anxiety. The left limbs were asymptomatic. Starting at least 10 years ago, he had occasional dream enactment including striking his wife on a few occasions while fighting during a dream; he had fallen out of bed once during a dream in which he was being chased. His sense of smell was never good but seemed to slowly worsen. There were no autonomic symptoms. He did not feel depressed but was more prone to anxiety.

On examination, there was mild hypomimia and hypophonia. He bounced one time when arising from a chair. He walked a little slowly and scuffed the right shoe; the right arm did not swing. He did not lose his balance on the pull test. There was moderate bradykinesia and mild cogwheel rigidity of the right limbs and slight bradykinesia on the left. Shrug of the right shoulder was slower than the left. No tremor was observed. His writing was done with significant effort and was small, especially at the end of a long word and at the end of a sentence.

Treatment options were reviewed with the patient and his wife, and a mutual decision was reached about which medication to start.

Discussion

There are three steps to follow when initiating treatment for PD. The first is to avoid a standardized or strictly algorithmic treatment approach applied indiscriminately to all patients. The second is to disregard the widespread myth that levodopa should never be the initial therapy. Third, and most important, is to recognize the need to *individualize* treatment. There are many options available for initiating treatment of PD, and the choice is based on careful consideration of how PD is affecting *the patient in front of you*, a discussion of the pros and cons of each option, and reaching a mutual decision with the patient about what is most appropriate.

Decisions about treatment rely on a detailed interview with the patient and family members about how PD is affecting their personal and occupational functioning. Early in the disease, if there is no meaningful impact on functioning, then treatment can be delayed with the caution that it is not uncommon for people to underestimate the effects of PD since it progresses so gradually. In addition to inquiring about physical functioning, it is also important to also ask about the psychological effects of PD, for instance, tremor may not be physically limiting but can be embarrassing, and that is justification for starting treatment. For a patient who is not in need of symptomatic treatment, he or she might be a candidate for participation in a neuroprotective trial and, if interested, referred to a specialty center. All patients should be counseled about the importance of exercise although it is currently not known if one exercise is better than another, but

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both strength training and aerobics are important. There are no definitively proven neuroprotective therapies for PD; some specialists do recommend a MAO-b inhibitor, but I do not find the data sufficiently convincing to do so.

Regardless of which medication is chosen as initial therapy, there are a few principles that apply to all patients. First is to have a clear idea of the aims of treatment. Patients should be counseled that therapy will not alleviate all symptoms and signs, but they should expect improvement with greater ability to function, and the latter is the best barometer for judging the effectiveness of therapy. With the exception of levodopa, most PD medications take time (weeks to even a few months) and a slow escalation of the dose to eventually take effect, and patients need to understand this. This is especially true with dopamine agonists. Similarly, it is important to warn patients about potential side effects, most of which are mild and usually transient, for instance, nausea from levodopa, but they should also be aware of more serious side effects including orthostatic hypotension, confusion, hallucinations, sleepiness, and impulse control disorders. Most patients with PD have comorbid medical problems and are on other medications; drug interactions are uncommon with PD medications, but they can combine to cause side effects, such as low BP in those on antihypertensives. Patients should understand that there is no standardized approach to treating PD and that treatment can be a matter of trial and error to find the right medication or combination of PD drugs to allow the person to function at an acceptable level with minimal side effects. Many patients, like many physicians, are under the mistaken impression that levodopa should be delayed as long as possible and that it "stops working after 5 years." It is important to educate and reassure patients that these are myths and often serve to deny patient's optimal therapy.

Most neurologists today are under the impression that the initial treatment for PD should always be an MAO-b inhibitor or a dopamine agonist and while both are fine to use, the choice of therapy should be individualized. An MAO-b inhibitor has the advantages of being once per day and is relatively free of side effects. As long as the recommended dose for PD is not exceeded, there is no need to follow a tyramine-free diet or avoid SSRIs or TCAs. Either rasagiline or selegiline or may be used. Their effectiveness is usually mild but often sufficient as initial therapy for the patient with mild PD.

Initiating therapy for PD with a dopamine agonist gained favor after several influential studies demonstrated that when used as initial therapy, compared to levodopa, there was a delay in the development of motor fluctuations and dyskinesias. Yet, the fluctuations and dyskinesias in these studies were typically mild, and several long-term studies have demonstrated that this early advantage of an agonist is largely lost over time. In contrast to the short-term benefit of an agonist as initial therapy, in terms of forestalling fluctuations, are two important drawbacks. First, agonists are less effective than levodopa for reducing symptoms, and second, they have more side effects, some of which can be severe. These include pedal edema, weight gain, and hallucinations, although the latter are usually not seen in early PD and the elderly are more susceptible. More concerning side effects include daytime sleepiness and impulse control disorders. Because of the risk of daytime sleepiness and the potential for falling asleep while driving, I avoid agonists in patients with insomnia or other sleep disorders, such as obstructive sleep apnea, and in patients who are already sleepy during the day; a careful sleep history is important in all patients with PD but especially when considering an agonist.

About 15% of patients with PD develop an impulse control disorder, and they are most closely associated with the use of dopamine agonists. If there is any evidence of a prior or current impulse control disorder (smoking, alcoholism, etc.), an agonist is best avoided. Both the patient and spouse need to be warned about the possibility of an ICD, and screening should be done each visit. The above notwithstanding, an agonist is a reasonable starting drug for the patient with mild PD after careful discussion of potential side effects. Early use of an agonist may allow for reduced levodopa dosing in the future leading to less levodopa-induced side effects as total daily levodopa dose is becoming increasingly recognized as a primary risk factor for motor fluctuations. But, as mentioned above, long-term studies suggest that whatever early benefit is gained by delaying levodopa is probably lost as the disease progresses. Agonists come in several preparations (Table 2.1) including short-acting (requiring tid dosing), long-acting once-daily preparations as well as a skin patch (rotigotine) which is also dosed once per day. Agonists should be initiated gradually and escalated slowly to a therapeutic dose.

In addition to an MAO-b inhibitor or dopamine agonist, other options for initial therapy of PD include an anticholinergic or amantadine (Table 2.1). Anticholinergics are often thought to be better for tremor, but that has not been demonstrated convincingly. They are generally well tolerated in younger patients but are best avoided in the elderly due to side effects including confusion, impaired memory, blurred vision, constipation, dry mouth, and difficulty urinating. Anticholinergics are one of the oldest therapies for PD but became less popular when levodopa was introduced yet remain a good option for early treatment. The same is true with amantadine, an antiviral agent developed to treat the Asian flu, which has similar but milder side effects than an anticholinergic. It can cause livedo reticularis, a meshwork pattern of vascular dilatation usually seen in the limbs of light-skinned persons and is no cause for concern other than cosmetic. Amantadine can also cause pedal edema. In addition to being an acceptable option for treatment of early PD, more recently, amantadine has found a second important role

Table 2.1 Medical options for initial treatment of PD

Drug	Sizes	Usual starting dose	Usual daily dose
Anticholinergics			
Trihexyphenidyl	2 mg, 5 mg tablets	1 mg bid	6 mg per
Benztropine	0.5 mg, 1 mg, 2 mg tablets	0.5 mg bid	2–6 mg per
Amantadine	100 mg capsule/ tablet	100 mg bid	200–300 mg
MAO-b inhibitors			
Selegiline	5 mg capsule	5 mg bid	10 mg
Rasagiline	0.5 mg, 1 mg tablet	0.5–1.0 mg	1 mg
Dopamine agonists			
Pramipexole	0.125 mg, 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg tablets	0.125 mg tid	3–4.5 mg
Pramipexole ER	0.375 mg, 0.75 mg, 1.5 mg, 3 mg, 4 mg, 5 mg tablet	0.375 mg qd	3–4.5 mg
Ropinirole	0.25 mg, 0.5 mg, 1 mg, 2 mg, 3 mg, 4 mg, 5 mg tablet	0.25 mg tid	12–24 mg
Ropinirole XL	2 mg, 4 mg, 6 mg, 8 mg, 12 mg tablet	2 mg qd	12–24 mg
Rotigotine	1 mg, 2 mg, 3 mg, 4 mg, 6 mg, 8 mg patch	1 mg qd	6–8 mg
Levodopa			
Carbidopa/ levodopa	10/100 mg, 25/100 mg, 25/250 mg tablet	25/100, ½ tablet tid	300 mg
Carbidopa/ levodopa extended release	25/100 mg, 50/200 mg	25/100 bid	400–600 mg

as a suppressant of levodopa-induced dyskinesias (see chapter "Treatment of Levodopa-Induced Dyskinesia in Parkinson's Disease").

While acceptable options for the initial therapy of PD include a MAO-b inhibitor, dopamine agonist, anticholinergic, or amantadine – each has its advantages and disadvantages – none is as effective as levodopa. The traditional practice has been to delay levodopa as long as possible for fear that it will ultimately worsen PD by contributing to the ongoing death of nigral neurons and that there will be a loss of effectiveness over time and to forestall motor fluctuations and dyskinesias. A complete refutation and discussion of these long-held beliefs are beyond the limits of this chapter but are discussed in the references. Suffice to say that the tables have turned and it is now appreciated that the concerns about toxicity and tolerance of levodopa are unfounded and that patients generally do better with early levodopa. There is no longer justification for "levodopaphobia."

When levodopa is used as initial therapy, start with the 25/100 immediate release preparation of carbidopa/levodopa as it takes at least 75 mg of carbido initial pa to inhibit dopadecarboxylase and as such, prevent the peripheral conversion of levodopa to dopamine which does not cross the blood brain barrier. I have patients start with ½ tablet three times per day; it is important to instruct them on the times to be taken since if not, the last dose is often taken near bedtime and therefore largely wasted. For the occasional patient who is symptomatic near bedtime, then an extra dose around that time is appropriate. I suggest taking it upon awakening and two additional doses about 4–5 h apart.

Although levodopa is best absorbed on an empty stomach, having patients take it half an hour before or an hour after eating puts an extra layer of complexity for the person with early PD, and I emphasize instead taking it on time and eating at their regular schedule (later in the course, when patients are in need of greater benefit from levodopa, then taking it on an empty stomach is more important). For patients who experience nausea, taking carbidopa/levodopa with a meal can help. Some patients will experience sufficient benefit with this low dose, but if not, after taking it for 2 weeks, I increase to a full tablet each time. Most people with early PD will improve on this dose, but if not, there is still room to increase. Patients should be instructed that the goal of therapy is to use the lowest dose of levodopa that controls symptoms sufficiently to allow for "acceptable" functioning, and optimal dosing varies from patient to patient.

The assumption that providing more continuous dopaminergic stimulation would reduce the risk of fluctuations led to trials comparing initiating therapy with immediate release levodopa versus controlled release levodopa or a combination of levodopa with a COMT inhibitor. Unfortunately, neither of these approaches was shown to be more beneficial than immediate release levodopa. Nevertheless, the controlled release preparation can be used as initial therapy, and patients may be able to get by with twice-daily dosing. The CR preparation is less potent than IR levodopa (by about 30%), and the response may not be as predictable. At this time, Rytary, another long-duration preparation of levodopa, has not been demonstrated to be more advantageous than IR levodopa as initial therapy.

Levodopa is generally well-tolerated. Nausea is the most common initial side effect but is usually mild and transient. For the rare patient in whom it is more severe and persistent, options include taking it with meals, prescribing extra carbidopa, or using the antiemetic domperidone which, unlike other antidopaminergic antiemetics, does not cross the blood brain barrier. Levodopa can lower blood pressure, so it is important to screen for orthostatic hypotension before and after it is prescribed.

Back to the patient above: he was at the point that treatment was indicated as the symptoms of PD were bothersome. His most significant problem was handwriting

affecting his ability to practice as an attorney. We discussed treatment options. Given the impact of PD on his profession, I suggested carbidopa/levodopa as I did not think that other agents would provide the degree of improvement he needed and that certain side effects could be very problematic for him such as sleepiness from an agonist. It was a mutual decision, and he was started on carbidopa/levodopa 25/100, one-half tablet at 7 am, noon, and 5 pm for 2 weeks and then a full tablet each time. When he returned in 6 weeks, he and his wife reported improvement in many symptoms and signs including his handwriting and overall level of functioning.

There are many good options for initiating therapy of PD. The "best" one is the one which works best for the individual patient. This is determined by finding out how PD is affecting their daily life and assessing their susceptibility to side effects. For the patient at or near 70 years old, I usually go straight to levodopa as they are at much lower risk for developing fluctuations or problematic dyskinesias. For younger patients, options include a MAO-b inhibitor, dopamine agonist, anticholinergic, amantadine, or levodopa—each has its advantages and disadvantages which should be discussed with the patient in order to make a mutual decision.

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Medical Therapy for Fluctuations in Parkinson's Disease

3

Stewart A. Factor

Case

This man was 48 years old when diagnosed with Parkinson's disease (PD). He was an international banking consultant and working full time. Symptoms started in the right hand with micrographia, difficulty typing, and finger tremor. His right arm did not swing and felt "lifeless" to him. He also developed a frozen shoulder which was treated with steroid injections. In the first year, he was started on carbidopa/levodopa 25/100 up to one tablet TID which was extremely helpful; in fact it made him symptom-free. Rasagiline was then added because at that time, it was thought to possibly have a disease-modifying effect; 1 year later pramipexole was added because of an increase in tremor. Another troublesome early problem was REM sleep behavior disorder (RBD) which was treated successfully with clonazepam (see Chapter 22). During the next year, he developed mild end-of-dose wearing off, manifested by feeling like his right arm was limp and did not swing, and worsening of dexterity issues on the right. At this time medication doses were altered to carbidopa/levodopa 25/100, 1 tablet QID, and pramipexole 0.5 mg TID which effectively controlled the symptoms.

In the next year (year 3), wearing off returned and increased, and he developed morning akinesia. His off times were characterized by tremor and slowness with impaired dexterity, still worse on the right, but with some left-sided symptoms emerging. Despite reducing the dosing interval of carbidopa/levodopa to Q4 hour intervals for 5 doses, he continued to wear off. Entacapone (200 mg) was then added with each dose of carbidopa/levodopa. When "on" he remained near normal.

In year 5 he developed more unpredictable off times including dose failures. By now he was "off" 25–50% of the day characterized by shuffling gait as well as increased tremor and slowness. This was beginning to impact his work which required frequent traveling. An increase of individual carbidopa/levodopa doses did not help. The pramipexole was switched to rotigotine patch 3 mg one per day for a week and then 6 mg and ultimately up to 8 mg. This provided some benefit, but in the next 6 months "off" times were appearing more suddenly, and morning "off" was particularly troublesome. He was switched from carbidopa/levodopa 25/100 plus entacapone 200 mg to carbidopa/levodopa/entacapone 125 combination. He took one tablet every 3 h starting at 4 am for six doses and another if needed at night. He also added one half of a carbidopa/levodopa 25/100 with the first dose.

In year 6 it was decided to initiate apomorphine subcutaneous injections for the treatment of unpredictable "off" times. He was instructed to take trimethobenzamide 300 TID 3 days before initiation. He came to the office in the "off" state. A UPDRS motor score during "off" time was 23. He was given apomorphine 2 mg, and 25 min later, the motor score was 13 (Table 3.1). He experienced no nausea, vomiting, or orthostasis. He had no dyskinesia. He was able to discontinue the trimethobenzamide after 2 weeks as he had no nausea. His medications 6 months later included carbidopa/levodopa 25/100 tablets 2-1-1-1-1 at 4-h intervals starting between 3 and 5 am, rotigotine patch 8 mg per day, and entacapone 200 mg 5 doses/day with carbidopa/levodopa, clonazepam 0.5 mg one or two qHS for RBD, and apomorphine subcutaneous injection 2 mg 3–4 times per day which went up to 3 mg per injections because he was not getting a consistent "on" with 2 mg. Despite the medication regimen, he was still "off" nearly 50% of the time with stiffness and slowness. He was switched from entacapone to tolcapone 100 mg TID for 1 week and then 200 mg TID. It cut his "off" time from nearly 50–25%. He had minimal dyskinesia.

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Table 3.1 UPDRS motor scores before and after apomorphine 2 mg injection

	UPDRS Part III motor examination	Off 09:35 am	Injection 09:44 of apomorphine 2 mg On exam 10:05 am
18.	Speech	1	1
19.	Facial expression	2	2
20.	Tremor at rest		
	Face, lips, chin	0	0
	R/L hands	0/0	0/0
	R/L feet	0/0	0/0
21.	Action tremor R/L	0/0	0/0
22.	Rigidity: Neck	2	1
	R/L UE	2/2	0/1
	R/L LE	0/0	0/0
23.	Finger taps R/L	1/2	0/1
24.	Hand grips R/L	0/0	0/0
25.	Hand pron-sup R/L	0/1	0/0
26.	Leg agility R/L	2/2	2/2
27.	Arise from chair	1	0
28.	Posture	2	1
29.	Postural stability	0	0
30.	Gait	1	0
31.	Body bradykinesia	2	2
	18–31 subtotal	23	13

By year 7 he developed dyskinesia and was "off" 25% of the time. Work had become increasingly challenging, so he changed his position in the company to avoid long travel. Amantadine up to 100 mg TID was ineffective for treating dyskinesia. We discussed, for the first time, continuous intrajejunal infusion of carbidopa/ levodopa gel and deep brain stimulation (DBS). He chose DBS (see Chapter 6).

Discussion

A discussion on which agents to use when initiating therapy for PD is covered in chapter "Initiating Treatment for Parkinson's Disease". Suffice it to say that this young man was started on levodopa because data supports that it is not toxic, that it is the most effective symptomatic drug available, and that he was working full time in a demanding job at the time and needed the rapid and significant improvement expected with levodopa. We kept the dose on the lower side to avoid dyskinesia as long as possible (they developed in year 7). The American Academy of Neurology (AAN) guidelines indicate that "in patients with PD who require the initiation of dopaminergic treatment, either levodopa or a dopamine agonist may be used." I usually avoid anticholinergics because of their adverse side effect profile and potential to worsen dyskinesia in patients on levodopa; the only situation where I consider an anticholinergic is in young patients with severe tremor.

This patient demonstrates the typical evolution of fluctuations seen in PD. He was fairly young at onset, age 48, which increases the risk of developing response fluctuations. According to work from the Mayo Clinic, the 5-year risk of developing fluctuations in this age group is approximately 40%, similar to earlier estimates and similar for dyskinesia. It is important to bear in mind that these can be motor or non-motor fluctuations. In about one-third of patients, the non-motor fluctuations are most prominent including those which take the form of sensory (pain, akathisia, internal tremor), autonomic (sweating, hypotension), psychiatric (psychosis, depression, panic disorder), and cognitive (slow thinking, fatigue). As is usually the case, the initial fluctuation this patient experienced was end-of-dose wearing off of motor symptoms. There are several options to treat this, most of which were tried in him (see Table 3.2 for drugs, doses, and impact on "off" time). They include shortening dose intervals for levodopa or switching to long-acting formulations such as the older Sinemet CR® or Rytary®. Sinemet CR® is a slow release matrix tablet developed in the late 1980s, while Rytary® is a capsule containing beads of carbidopa and levodopa that dissolve at different rates, approved in 2016. There are issues of cost, particularly with Rytary®. Rytary® decreases off time by an average of 1.2 h per day when patients are switched from immediate release carbidopa/ levodopa. Sinemet CR® often is not as effective as standard release formulations because of slower absorption and lower blood peak levels and impact of food to absorption, so it is often used in combination with standard carbidopa/levodopa, for example, in the morning to provide a quicker time to "on." For both long-acting formulations, higher doses are required compared to regular carbidopa/levodopa. Bioavailability is about 70% for Sinemet CR® and 30% for Rytary®, so transitioning to Rytary® requires about twice the dose or immediate release levodopa (see Hauser reference for details).

Another option for treating end-of-dose wearing off is adding a dopamine extender such as monoamine oxidase B inhibitors (MAOBI) such as rasagiline, selegiline, or safinamide which block metabolism of dopamine within the brain or a catechol-o-methyltransferase inhibitor (COMTI) such as entacapone or tolcapone that block the metabolism of levodopa in the periphery much like carbidopa. Entacapone will increase on time by up to 1 h per day, while tolcapone may increase on time by more than 2 h per day (see Table 3.2). There is currently a new COMTI under investigation, opicapone. There have been concerns about MAOBI and development of the tyramine effect or serotonin syndrome when used in conjunction with antidepressants, but these have not been borne out as long as they are used at the recommended dose which selectively inhibits the B form of the enzyme. Selegiline is metabolized to amphetamine so it is best taken at breakfast and lunch; because of this metabolite, it may be helpful in the treatment of PD-related fatigue.

Table 3.2 Summary of medications used to treat motor fluctuations and dyskinesia in PD

Drug name	Route of administration	Initial dose	Recommended max dose	Hours of improvement in off time
MAOI				
Selegiline	Oral/oral disintegrating	5 mg per day	5 mg BID	0.9 (oral disintegrating)
Rasagiline	Oral	0.5 mg per day	1 mg per day	0.8–0.95
Safinamide	Oral	50 mg/day	100 mg per day	1
COMTI				
Entacapone	Oral	200 mg with each levodopa dose	200 mg with each levodopa dose	0.4–1.2
Tolcapone	Oral	100 mg TID	200 mg TID	0.9–2.2
Dopamine agonists				
Pramipexole	Oral	0.125 TID	1 mg TID	1.9–2
Pramipexole ER	Oral	0.375 per day	3 mg per day	0.7
Ropinirole	Oral	0.25 TID	5 mg TID	1.1
Ropinirole XL	Oral	2 mg per day	15 mg per day	1.8
Rotigotine	Patch	2 mg per day	8 mg per day	1.2–1.8
Apomorphine	Subcutaneous injection	0.2 cc per injection	0.5 cc per injection	2
Levodopa formulations				
Carbidopa levodopa ER	Oral	Dose of standard levodopa times 1.25	Individualized	
Rytary	Oral	Based on patient levodopa doses (see Hauser Table 1 or table in labeling)	Based on clinical response (approximately twice the levodopa dose in standard formulations)	1.2
Carbidopa/ levodopa gel	Intrajejunal infusion	Based on patients levodopa equivalent dosing (see discussion for the formula)	Adjusted as needed	1.9
Other				
Amantadine	Oral capsules or tablets	100 mg per day	100 mg QID	For dyskinesia
Long-acting amantadine	Oral	260 mg per day	420 mg per day	For dyskinesia

Recommended max dose is the authors, not based strictly on literature
Hours of improvement in off times are from blinded randomized trials

Other medications with a greater effect on decreasing off time include dopamine agonists: pramipexole, ropinirole as oral agents, and rotigotine cutaneous patch. The oral agents also have extended release formulations allowing for once-daily use that may be more helpful but are more expensive, and there may be issues with insurance coverage. However, they decrease off time by 1–2 h per day (Table 3.2). Potential side effects from agonists primarily include non-motor complications such as psychosis (in older patients mostly – some younger patients may develop an isolated delusional state) and impulse control disorders (mostly in younger patients), orthostatic hypotension, pedal edema, insomnia, and hypersomnia. In those already on an agonist, the dose can be increased to treat off time (see Table 3.2 for my recommended maximum doses) or switch from a short-acting to a longer-acting formulation including of the continuous cutaneous patch. There is no evidence to demonstrate that the rotigotine patch further increases on time over oral agonists, but this certainly is a reasonable option to try.

With time, fluctuations often become less predictable, as seen in this case, including complicated wearing off with variable latency for levodopa to kick in (delayed on), dose failures, and sudden offs unrelated to the timing of levodopa. Patients may also experience morning akinesia before the first dose of levodopa kicks in as well as troublesome night "off" times that impact sleep with inability to move in bed or problematic tremor. After one optimizes the adjunctive therapies mentioned above, then the treating physician can start using more advanced therapies. There is one oral medication the treating physician can go to in more severe fluctuators, and that is tolcapone. It is a COMTI that provides 80% COMT inhibition compared to 60% for entacapone and with twice the potency of entacapone with regard to decreasing "off" time. As seen in this patient, it cut the off time in half. Unlike entacapone, which is taken with every dose of carbidopa/levodopa (up to 8 per day), tolcapone is a TID drug with the first dose taken with the first levodopa dose. The primary concern with tolcapone is hepatic toxicity occurring in 1–3% of patients, depending on the dose, and requires monitoring AST and ALT every 2–4 weeks. The peak effect of hepatic enzyme elevation is between 6 and 12 weeks of treatment, but monitoring is required for 6 months. It is for

this reason, and cost, that this very good drug is underutilized. It can be tested on the patient with limited risk. After a baseline AST and ALT, I start a patient on 100 mg TID for 1 week. If that response is not superior to entacapone, then I suggest increasing to 200 mg TID. If that is not superior to entacapone, then I switch back to entacapone to avoid the monitoring, but if 100 or 200 mg is superior to entacapone, then I maintain tolcapone. Limitations to this drug include cost and insurance coverage as it is a low-tier drug. Both COMTI may cause mild and transient diarrhea (it is rarely severe or long-lived and occurs twice the frequency with tolcapone 5% vs 10%) usually in that 6–12-week period, and both turn urine color into orange.

The next step for treating off time is acute rescue therapy. The only true rescue drug available at this time is injectable subcutaneous apomorphine. It has been demonstrated to have a similar magnitude of response to levodopa. This drug is very fast acting (on within 10 min) and has a short duration of action, 40–120 min. So it is used not to replace oral medications but to fill the gaps of "off" times. At the correct dose, there are few dose failures, and it demonstrates long-term consistency of response. It is recommended that it be used up to five times per day as needed, but I have had some patients using it six to eight times. The use of apomorphine requires 3 days of pretreatment with the antiemetic trimethobenzamide 300 mg TID, but in most patients, it can be stopped within 8 weeks. This is also an underutilized PD drug because of concerns about the complexity of dose finding at the start (it is not really that complicated) and the fact that it is an injection. We initiate apomorphine in the office. Patients come in "off" and after 3 days of trimethobenzamide. After an examination they are injected with 0.2 cc (2 mg). They are then examined "on," and if fully on, they remain at that dose. If not, then increasing by 1–2 mg after an hour can be tried. Blood pressure should be monitored with initial dosing. Whatever the dose that brings the patient on will be their dose. Small changes can be made at home if needed for more than 5% dose failures. The company that markets apomorphine also provides a nurse for at-home dosing if the in-office approach is not feasible. Best locations for injection are the lower abdomen and thigh. Other forms of apomorphine including sublingual are currently being investigated. In addition, an inhaled form of levodopa for acute rescue is under investigation.

A final medical solution for treating off time is the initiation of continuous intrajejunal infusion of carbidopa/levodopa gel. This was recently approved in the USA for fluctuating patients. Data have demonstrated that its use decreases "off" time by about 2 h per day compared to oral levodopa. The procedure involves surgically placing a special percutaneous gastrostomy tube that reaches the jejunum to enhance levodopa absorption. The tube needs to be maintained. The levodopa and carbidopa are in a gel to prevent precipitation and tube clogging, a problem that occurred in the early years of attempting intra-intestinal infusions with dissolved carbidopa/levodopa tablets. Initial dosing includes a morning bolus: calculated as AM oral dose of levodopa × 0.8 divided by 20 mg/ml + 3 ml (for priming). The continuous rate is calculated as total LD equivalent dose (includes levodopa plus adjunct doses) – AM dose divided by 20 mg/ml then ÷ 16 h (the infusion is turned off at night). Titrations are performed daily for the first 2 weeks and weekly for weeks 3 and 4 (some do this faster). The continuous infusion obviates oral medications, but in some patients, "off" times still occur, and boluses can be given for that purpose. The pump is turned off at night and nocturnal symptoms are managed with long-acting levodopa formulations. Several issues accompany levodopa gel: the system is open, tubes come out of the abdomen, they need to be maintained, and a pump needs to be carried with the patient. Dosing in the test phase takes a mean duration of 5 days. Adverse events include hallucinations, increased dyskinesia duration by about 10% (no change in severity of dyskinesia), tube kinking, tube-device connection issues, and bezoars, among others. Long-term studies have found the dropout rate to be high because of lack of efficacy or adverse effects, 21% in first 3 months and 39% in first year. Our patient chose DBS over this therapy. Subcutaneous Apomorphine infusions, available in Europe, are under investigation in the USA. Further, levodopa subcutaneous infusions are also under investigation.

This patient started developing dyskinesia in year 7. The rate of dyskinesia at 5 years in someone his age is about 40%. The risk increases by 10% per year after that suggesting risk at 7 years is 70%. Dyskinesia can occur in several patterns: peak dose dyskinesia is most common; diphasic dyskinesia, which occurs as levodopa is kicking in or starting to wear off which reflects that plasma levels of levodopa are rising or falling but not necessarily at the peak (unless both are occurring) and involve the legs more often; and, "square wave dyskinesia" when it is present the entire time there is a levodopa response. Square wave type in particular more than the others leads to limiting dopaminergic therapies.

In the patient with dyskinesia, it is first important to address whether the dyskinesia is troublesome. Less than 20% of patients with dyskinesia at 5 years and 50% at 10 years require medication adjustment. Dyskinesia most often troubles the family more than the patient, and a majority of patients would rather have dyskinesia than off times. Since there is no medical treatment that stops dyskinesia completely, it is important to bear this in mind when making adjustments. There are, of course, exceptions. Thus education and reassurance may be all that is needed. If the dyskinesia is peak dose or square wave in variety and is troublesome, then options include eliminating adjunctive medications, MAOBI, COMTI, anticholinergics, and dopamine agonists. This would be followed by mild and gradual

reduction of levodopa, avoiding extended release formulations. These may lead to an increase in on time. One might consider reducing levodopa and replacing it with a dopamine agonist including apomorphine rescue. If worsening Parkinsonism occurs, then one can add amantadine including the newly approved long-acting formulations. Amantadine is the only medication available that has been demonstrated in several studies to treat dyskinesia often effectively and historically, it can improve Parkinsonism and "off" times as well. It is sometimes still used early in the disease course. The dose is between 100 mg BID and QID for standard amantadine and up to 420 mg once per day for the long-acting formulation. One should be careful in the elderly because of the potential for cognitive effects, hallucinations, bowel and bladder issues, as well as ankle edema and livedo reticularis. One other option to consider for dyskinesia is the β-blocker propranolol which has been shown in a small number of patients and animal models to be helpful. This requires further study. For diphasic dyskinesia, the best option is to minimize the wearing off with options described above that provide stable blood levodopa levels. If there is no response, then DBS is the next appropriate option.

"Off" times at night and in the morning can be particularly troubling to the patient. Long-acting dopamine agonists or levodopa formulations or the combination of levodopa and COMTI at bedtime can be helpful for nocturnal symptoms although may not carry patients through the entire night. For the morning the disintegrating form of levodopa (Parcopa®) can be used, or dissolving a carbidopa/levodopa in liquid and drinking it may shorten the time to on. For "off" symptoms that are present at bedtime or in the morning, apomorphine injections can switch them to the "on" state quickly. At bedtime this would improve mobility and comfort, so patients can sleep. In the morning patients can turn "on" quickly to prepare for the day, work, or other activities. Finally, infusions may be helpful in such situations, but more data is needed for that.

Some key points in relation to fluctuating symptoms in PD include the need to educate the patient with regard to definitions of "on" and "off" and differentiating dyskinesia and tremor. Make them pay attention. Address what fluctuates and discern a pattern with the use of diaries, prolonged office visits, or home videos (home movement devices are coming as well). It is also important to give patients realistic expectations. In more advanced patients, having some "off" time is the new normal for them. Address the following questions. When do off periods occur? How do they relate to dose and time of day? Are they predictable or unpredictable? How long are off periods? How soon before the dose does the prior one wear off? Are they sudden or gradual? How long does it take for the dose to kick in? Are there delays or dose failures? Is there dyskinesia? Answers to these questions will guide choices for agents and strategies. Alterations of medications should be gradual; make one change at a time. The goals of treatment are reduce off time, make the response as predictable as possible, at the same time simplify medications for compliance, and avoid adverse effects such as psychosis and dyskinesia. In the end, individualized polytherapy is the rule.

Suggested Reading

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Treatment of Levodopa-Induced Dyskinesia in Parkinson's Disease

4

Susan H. Fox

Case

A 59-year-old man with Parkinson disease (PD) for 6 years reports reduced benefit from his medication. He feels the improvement in slowness and tremor that he used to have all day is no longer guaranteed; he is aware that the positive effects of the medication do not last as long. He is on carbidopa/levodopa IR 25/100 mg, 1.5 tablets four times per day, spaced out at 5–6 h intervals with carbidopa/levodopa ER 50/200 mg at night. In addition, he is on entacapone 200 mg with each levodopa/carbidopa IR dose that was started 2 years ago because of tremor occurring in the late morning and late afternoon. He works in an office that he finds stressful and is aware that his head moves a lot when in meetings. His wife accompanies him and reports that she has also noticed that he has involuntary movements of his head, especially when talking or watching TV.

Examination 2 h after his last dose of levodopa reveals choreiform movement of his neck, as well as his right arm, while talking. Otherwise, he has mild bradykinesia in finger taps, is able to stand and walk easily, and has no balance issues.

The initial option was to reduce individual doses of levodopa to 1 tab (25/100 mg) but spaced at 4-h intervals, with a total of six times a day. This helped, but after 6 months, he still had some neck dyskinesia, so amantadine 100 mg BID was added with moderate benefit.

Discussion

Managing levodopa-induced dyskinesia depends on the level of disability the patient is experiencing, as well as the associated wearing-off problem. Many people with PD prefer to put up with dyskinesia rather than suffer the off-period symptoms. Be aware of treating symptoms that only the family members report. Patients themselves are not necessarily aware of mild movements disabled by the dyskinesia. There is often a reported fear of developing dyskinesia in early, untreated PD subjects as they have read or seen videos of affected people. This can lead to "levodopa phobia" and avoidance of starting drug with consequences of significant bradykinesia and suboptimal functioning.

Severe, bothersome dyskinesia is less common in recent times due to the practice of keeping individual levodopa doses as low as possible. When dyskinesia is significant and affects the limbs and trunk for prolonged periods of the day, then the involuntary movements can impact quality of life and cause patients to fall, slide out of a chair, and interfere with ADLs; for some patients, embarrassment may be most "disabling" effect of dyskinesia. Severe dyskinesia, which cannot be managed by medication adjustment, is usually best treated long term by bilateral deep brain stimulation surgery targeting either the subthalamic nucleus (STN) or internal globus pallidus (GPi) DBS.

Recognizing the pattern and timing of dyskinesia in relation to a dose of levodopa is important in the initial medical management. The commonest type of dyskinesia is the so-called peak-dose dyskinesia and occurs 1–2 h after the levodopa dose has been taken, at the peak levels of dopamine stimulation. Such movements are typically choreiform, affecting the neck, face, and limbs, but can often be mixed and include dystonia and ballism. Rarer features of peak-dose dyskinesia include myoclonus, respiratory dyskinesia with dyspnea, and ocular dyskinesia (slow and smooth "to-and-fro" pattern or an upward gaze deviation as seen in oculogyric crisis). Such dyskinesia is also referred to as "high-dose dyskinesia" as it will improve with a reduction in the dose of levodopa (or dopamine). This patient has typical peak-dose neck chorea.

The peak-dose timing of the dyskinesia means that reducing dopamine levels is the aim of management strategies. The first step is generally to reduce add-on therapy. Entacapone is a

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COMT inhibitor that is often used to enhance levodopa duration of action but can also increase peak-dose dopamine levels, with a tendency to induce peak-dose dyskinesia. One option therefore is to either reduce or stop entacapone to reduce the likelihood of peak-dose dyskinesia. Reducing individual levodopa doses when combined with entacapone is also an option. However the downside is that wearing-off symptoms may worsen. MAO-B inhibitors also have the same effect on increasing or inducing peak-dose dyskinesia and can be discontinued, but again, at the potential risk of increased off time.

The next step involves altering the timing of levodopa to a "lower dose, more often" approach with the aim of "smoothing" out dopamine levels. Thus 1 tab (25/100 mg) every 3–4 h would be an initial option to reduce peak-dose dyskinesia but maintain an effective on time. The balance is between enough levodopa at a reasonable time interval to ensure a reversal of PD motor symptoms without generating bothersome peak-dose dyskinesia, so-called good-quality on period.

If the peak-dose dyskinesia persists, despite the above measures, and is bothersome, then the next strategy is to add in amantadine. Amantadine is principally a nonselective N-methyl-*D*-Aspartate (NMDA) receptor antagonist. Enhanced glutamate neurotransmission, particularly via the NMDA receptor, appears to be a key factor underlying LID. The NMDA receptor is critical to synaptic plasticity and the secondary striatal circuitry changes; thus the neural mechanisms underlying LID have been likened to the process of plasticity as once a patient exhibits LID in response to levodopa, it is virtually impossible to completely reverse the process. Amantadine dosing is usually started at 100 mg daily, in the morning, with an increase to 2–4 doses per day (400 mg maximum). Lower doses can be used with liquid preparations that can be titrated at 50 mg dose intervals. Avoiding evening dosing reduces nocturnal issues of insomnia and possible hallucinations/confusion. Other side effects that patients need to be counseled about include livedo reticularis, a skin reaction on the lower limbs, and peripheral edema. Amantadine has some anticholinergic properties as well and can cause dry mouth or aggravate constipation. Rarer adverse effects include myoclonus in patients with impaired renal clearance, and corneal pathology has been described. Amantadine has been shown in clinical studies to reduce dyskinesia and is recommended as a treatment for dyskinesia in evidence-based medicine reviews. Some patients appear to lose this benefit with time, although clinical trials did not confirm this clinical observation. Longer-acting preparations of amantadine are in clinical studies, the rationale being that these will reduce nocturnal side effects.

Studies are ongoing to evaluate potential novel drugs for dyskinesia, due to the lack of benefit with amantadine in some individuals and side effects. More selective (thus with less side effects) glutamate receptor targets, in particular the metabotropic mGluR5 subtype, have been investigated. Preclinical studies have shown reduced LID with selective mGluR5 antagonists, but to date, clinical studies have been disappointing. Serotonin is another monoamine neurotransmitter implicated in PD, with relative preservation of serotonergic terminals compared to dopaminergic particularly in PD subjects with LID. Preclinical studies have shown that 5-HT_{1A} agonists may reduce LID, and clinical studies are ongoing. Several other non-dopaminergic targets have been investigated, but these are beyond the scope of this article.

A rarer form of dyskinesia can occur when the levels of levodopa (and dopamine) are low and is thus termed "low-dose dyskinesia." This form of LID can occur at the beginning (about 15–20 min after taking levodopa) and toward the end of the levodopa dose, so-called "diphasic" dyskinesia. The dyskinesia often manifests as leg or foot dystonia with abnormal posturing of limbs or leg kicking and can cause abnormal gaits. An alternative name is thus "dystonia-improvement-dystonia (D-I-D)." Dystonic-type dyskinesia can also occur in full off periods such as on waking in the morning – called off-period dystonia. Such dyskinesia affects the lower limbs with a fixed contraction of the foot and toes and is often painful and extremely bothersome (Fig. 4.1).

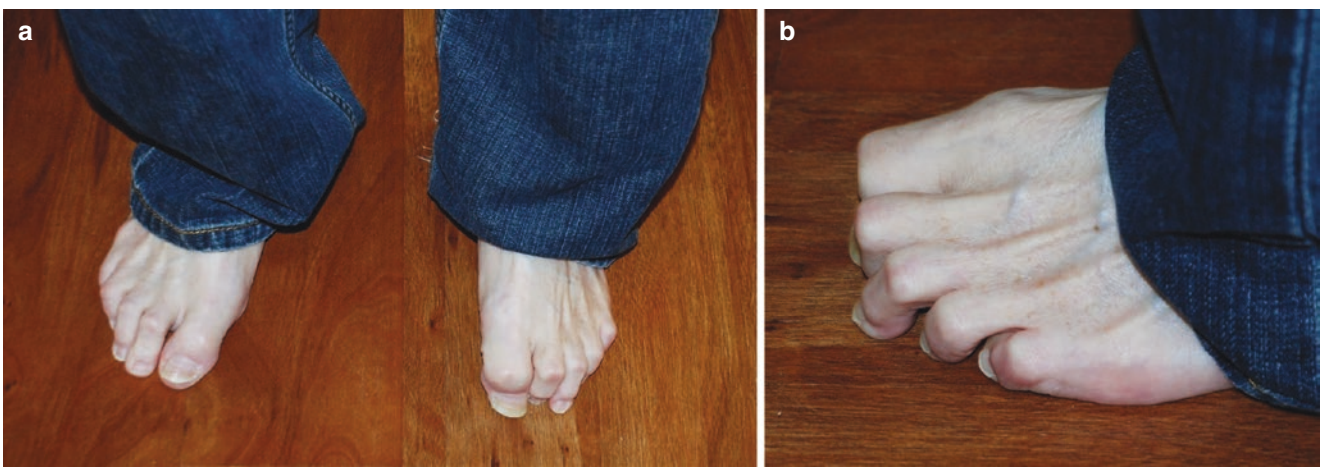

Fig. 4.1 (**a**, **b**) Off-period painful toe dystonia in Parkinson's disease

In more advanced patients, a mixture of dyskinesia may be present, although patients tend to develop a stereotyped pattern, which will affect a certain body part or regions, usually the most affected side, and the dyskinesia will always manifest as this set pattern, regardless of dose, etc.

The management of low-dose dyskinesia thus involves increasing dopamine levels. Off-period dystonia and diphasic dyskinesia respond to treating off periods. Dopamine agonists can often be very helpful for D-I-D type of dyskinesia, but care needs to be taken with possible exacerbations in peak-dose dyskinesia. In practice, patients with bothersome D-I-D often require surgery (bilateral STN DBS) if suitable. For focal dystonias in PD, e.g., foot/toe dystonia, localized botulinum toxin injections can often be helpful. Anticholinergics to treat dystonia are rarely tolerated in adults with PD and potentially can also worsen chorea.

Overall 10% of PD patients, per year, develop dyskinesia after the initiation of levodopa therapy. The main risk factors for developing LID are (a) higher individual doses of levodopa resulting in abnormal pulsatile dopamine receptor stimulation, (b) longer disease severity with associated nigrostriatal dopamine deficiency and consequent altered levodopa pharmacokinetics, and (c) possible genetic predilection.

(a) Individual doses of levodopa in early PD are a known important risk factor. Careful evaluations during clinical trials have demonstrated this finding showing that higher daily pulsatile doses compared to lower doses of levodopa increase the risk of dyskinesia, e.g., the Early vs Late Levodopa (ELLDOPA) trial and early use of levodopa vs levodopa/entacapone (STRIDE-PD). Thus, early use of dopamine agonists was previously investigated as a method of keeping levodopa doses low, as well as preventing pulsatile dopamine receptor stimulation (termed continuous dopamine stimulation). However, this practice is now waning due to significant and very common side effects of impulse control disorders that occur with dopamine agonist use plus a less effective motor benefit than levodopa. In more advanced PD subjects, reducing dyskinesia is possible with intrajejunal infusion of levodopa/carbidopa gel infusion that also leads to continuous dopamine stimulation. Thus judicious use of levodopa – keeping individual doses low – is the better option to reduce long-term issues of all motor fluctuations. Equally important is the need to ensure adequate amounts of levodopa to maintain good antiparkinsonian control and educate patients not to be too concerned about mild amounts of dyskinesia.

(b) Disease severity is also a risk factor for LID, as early and more severe dyskinesia occurs in patients with more severe dopamine depletion and is more prominent on the most affected side of the body. The central pharmacokinetics of levodopa means that greater nigrostriatal dopamine terminal loss likely leads to greater swings in intrasynaptic dopamine levels, with a consequence of exacerbating the abnormal dopamine receptor stimulation, and thus leads to LID. Tremor dominant PD may have a negative correlation to risk of LID.

(c) Genetic subtypes of patients appear to have altered sensitivity to developing LID. Young-onset PD – *parkin*, *PINK1*, and *DJ-1* gene mutations – appears to be more likely to develop LID earlier or after shorter exposure to levodopa. Other genetic factors possibly implicated in the risk of earlier LID include variations in dopamine receptor genes *DRD2* and *DRD3*, dopamine transporter (*DAT*), opioid receptor (*OPRM1*), polymorphism Val66Met in the *BDNF* gene, and the A-allele of the *COMT* Val158Met polymorphism. However studies are inconsistent.

Overall the medical management of LID requires care in early PD to reduce the likelihood of LID developing. Once present, the aim then is to maintain a good level of antiparkinsonian motor control without bothersome LID.

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Deep Brain Stimulation for Tremor in Parkinson's Disease

5

Mahlon R. DeLong and Stewart A. Factor

Case

This patient is a 69-year-old woman who presented at the age of 56 with a 3-year history of micrographia and right-hand tremor, followed 2 years later with right leg tremor. On examination she demonstrated mild to moderate right upper extremity and mild right lower extremity rest tremor along with minimal rigidity and bradykinesia. She also exhibited mild postural/action tremor involving the right arm. With walking, she had deceased right arm swing. The rest of the neurological exam was normal. She was diagnosed with Parkinson's disease (PD) and initially treated with dopamine agonists including ropinirole and then pramipexole, but both were discontinued due to a complaint of "pressure in the head." Amantadine and trihexiphenidyl reduced her tremor to a degree but caused troublesome dry mouth. When she returned to our clinic 5 years later, the rest tremor had worsened and spread to the left side and chin. When seen, she was taking a modest dose of carbidopa/levodopa (½ tab 25/100 mg q 3 h from 9 am to 9 pm) with only minimal benefit for tremor. Her levodopa was doubled over the next 3 weeks with notable improvement in tremor, but it was accompanied by occasional nausea and sweating and recurrence of tremor at night, which impacted her sleep. This was controlled with the addition of long-acting CR at bedtime. The UPDRS part III motor score at this time was 37 with the highest scores for both rest and action tremor and bradykinesia. No motor fluctuations or dyskinesias were reported, but increasing wearing off developed over the next 6 months with worsening of tremor as the primary feature. Despite an increase in levodopa to 1400 mg/day and unsuccessful attempts to retreat with trihexiphenidyl, ethopromazine, and rotigotine and then adding entacapone first and then tolcapone, her tremor had become increasingly troublesome and interfered increasingly with her work as a piano teacher. She still had normal gait and balance and no dyskinesias. She was managed with carbidopa/levodopa 25/100 mg q 3 h and carbidopa/levodopa 50/200 CR at bedtime and atenolol 25 mg daily. It was at this point, at age 66, with a history of PD for 13 years consistent with tremor-predominant PD, that she was evaluated for deep brain stimulation (DBS). Following neuropsychological testing, psychiatric interview, head MRI, motion analysis assessment, a visit with the neurosurgeon, and review by a multidisciplinary committee, a recommendation was made for subthalamic nucleus (STN) DBS. She then underwent left STN DBS with excellent results with complete control of both rest and action tremor of the right upper extremity and right-sided leg rest tremor. She responded well to monopolar high-frequency (120 Hz) stimulation at 2.1 V. She required few subsequent adjustments. Her

Table 5.1 UPDRS part III scores pre- and postprogramming

	Meds/stim		
UPDRS part III	Off/off	Off/on	On/on
Speech	0	0	0
Facial expression	1	1	1
Tremor: face/jaw	0	0	0
Rest tremor: Rt hand	2	0	0
Rest tremor: Lt hand	2	2	1
Rest tremor: Rt leg	1	0	0
Rest tremor: Lt leg	1	1	1
Action tremor: Rt	1	0	0
Action tremor: Lt	2	1	1
Rigidity: Neck	1	0	0
Rigidity: RUE	1	0	0
Rigidity: LUE	2	1	1
Rigidity: RLE	1	0	0
Rigidity: LLE	1	0	1
Finger tap: Rt	1	1	0

(continued)

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Table 5.1 (continued)

	Meds/stim		
UPDRS part III	Off/off	Off/on	On/on
Finger tap: Lt	2	2	1
Hand grips: Rt	2	0	0
Hand grips: Lt	2	1	1
Pron/Sup: Rt	1	1	0
Pron/Sup: Lt	2	1	0
Leg agility: Rt	1	1	0
Let agility: Lt	2	2	0
Arise chair	1	0	0
Posture	1	1	1
Gait	0	0	0
Postural instability	0	0	0
Body bradykinesia	1	1	0
Total	*32*	*17*	*9*

UPDS part III motor score dropped from 32 to 27 with stimulation and 9 with both meds and stimulation (see Table 5.1). She is now undergoing screening for right STN DBS, because of worsening left arm tremor.

Discussion

Rest tremor is a defining feature of classical PD, which is characterized by the combination of tremor with akinesia/bradykinesia and rigidity. Rest tremor, present in over 70% of patients, frequently occurs early and is often the major feature of disease. Patients with prominent akinesia/bradykinesia and rigidity are known as having the *akinetic-rigid* form of PD, in contrast to patients with prominent tremor, who have so-called *tremor-predominant* PD. In contrast to akinetic-rigid PD patients, tremor-predominant patients show limited progression of disease over relatively long periods, with varying degrees of rigidity and bradykinesia. Tremor-predominant patients often respond well to levodopa and other antiparkinson medications, but in some cases, tremor may not be adequately controlled. Tremor-predominant PD patients, in addition to rest tremor, may also have varying degrees of postural/action tremor, which, by some estimates, may be present in nearly half of all patients with PD.

In addition to tremor-predominant PD, there is a syndrome referred to as benign tremulous Parkinsonism (BTP), which may make up to 10% or so of PD cases. Such patients may sometimes blur the line between PD and essential tremor, and the correct diagnosis can be a challenge. In BTP, asymmetric or unilateral resting tremor is the primary feature with varying degrees of accompanying postural/action tremor. Bradykinesia, rigidity, and gait problems as well as non-motor PD features are mild or nonexistent. The tremor can be moderate to severe and quite disabling. It is also usually not alcohol responsive. In about half of the cases, the tremor is partially responsive to high doses of levodopa early on, while the other half have no response. This syndrome progresses more slowly as reflected by a pathological study by Selikhova et al., revealing moderate parkinsonian pathology, but generally progresses to a typical PD picture after a decade in a majority of cases. Despite requiring high levodopa doses, such patients rarely develop dyskinesias. There are also a small number of patients with a monosymptomatic disorder with only isolated rest tremor that would not meet diagnostic criteria for PD. These cases may represent a variant of BTP. In tremor-predominant PD, the diagnosis is usually clear, since the other cardinal features are present and responsive to levodopa. In patients with BTP or isolated rest tremor, the dopamine transporter SPECT scan (FP-CIT-SPECT or DaTscan®) can be helpful when demonstrating decreased putaminal binding, reflecting presynaptic dopamine deficiency. A clear finding in BTP is the high frequency of a positive family history of tremor, which is seen in nearly a third of cases. In some patients diagnosed clinically with BTP, classic alpha synuclein pathology has been reported, and, in some cases, genetic factors consistent with PD have been found. The question of whether BTP should be termed "benign" is often questioned, since, although progression is slow for many years, the tremor is often disabling and there may be a rapid worsening of gait and motility in later stages. Regardless of the tremor type (rest tremor with or without postural/action tremor, as seen in tremor-predominant PD or benign tremulous Parkinsonism), patients whose tremor cannot be controlled adequately with medications are excellent potential candidates for DBS therapy.

DBS was initially developed for the treatment of tremor in PD and essential tremor. Although stimulations of the thalamic nucleus ventralis intermedius (VIM) and STN have both been highly successful for tremor control in PD, it is well known that VIM has little or no effect for bradykinesia or rigidity, while STN DBS is highly effective for these as well as levodopa-related motor complications. Both VIM and STN DBS have been shown to be highly effective for both resting and action/postural tremor in tremor-predominant PD and BTP in small numbers of patients, but there have been no adequate randomized clinical studies of the long-term outcomes or relative effects of DBS targeting the STN for postural/action tremor and the relative outcomes of head-to-head trials between STN and VIM.

For both action and rest tremor, the cerebello-thalamocortical network is strongly implicated as the causative network, and VIM, the recipient of cerebellar input, is well recognized as an effective target for both types of tremor. As seen in Table 5.1, STN DBS was highly effective for both rest and postural/action tremor in our patient. The finding that STN DBS is effective for postural/action as well as rest tremor is not so widely appreciated or as well understood. Whether the action tremor seen in PD is different from that of ET is uncertain. As now discussed widely, the association of an ET-like tremor with a variety of

movement disorders such as PD and dystonia has raised questions about the nature of ET as a discrete entity. The recent demonstrations of close anatomical subcortical basal ganglia and cerebellar connections, particularly between the STN and the cerebellum, have reawakened questions, as well, on the interactions and role of the two cortico-subcortical systems in the pathophysiology of what were previously considered pure basal ganglia and cerebellar disorders, i.e., PD and ET, respectively.

In the case of the patient presented here, DBS was performed somewhat late in the course of her PD, after her tremor had become a clear burden. It would have been reasonable to have considered surgery earlier, since the overall impact of DBS on quality of life and the stigma of PD and socioeconomic factors are well recognized.

Our patients' resting and action/postural tremor responded well to STN DBS with low-voltage standard high-frequency monopolar stimulation, indicating a good placement of the electrode. In general, programming of DBS patients is rather straightforward, beginning with a determination of thresholds for tremor control as well as sensory and motor side effects for each of the four available contacts, using monopolar stimulation with constant high-frequency stimulation (120–150 Hz) and short pulse duration (60–90 μs). The contact with the best stimulation benefit for tremor, without untoward side effects, is selected. If sensory or motor side effects of stimulation limit full benefit for tremor with monopolar stimulation, bipolar stimulation can be highly effective with reduced unwanted side effects due to decreased spread of current. In an effort to lengthen battery life, the minimal required frequency and voltage for tremor control are determined. In this patient, contact 2 was found to provide optimal control. Contact 2 was located in the dorsolateral, sensorimotor, portion of the STN, as reflected in the imaging of lead location as demonstrated by proprietary software (Fig. 5.1).

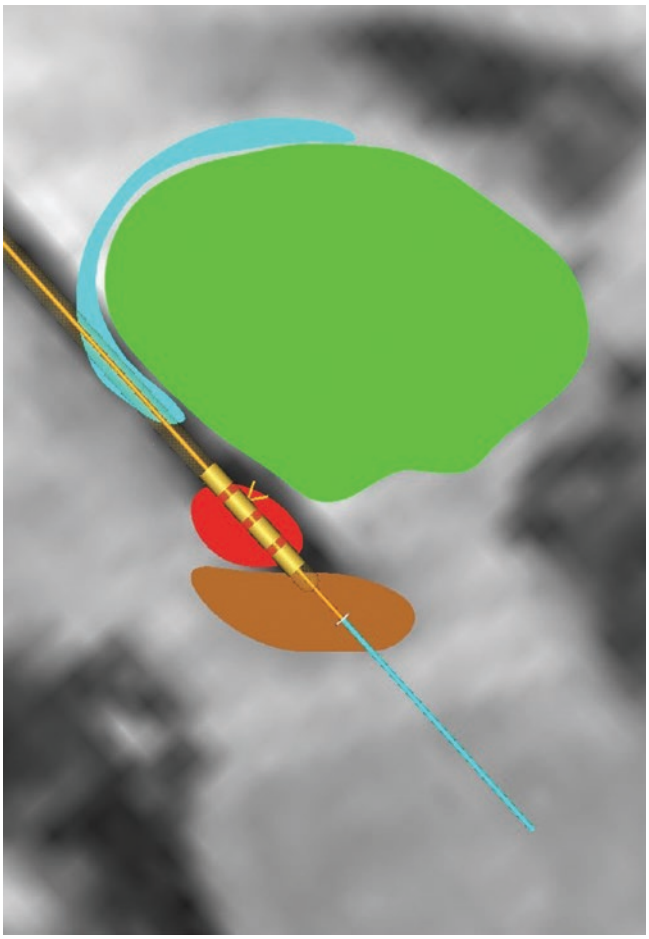

Fig. 5.1 Location of DBS lead and available contacts in the STN (red) shown in the parasagittal view. The contact selected for stimulation (arrow) is the third from the bottom, located in the dorsolateral STN. The adjacent thalamus (green) and substantia nigra (brown) are shown as well

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Deep Brain Stimulation for Fluctuations and Dyskinesia in Parkinson's Disease

6

Jill L. Ostrem

Case

This patient is a 65-year-old man with Parkinson's disease (PD) who was referred for consideration of treatment with deep brain stimulation (DBS). His motor symptoms were first noticed at age 58, presenting at that time with unilateral right hand tremor and reduced dexterity and stiffness in his right arm. He also reported a weaker voice, reduced sense of smell, acting out of his dreams while sleeping, worsening constipation, and mild depression. He was evaluated by a neurologist and diagnosed with PD after secondary causes of parkinsonism were ruled out. When motor symptoms became bothersome to him, he was started on PD medication. Initially he was prescribed an MAO-B inhibitor, with minimal benefit, followed by pramipexole with titration up to 1.5 mg TID. He tolerated this medication well for 2 years but then experienced worsening motor symptoms including arm tremor. A higher pramipexole dose was not well-tolerated, so carbidopa/levodopa 25/100 mg 1 ½ tabs TID was added. After 2 years of stable response, he noticed wearing off every 4 h and less consistent "on times," with development of concomitant mild dyskinesia. The carbidopa/levodopa dose was adjusted to 25/100 mg 2 tabs 5× a day. One year later entacapone 200 mg QID was added to help treat worsening motor fluctuations and wearing off but resulted in increased dyskinesia. His medication schedule was again adjusted and included the reduction of the dose of C/L 25/100 to 1 ½ tab 5× a day with entacapone. His depression was somewhat worse, and he was wondering how much longer he might be able to work given the unpredictable PD symptom control. He was referred for DBS surgery evaluation.

Medications at the initial surgical evaluation visit included rasagiline 1 mg daily, pramipexole 1.0 mg TID, carbidopa/levodopa 25/100 1 ½ tab 5× a day, carbidopa/levodopa CR 50/200 qHS, entacapone 200 mg 5× a day, melatonin 3 mg qHS, Colace qHS, and MVI.

The patient was evaluated after having held PD medication for 12 h. Blood pressure was 125/81 and heart rate 74. The MDS-UPDRS was performed. His UPDRS motor subscale (III) score was 55 in the off state. He had a soft voice; decreased facial expression; prominent rest arm and leg tremor worse on the right side; mild postural hand tremor; moderately increased tone in his neck, arms, and legs (again worse on the right side); moderate bradykinesia in arm and leg testing; slowness in standing from a chair; some postural instability on pull test; gait festination when turning; reduced arm swing; and slight inversion of this right ankle. In the on state, (1 h after taking his usual morning dose of PD medications), his UPDRS motor subscale (III) score improved to 20 reflecting better voice, tremor, rigidity, bradykinesia, gait, and balance. Stereotypic axial (neck and trunk) swaying movement (dyskinesia) was also noted. The next day the patient underwent comprehensive neuropsychological testing. The patient scored in the low normal range for overall cognition and was in the impaired range for tests of executive function. The Beck Depression Inventory documented moderate depression. An MRI obtained within the last 2 years showed mild atrophy, mild periventricular white matter changes, and no serious structural abnormalities.

Discussion

Deep brain stimulation is a highly effective treatment for PD patients experiencing dyskinesia and motor fluctuations not successfully controlled by dopaminergic medications. It has now been applied to over 100,000 patients worldwide with PD and other movement disorders. Some people believe the effect DBS has on PD motor symptoms is akin to the breakthrough the field experienced when levodopa was discovered. When an ideal DBS candidate is selected, has appropriate DBS lead placement, and optimized

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programming, the positive effect on motor fluctuations, reduction in medication requirements, and improved quality of life can be dramatic.

When a PD patient should be considered for DBS therapy is an evolving issue with some arguing DBS should be applied earlier in the disease course just after motor fluctuations develop. However, today most experts will agree on the following criteria: clear PD diagnosis, motor fluctuations, no room for further refinement of medication to help symptoms, levodopa responsive, target symptoms known to improve with DBS, lack of dementia, no severe mood disorder, realistic expectations, and no medical or surgical comorbidities resulting in an unfavorable risk/benefit ratio (Table 6.1).

This patient has a clear history and exam consistent with idiopathic PD, with motor fluctuations and dyskinesia, taking multiple PD medications, multiple times per day. Additional medication strategies including adding amantadine and/or a trial of longer-acting formulations of levodopa may help some, but he will still require frequent dosing throughout the day, and motor control will continue to be a challenge as the disease progresses. He has a favorable surgical risk/benefit ratio with no significant medical comorbidities including a nonconcerning brain MRI. It would be wise to treat his depression and establish the patient is psychiatrically stable before proceeding with DBS. The postoperative course can be challenging, untreated depression worsens quality of life, and the risk of suicide is slightly higher in patients treated with DBS. The patient has an excellent response to levodopa (64%). Patients who are highly levodopa responsive tend to have a more robust response to DBS. Some private insurance companies will not approve DBS surgery unless a patient has a minimum UPDRS III "off medication" score of 30 and at least a 30% improvement in the "on" state. Patients with levodopa-unresponsive freezing of gait or significant postural instability are unlikely to have these symptoms improve with DBS, unlike levodopa-refractory tremor which is highly responsive to DBS. Dyskinesia is also usually improved after DBS from a direct stimulation effect and/or reduction in antiparkinsonian medications. Other non-motor PD symptoms are not likely to improve with DBS, including cognitive change, mood disorders, RBD, constipation, anosmia, and fatigue, unless these symptoms were being exacerbated by PD medications. It is important that the patient be fully informed about the risks of DBS surgery and the therapy itself. Although the risk of brain hemorrhage is small (0.5–2%), morbidity is possible. More common is the risk of infection (5%) which may require explantation of the device. Stimulation side effects are reversible, but sometimes not appreciated, and optimization of DBS settings and medication adjustment can be a drawn-out process for some patients.

Table 6.1 PD patient candidacy for DBS

Inclusion criteria	Exclusion criteria
Diagnosis of idiopathic PD	Serious surgical comorbidities
Troubling motor symptoms, including motor fluctuations, dyskinesia, despite optimized pharmacological treatment[a]	Uncontrolled psychiatric illness, including anxiety and mood
Robust motor response to levodopa (exception tremor)	Dementia
Clear understanding of surgical risk and realistic expectations	Preoperative MRI with extensive white matter changes or severe cerebral atrophy

[a]Current Medtronic Inc. FDA labeling indications for Parkinson's disease: bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic DBS therapy for Parkinson's disease is indicated for adjunctive therapy in reducing some of the symptoms in individuals with levodopa-responsive Parkinson's disease of at least 4 years' duration that are not adequately controlled with medication, including motor complications of recent onset (from 4 months to 3 years) or motor complications of longer-standing duration

Once a patient is deemed a surgical candidate, other surgical decisions still need to be addressed which are best determined with by a multidisciplinary team familiar with the patient's case. If PD symptoms are predominately unilateral, then a contralateral implant may be sufficient. Some centers favor staged implants (implantation of one hemisphere followed by a recovery window before implantation on the second hemisphere) especially in more cognitively fragile patients. For this patient bilateral implants are needed. The DBS brain target also needs to be chosen. Both the subthalamic nucleus (STN) and pallidal brain targets have been shown to be equally effective in multiple randomized clinical trials, so for this patient, either target would be appropriate. Patients treated with STN DBS can usually reduce their PD medications to a greater extent; therefore the STN target may be preferable for patients experiencing side effects from high medication requirements. The pallidal target has been associated with somewhat lower levels of postoperative mood symptoms and greater dyskinesia response. Some groups favor the pallidal target in more borderline cognitive candidates, but this has not been well studied, and there is limited evidence. Lastly thalamic VIM DBS can used in PD but will largely only impact tremor, which would result in incomplete symptom control for this patient. Another factor to consider includes the method of surgery. DBS lead placement has traditionally been performed using a microelectrode recording-guided approach, requiring the patient to be awake and participate in the OR with test stimulation. Methods now exist allowing patients to be asleep for the procedure, which is guided by imaging-based targeting alone. Although not extensively studied, this approach seems to result in similar outcomes and is gaining in popularity. Lastly, a choice needs to be made for the type of DBS system to implant. Today, both rechargeable and non-rechargeable neurostimulators are available, but in the near future, multiple manufacturers will provide DBS systems with varying features.

This patient was implanted with bilateral STN leads, using an asleep interventional MRI method approach because he was fearful of being awake for the procedure. He was implanted with a non-rechargeable neurostimulator, as he preferred to not have the "burden" of charging the device, but realized he may require a battery replacement after 3–5 years with the non-rechargeable device.

The patient tolerated surgery well and 1 month later was seen in clinic for initial programming of the device in a relative off medication state (allowing for greater determination of symptom improvement from stimulation). Before initiating programming, an electrode impedance check of the system was performed with normal results, indicating integrity of the system with no open or short circuits. In the case of high or very low impedances are found, this would require an investigation into the electrical issues of the system before programming. A monopolar review using a standard 60us pulse width and a 130 Hz frequency was then performed to test the effect of stimulation across each single contact/electrode (there are four on each currently available Medtronic lead). The contact producing the greatest therapeutic effect at the lowest amplitude, without resulting in stimulation-induced side effects, was chosen for initial stimulation. The patient's postoperative CT scan was merged with the preoperative MRI, to confirm lead location and help inform which contact(s) were in the posterior lateral motor region of the STN. Contact 1 on the left hemisphere and contact 9 on the right hemisphere were chosen to initiate chronic stimulation (see Fig. 6.1).The amplitude was set at 1.0 mA on both sides with instructions to slowly increase the amplitude every other day by 0.1 mA using the patient programmer at home. When reaching 1.5 mA, he began experiencing dyskinesia on the right body. His medications were then reduced by cutting his pramipexole dose to 0.5 mg TID and cutting carbidopa/levodopa 25/100 to 1 tab five times a day. His DBS settings could be further increased without the development of dyskinesia, but at 2.3 mA he developed difficulty with this speech. When turning off the right brain lead, his speech was no longer strained helping to confirm this was a stimulation-induced symptom coming from the right brain lead. This lead was then reprogrammed using a bipolar mode using contact 9− and 10+ (a programming strategy that narrows the stimulation field and is often used when stimulation side effects occur using monopolar stimulation mode). This resulted in near resolution of his parkinsonism at 2.9 mA and no speech difficulty. After 4 months of tailored programming and medication adjustment, he was experiencing minimal tremor, greatly improved motor fluctuations, resolution of dyskinesia, and required 50% less parkinsonian medication than before surgery. The patient was pleased with his outcome and was able to continue working. He remained on an antidepressant to treat his depression. Five years later he was experiencing minimal motor fluctuations but had developed worsening postural instability and intermittent freezing of gait, requiring the use of a cane and physical therapy to reduce his fall risk. Adjustment of DBS settings and medications did not result in any additional appreciable benefit, but the patient was still very grateful for the overall improvement in symptoms and if given the choice would have DBS surgery again.

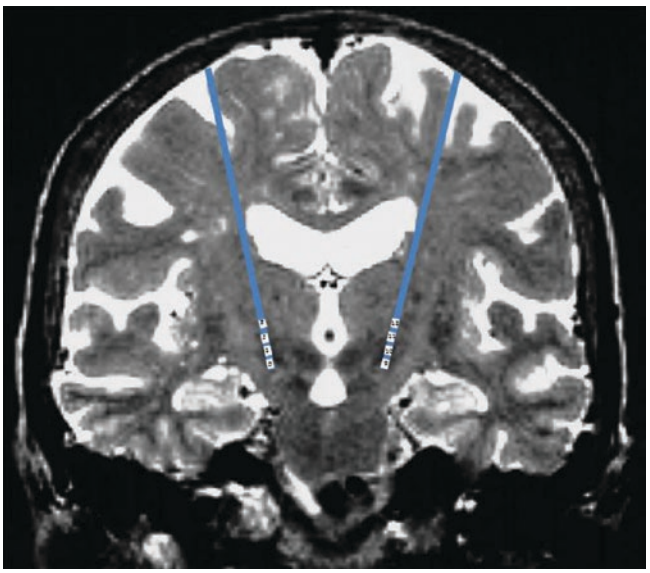

Fig. 6.1 Coronal brain MRI image with superimposed Medtronic 3389 DBS brain leads placed in the subthalamic nucleus. Brain leads have four contacts/electrodes (designated as 0, 1, 2, 3 on the left and 9, 10, 11, 12 on the right)

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Treatment of Falls in Parkinson's Disease

7

Jorik Nonnekes and Bastiaan R. Bloem

Case

A 65-year-old man with an 8-year history of Parkinson's disease (PD) was seen at our outpatient clinic because of recurrent falls (about two each month) that had gradually emerged in the past year. He was treated with a half tablet of levodopa/carbidopa 25/100 mg/tid, and this regime had remained stable during the past few years, despite development of some wearing off, particularly in the early afternoons. The falls and their consequences had a disabling effect on his quality of life. Apart from frequent bruises and lacerations, one fall 6 months earlier resulted in a hip fracture – necessitating hospital admission and surgery. Because of these injuries, and even more so because of a growing fear of falling, this man had markedly restricted his activities, leading to reduced mobility and loss of independence.

During the interview, he denied having experienced any transient loss of consciousness prior to the falls. When asked whether there was a stereotypical pattern to the falls, he reported that he predominantly fell in a forward or lateral direction. He reported that falls were usually preceded by a typical feeling as if the feet suddenly got "stuck" to the floor, usually when manoeuvring in a narrow space. But his walking could also be relatively good at other moments, for example, when walking outdoors. He had also occasionally slipped over a loose carpet in his hallway, but that type of falls was distinctly much rarer.

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Upon clinical examination, we observed a gait pattern with slow, short shuffling steps. When we asked him to perform a full and narrow turn with rapid small steps, clear freezing of gait appeared. During the retropulsion test, he needed five balance corrective steps (which were small in amplitude) to recover balance. Visual examination revealed binocular diplopia. There was no orthostatic hypotension (simple sphygmomanometer assessment), and there were no signs of polyneuropathy or weakness. He wore appropriate footwear.

We installed a multidisciplinary treatment program. We gradually increased the dosage of levodopa/carbidopa to 25/100 mg/qid, which led to marked improvements of gait, although occasional freezing (as an end-of-dose phenomenon) persisted. A physiotherapist specializing in Parkinson management instructed our patient to use cueing strategies to overcome the remaining freezing of gait episodes – both visual and auditory cues were tested, and our patient clearly preferred rhythmic auditory cues provided by a metronome. He also received balance training, because recovery on the retropulsion test remained inadequate despite the medication changes. Together with the patient, the physiotherapist also developed a customized exercise program (cycling on a stationary bicycle at home, at least three times a week). A specialized occupational therapist advised on domestic adaptations, including removal of the one loose carpet in the hallway, and on optimising lighting conditions throughout the house. A referral to an ophthalmologist (to evaluate diplopia) could be cancelled because the double vision disappeared with higher levodopa doses. Using a fall diary, the number and circumstances of falls were monitored. Following introduction of this multidisciplinary treatment program, the incidence of falls reduced to once every 3 months, all of which were related to the residual freezing episodes. His fear of falling also reduced gradually, and he was able to resume usual activities.

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Discussion

Falls are common in PD, and they can result in fall-related injuries. These injuries are usually relatively mild (e.g., bruises or lacerations) but can occasionally be severe (e.g., hip fractures or head trauma). As illustrated by our case report, fall-related injuries subsequently can result in a limited mobility, which in most patients is reduced further by a concurrent fear of falling. This induces a vicious circle, as a limited mobility will lead to muscle weakness and reduced fitness, both of which increase the risk of a renewed fall. In addition, immobility promotes osteoporosis, thus increasing the chance of severe fall-related fractures. To break this vicious cycle, an individually tailored and multifaceted intervention is needed. This starts with identifying which risk factors contribute to the falls in each patient (for most patients, falls are related to multiple co-existing risk factors, so clinicians should not stop their evaluation when one has been identified). This obviously includes a wide range of factors that are related directly to PD, such as freezing of gait. Importantly, however, patients with PD are not exempt from "generic" fall risks that are common to the elderly. Hence, a broad range of factors should be considered when evaluating falls in PD. A Falls Task Force identified no less than 16 generic risk factors and 15 PD-specific risk factors for falls (see Table 7.1 and recommended literature). Most of these can be identified by careful history taking and clinical examination. Identification of all potentially contributing risk factors for falls then serves as a basis for subsequent interventions, typically using a multidisciplinary approach.

Table 7.1 Overview of generic and disease-specific risk factors for falls in Parkinson's disease

Generic	Age
	Gender
	(Sedative) medication
	Polypharmacy
	Postural hypotension, orthostatic syncope, autonomic dysfunction
	Cardiac arrhythmia
	Arthrosis
	Incorrect use of an assistive device
	Anxiety
	Weakness due to inactivity
	Visual and ocular motor impairment
	Daily use of alcohol
	Environmental hazards
	Other co-morbidities (e.g. vertigo, peripheral neuropathy, diabetes)
	Depression
	Osteoporosis
PD-specific	Fall history
	Disease severity
	PD medication (e.g. when falls are related to violent dyskinesias or delirium)
	Slow mobility
	Shuffling and small scaled gait
	Freezing of gait and festination
	Posture (stopped posture protects against backwards falls but may worsen festination and forward falls)
	Postural instability
	Transfers
	Cognitive impairments
	Axial rigidity
	Dyskinesias
	Long-term adverse effects of DBS of the subthalamic nuclei and GPi
	Dual tasking
	Urinary incontinence

Adapted from van der Marck and colleagues, Parkinsonism and related disorders, 2014 (see Suggested Reading list)

Assessment of Risk Factors

History Taking

An essential first step is to ascertain whether or not the falls were preceded by a transient loss of consciousness (not to be mistaken for unconsciousness that occurs *after* the fall, e.g., due to head trauma). Compared to falls where consciousness remains intact, falls that are preceded by transient loss of consciousness require a completely different work-up and treatment approach. It can be rather difficult for patients to make this distinction. When patients recall hitting the floor after the fall, consciousness was likely preserved. The nature of the injuries can also be informative: specific injuries such as wrist or collarbone fractures indicate that the patient attempted to break the fall, suggesting preserved consciousness. Conversely, the presence of severe facial injuries might reflect the absence of defensive reactions due to the loss of consciousness. Exemptions of this rule are patients with progressive supranuclear palsy, who can present with facial injuries despite preserved consciousness, due to motor recklessness and absent defensive reactions.

If a fall is preceded by loss of consciousness, a broad differential diagnosis should be considered (see recommended literature). Syncope (caused by failure of the cerebral circulation) is the most common cause of falls preceded by loss of consciousness. Syncope is usually preceded by presyncopal symptoms caused by cerebral hypoperfusion, such as blurred vision, loss of colour vision, tunnel vision, hearing loss, or a feeling of dizziness. In the setting of PD, syncope is most likely related to the side effects of dopaminergic medication, although in advanced cases PD-related autonomic dysfunc-

tion can also contribute. Syncopal falls early in the course of Parkinsonism may suggest autonomic failure due to atypical Parkinsonism (most notably multiple system atrophy or Lewy body dementia).

When falls appear unrelated to any preceding loss of consciousness, we specifically search for the presence of both extrinsic risk factors (related to the environment) and intrinsic risk factors (related to the patient) (see recommended literature). Examples of extrinsic risk factors include loose carpets (as in our patient), wet bathroom tiles, poor lighting, or inappropriate footwear. Examples of intrinsic risk factors include PD-related features such as freezing of gait or postural instability and more generic factors such as muscle weakness or co-morbid polyneuropathy. Some factors can be related to PD, its treatment, or both; an example here is orthostatic hypotension. Other factors can be either PD-related or simply reflect co-morbid pathology; important examples here include visual problems and cognitive disorders. Most falls in PD are related to intrinsic risk factors, the most common one being freezing of gait. Useful questions to detect freezing include asking whether a patient ever experiences a feeling "as if the feet are being glued to the floor", although many patients simply say that their feet suddenly get stuck. An important feature is the episodic character of freezing: it is sometimes there, but often it isn't. Always ask about the typical provoking circumstances, such as turning in tight quarters, or while trying to cross a doorway. Another common intrinsic risk factor for falls in PD is the presence of postural instability. To screen for the presence of postural instability, we ask whether patients are easily outbalanced, for example, during gait initiation, and whether they have difficulties to arise form a chair.

It helps to ask whether the falling pattern is stereotypical (when the answer is no, multiple fall types might be present, and each should be worked up separately). We always ask whether the patient falls predominantly into a particular direction. Forward falling suggests freezing of gait and so does falling sideways (when turning provokes freezing); these lateral falls may result in hip fractures. Backward falling suggests small or absent balance correcting steps, and falling vertically down could indicate syncope or drop attacks as the underlying mechanism. Falls that occur immediately after rising from a chair or bed suggest either postural instability or orthostatic hypotension (but note that syncopal falls can also occur after prolonged standing).

History taking alone may not suffice to obtain all necessary details related to falling, particularly when patients have cognitive disturbances (which is not uncommon). A dedicated falls diary (to record the actual circumstances immediately after a fall) can be helpful, also to document the effects of treatment recommendations. The interview is incomplete without asking for cognitive decline – talking to caregivers is essential here – and in particular, to ask about frontal executive or behavioural changes.

Evaluating medication is another vital element of the assessment. Polypharmacy is a notorious risk factor for falls and so is the use of benzodiazepines, antidepressants, neuroleptics, antihypertensive medication, and antiarrhythmics. The effect of dopaminergic medication can be twofold. Usually, dopaminergic medication reduces fall risks by decreasing freezing and gait hypokinesia. However, dopaminergic medication can also paradoxically increase fall risks by inducing orthostatic hypotension, violent dyskinesias or – rarely – ON-state freezing.

Clinical Examination

The neurological examination is important, but is not infallible. First, most patients perform paradoxically much better in the hospital or office than at home. Second, patients usually present in clinic during an ON phase, whereas most difficulties at home are experienced during an OFF phase. Wearable sensors for ambulatory gait monitoring at home hold great promise here but are yet to find their way to clinical practice. When the exam is at odds with the interview (remarkably good performance in clinic, despite many falls at home), we re-examine patients during a practically defined OFF phase (when they experience an end-of-dose effect prior to the intake of their next medication dose).

Gait evaluation is the first key element. The shuffling gait, with a reduced step height, can lead to falls due to stumbling over obstacles. Freezing of gait is usually difficult to provoke in clinical practice. The most sensitive single test to provoke freezing is asking the patient to make a full (360°) turn from standstill, on the spot, as rapidly as possible, and in both directions. If this does not provoke freezing of gait, we instruct patients to walk with short steps as rapidly as possible.

Talking to the patient during walking offers a general impression of the ability to perform a dual task while walking – fall risks are markedly increased when patients "stop walking while talking", presumably because inability to handle multiple tasks simultaneously comprises the safety of walking in daily life, particularly in complex environments with many distracters.

The presence of postural instability can be evaluated by performing the retropulsion test (see recommended literature). The retropulsion test entails a rapid balance perturbation in the backward direction (typically a sudden pull to the shoulders, delivered by an examiner standing behind the patient. Importantly, the examiner should be sure to have some support behind them when doing the test). The number and quality of balance correcting steps (or the total absence thereof in case of severe balance problems) are used to rate

the degree of postural instability. Patients with good balance respond by taking one or two large correcting steps. In contrast, patients with balance impairment take smaller corrective steps, forcing them to take more than two steps. Markedly impaired patients must be caught by the examiner.

We always screen for presence of visual disorders, because many patients compensate for their motor deficits by guiding their movements visually; ophthalmological disorders might hamper this compensatory ability. Some patients require referral to an ophthalmologist for further evaluation and possible treatment.

We routinely test for orthostatic hypotension, particularly because history taking is unreliable. Orthostatic hypotension is defined as a decrease in systolic blood pressure of 20 mmHg or a decrease in diastolic blood pressure of 10 mmHg within 3 min of rising from sit to stance. These cut-offs have a high sensitivity but low specificity. We prefer to use a drop of 30 mmHg in systolic blood pressure, which has a higher specificity and is therefore clinically more relevant. The "bedside" sphygmomanometer assessment can miss relevant orthostatic hypotension occurring immediately after rising or – more commonly – well after the 3-min interval. When in doubt, we refer patients for tilt table testing. Finally, we evaluate the quality of the patient's footwear, checking for, e.g., slippery soles.

Treatment

It is impossible to summarize the management of every risk factor for falls. However, we will discuss several common and relevant examples. The first relates to the multidisciplinary approach to parkinsonian gait, including freezing, which includes both medical and non-medical interventions (see recommended literature). Most gait problems are levodopa-responsive, so the first step is to initiate (in naïve patients) or increase the dose of levodopa, to 1000 mg/day if so required. Moreover, we recommend physiotherapy to all patients, to teach them dedicated strategies to improve the small steps or overcome freezing episodes (e.g. conscious movement strategies to make a big step, to use external cueing strategies, to make lateral weight shifts, to direct attention to gait, or to make wide arcs when turning). All strategies have been detailed in a recent guideline (see recommended literature). Additionally, we recommend engaging an occupational therapist who can advise on possible domestic adaptations, such as removal of obstacles, optimising lighting conditions, or providing safety rails.

The second example relates to the multidisciplinary management of postural instability. A trial of adequately dosed levodopa is always justified, but postural instability generally does not improve much with dopaminergic medication. There is hope that cholinesterase inhibitors might reduce postural instability (see recommended literature), but ongoing trials should further define their role. We always refer patients with postural instability to a specialized physiotherapist for guideline-based balance training (see recommended literature). A physiotherapist can also assess whether the patient may benefit from a walking device and can train its actual use.

Conclusion

Falls in PD are common, and the underlying mechanism is often multifactorial. Falls prevention is difficult but not impossible. It requires a thorough assessment of all possible risk factors that may contribute to falls, so that an individually tailored and multidisciplinary treatment program can be installed to reduce the incidence of falls, thereby improving the quality of life of affected individuals.

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Treatment of Freezing of Gait in Parkinson's Disease

8

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Case

A 65-year-old man presented to his local neurologist with worsening dexterity of his right dominant hand accompanied by smaller handwriting. He was found to have asymmetric bradykinesia and rigidity on examination, leading to a diagnosis of Parkinson's disease (PD). He was started on carbidopa-levodopa 25–100 mg three times a day. The patient had a robust response to this regimen and did not require any adjustments for 18 months. At that time there was some progression of motor symptoms including hypokinetic gait and mild forward flexion at the waist and neck. The dose of levodopa was increased to 400 mg daily with further improvement. One year later there was evidence of motor fluctuations, with off periods occurring 3.5 h after each levodopa dose, difficulty turning in bed, and arising in the morning. At this time the dosing interval of levodopa was reduced, and an extra dose was added (600 mg total daily dose of levodopa), with the subsequent addition of a monoamine oxidase inhibitor (MAO-I) the following visit.

The patient did well on this regimen, with minor adjustments for two more years. At this time, there were marked episodes of wearing off manifested primarily by freezing of gait (FoG) and frequent dyskinesias in the on state. The addition of amantadine improved both the FoG and the dyskinesias; however, the levodopa dose could not be increased further at the risk of worsening dyskinesias. After another year of minor adjustments, the patient was burdened with frequent dosing and the emergence of sudden unpredictable wearing off. At this point (6–7 years of disease duration), the patient was referred for deep brain stimulation (DBS). Following bilateral subthalamic nucleus (STN) DBS, the patient had profound improvement in motor fluctuations and dyskinesias. At the 1-year postoperative appointment, the patient reported no further FoG and was only taking an MAO-I and 200 mg of levodopa daily. The patient was followed and treated for non-motor symptoms including mild to moderate constipation and memory loss without significant adjustment in stimulation parameters or his dopaminergic regimen.

At a follow-up visit 2 years postop, he reported mild start hesitation without any evidence of motor fluctuations. His levodopa dose was slowly increased to 300 mg daily, and he developed worsening dyskinesias, but his FoG did not improve. He was reprogrammed at lower rates with some improvement. Amantadine was subsequently reintroduced, but cognition worsened. He was referred for neuropsychological testing which revealed impairment in attention and executive function. At this point the patient was started on atomoxetine resulting in improvement in cognition and a subjective reduction in FoG severity. In the following years, FoG re-emerged, and cognition worsened further. Therapeutic interventions included the elimination of amantadine, stimulating at more ventral contacts with lower frequencies and regular referrals to physical therapy. As the disease progressed to more advanced stages, the patient was diagnosed with dementia and developed impulsivity and postural instability, which led to frequent falls. One of the more severe falls resulted in a hip fracture placing him in a nursing home. Initially he seemed to recover and regain some mobility with the use of a walker; however, the combination of worsening impulsivity and postural instability limited him to ambulation with assistance only or wheelchair use.

Discussion

FoG is a debilitating condition, which occurs frequently in PD and related parkinsonian syndromes. FoG is defined as the episodic inability to generate effective stepping despite the intention to do so. Reported prevalence rates vary widely; however, it is likely universal in advanced disease, particularly

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if dopaminergic therapies were not available. FoG impairs quality of life, function, and independence and is a frequent cause of falls, which can lead to fractures, hospitalization, and nursing home placement. The pathophysiology of FoG is poorly understood. Associations with cognitive dysfunction (particularly executive functions) have been reported. Multiple theories have been proposed including four models implicating motor, cognitive integration, and processing deficits. An intrinsic locomotion deficit is clearly present. When compensatory mechanisms break down (perhaps due to executive dysfunction), FoG becomes problematic.

Two main issues need to be considered when addressing FoG clinically: (1) Is there a relationship between FOG and dopaminergic response? and (2) What other factors are contributing to gait impairment? The potential relationships between levodopa and FOG include levodopa-induced FoG or so-called "on" FoG (a rare phenomenon); levodopa-unresponsive FoG or dopa-resistant FoG (more common in atypical parkinsonian syndromes); pseudo-on-state FoG (off-state FoG that is partially relieved by dopaminergic therapy but still present in the on state); or dopa-responsive FoG (off-state FoG). Therefore, the first step in addressing FoG is to determine if it is associated with off periods exclusively. If so, then the treatment strategy is to address motor fluctuations with the goal of reducing off time (see Fig. 8. 1). If a relationship between FOG and levodopa cannot be established by history, or there is uncertainty of the type of response, a dopaminergic challenge in the clinic or a more aggressive dopaminergic regimen is typically recommended with close monitoring of the patient by the use of diaries or wearable tracking devices, which can clarify this issue. The recommendation of a more aggressive dopaminergic regimen should be weighed carefully with the risk of precipitating levodopa-induced dyskinesias (LID) and other side effects. An extended period of observation in the clinic, with the patient in the on and off state can be very helpful at this point as well.

When FOG occurs in a patient who has had DBS, the first step is to determine if DBS has an effect on FoG. The simplest way of determining the positive or negative contribution of DBS to FoG is by turning the device off and examining the patient. If FoG worsens, then attempts at reprogramming with the aim of maximizing the benefit of DBS on FoG are indicated. If FoG improves with the device off, then attempts at reducing the rate, and simplifying stimulation parameters, perhaps using more ventral contacts, can also be considered.

For patients with dopa-unresponsive FoG, non-dopaminergic therapies need to be considered (see Fig. 8.1). Rehabilitation modalities are central to the treatment of any gait disorder. Attempts at improving automaticity of gait can be helpful, particularly exercise or Lee Silverman Voice Therapy modified to address gait (LSVT-BIG). Compensatory strategies can also be considered, including laser canes and walkers (U-step), metronome devices, or other cues. Therapists can also recommend appropriate assist devices for each patient and aid in the proper use. Non-dopaminergic medical therapies, which can be tried, include noradrenergic replacement (droxidopa or atomoxetine), stimulants (methylphenidate), amantadine, or antidepressants. The use of these treatments is off label and has limited or no evidence supporting their use (mostly anecdotal or expert recommendation), therefore should only be consid-

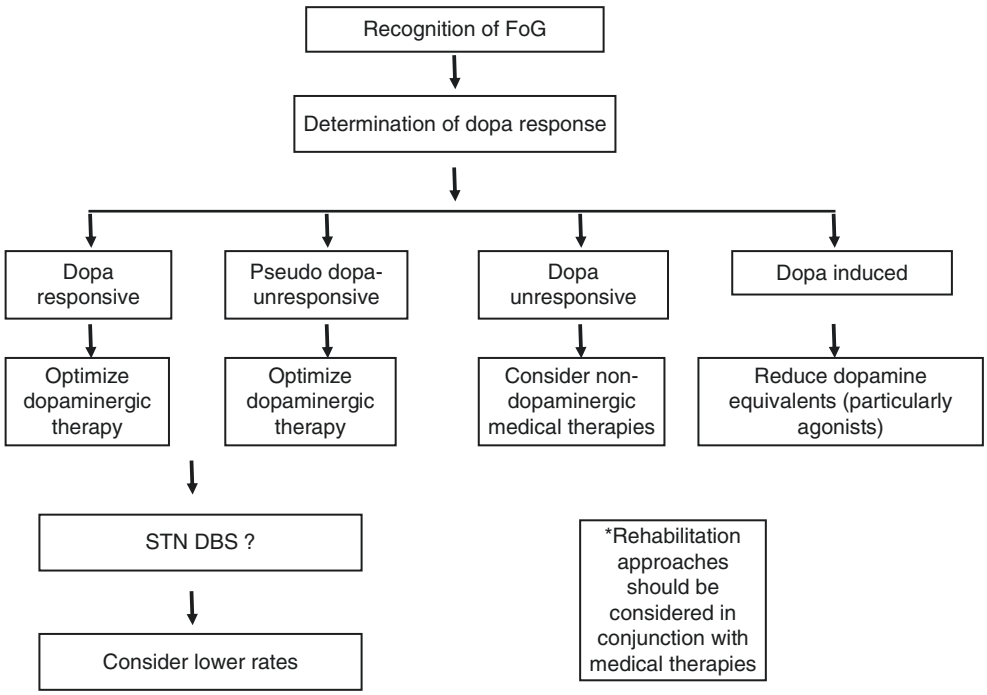

Fig. 8.1 Treatment algorithm

ered in individual cases with caution. DBS targeting the pedunculopontine nucleus (PPN) has received significant attention in recent years; however, results are mixed and preliminary, and due to the invasive nature of this therapy, it should be considered investigational.

Clinicians treating patients with any gait abnormality must recognize that this is a multifactorial problem, and treatment should be individualized. FoG becomes especially problematic when seen in combination with balance impairment and when cognition is impaired. Cognitive impairment (e.g., executive dysfunction) makes it difficult for patients to participate in rehabilitation programs and puts patients at increased fall risk due to impulsivity, poor judgment, and insight. A careful evaluation of the entire neuro-axis is required to consider the contribution of peripheral neuropathy, spinal abnormalities, cerebellar abnormalities, hypokinetic parkinsonian gait (which may be dopa responsive), dystonic posturing (including camptocormia and anterocollis which can displace the center of gravity) and dyskinesias, attention deficit, orthostatic hypotension, visual disturbance, and hearing impairment. Festination, whereby a patient is observed to walk faster with forward displacement of the center of gravity can be confused with FoG, can coexist in PD, and is also a common cause of falls. A careful evaluation of concomitant medications is recommended, particularly removing sedating drugs during the day like benzodiazepines and minimizing the use of dopamine agonists, which may exacerbate FoG (anecdotal evidence only). Orthopedic abnormalities are also common, not just of the lower extremities and spine, but also shoulder issues can affect gait significantly by further impairing arm swing. An evaluation of the home, including high traffic areas to remove clutter and simplify floor patterns, assist device training (ensuring proper use), and resources to minimize falls (handle bars, nonslip pads, shower benches, etc.) can be effective tools in fall reduction.

In summary, the management of a patient with FoG begins with appropriately recognizing the presence of FoG and its impact on the patient's daily life. A thorough history should include educating patients on FoG (often facilitated by showing them examples of FoG on video and excluding FoG mimics like festination), identifying other factors contributing to gait dysfunction, and determining whether or not there is a response to dopaminergic therapy. At this point, safety concerns are addressed first, primarily falls. Significant reduction or elimination of falls due to FoG may be as simple as identifying common FoG triggers and teaching the patient cues to break the FoG episode in those situations or may require gait restrictions, e.g., limited to a walker, assistance or wheelchair only. Once safety concerns have been addressed, the clinician determines if FoG is dopa-responsive, if so, dopaminergic therapy is optimized. If there is no dopaminergic response, treatment is individualized for each patient using rehabilitation strategies accompanied by therapies aiming at comorbidities that may affect FoG (e.g., balance, cognitive dysfunction, etc.).

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Treatment of Dysarthria in Parkinson Disease

9

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Case

A 68-year-old man diagnosed with idiopathic Parkinson disease (PD) was referred for a speech assessment and treatment by his movement disorder neurologist. The patient reported that he was diagnosed 4 years earlier and described his initial symptoms to include tremor in the right hand and an occasional hoarse voice. At the time of speech assessment, he was at stage II Hoehn and Yahr, and his medication was considered optimized. The referral to a speech therapist was based upon the spouse's complaint of her inability to understand her husband. *"His voice is soft and monotone and I ask him to repeat all the time. But he tells me that I have a hearing loss. I am tired of nagging him to speak louder!"* The patient reported that he did not feel his voice was softer but that he sometimes experienced vocal fatigue at the end of the day with a slower speech rate (without medication). The patient is retired and lives at home with his wife. He uses his voice for daily communication with his spouse and at social engagements with friends and family. He expressed growing frustration with not being understood (even though he feels he is loud enough) and indicated there are increasing episodes when he avoids communication interactions altogether.

A voice and speech assessment included a range of tasks and measures. An *oral mechanism exam* revealed structure and function consistent with PD (i.e., reduced amplitude of movement across the speech mechanism). *Perceptual ratings* from single words, sentences, reading, spontaneous speech, as well as sustained phonation revealed classic symptoms of PD: reduced loudness, monotone, and a breathy, hoarse voice, articulatory imprecision. *Acoustic measures* of sound pressure level (SPL), a correlate of loudness, and fundamental frequency, a correlate of pitch, were consistent with these perceptual observations. Vocal SPL for speech production ranged from 60 to 65 dB and sustained phonation ranged from 65 to 70 dB (both at a distance of 30 cm). These results represented reading and conversation vocal SPL levels that may significantly reduce his speech intelligibility and communicative effectiveness. Fundamental frequency range was reduced (100–250 Hz). Taken together, these symptoms require a listener to "work hard" to understand this patient. Even in a quiet environment, his spontaneous speech was intelligible only 75% of the time. *Stimulability testing* across a range of speech tasks demonstrated that the patient could increase loudness and improve voice quality and enhance articulatory precision when cued to "speak louder." Referral to *otolaryngology* for a laryngeal exam revealed reduced vocal fold closure and no gastric reflux or lesions.

Based upon these findings, Lee Silverman Voice Treatment (LSVT LOUD®), a voice treatment for PD with demonstrated efficacy, was recommended for this patient. He participated in the standard dosage of 16 individual 60-min sessions in 1-month time with daily homework and carryover activities, administered by an LSVT Certified Clinician. To ease accessibility, one session a week was delivered to the patient in his home online using telepractice, an efficacious delivery mode of LSVT LOUD.

Posttreatment data documented increases in vocal loudness, improved intonation, better voice quality, and increased articulatory precision. Vocal SPL was 70–74 dB in speech and 85–88 dB in sustained phonation (at a distance of 30 cm), and frequency range increased 80–300 Hz. Intelligibility in spontaneous speech increased to 90%. The patient's spouse

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reported a significant improvement in her ability to understand him and declared, *"That's the voice I fell in love with!"*

During treatment, the patient learned how to maintain and advance his speech and voice improvements after he completed treatment through participating in follow-up voice exercise classes and using voice exercise videos and software systems. The patient was seen every 6 months for 1–2 follow-up treatment sessions over 4 years and was able to maintain functional speech production throughout this time.

Discussion

Research shows that up to 89% of people with PD will experience speech and voice disorders called *hypokinetic dysarthria* which includes disorders of voice (e.g., reduced loudness, monotone, breathy and hoarse quality), articulation (e.g., imprecise or weakened consonants and vowel centralization), and rate (increased, decreased, or variable). These symptoms can occur across all stages of PD and lead to significant reductions in functional communication and quality of life.

Historically, these speech disorders were thought to be primarily motor disorders resulting from hypokinesia and rigidity. However, today abnormalities in sensory processing, internal cueing, and self-monitoring of speech output are now thought to contribute and may help explain why speech symptoms are generally unresponsive to pharmacological or neurosurgical treatments and why traditional motor speech therapy has been largely unsuccessful in sustaining an effect beyond the treatment room.

Today, people with PD can make lasting changes in their speech and voice that significantly improve their functional communication. LSVT LOUD is an effective speech treatment for people with PD. Named for Mrs. Lee Silverman (Lee Silverman Voice Treatment), a woman living with PD, it was developed by Dr. Lorraine Ramig and her colleagues and has been scientifically studied for over 25 years with support from the National Institute on Deafness and Other Communication Disorders within the National Institutes of Health (NIH) and other funding organizations. Three randomized control trials (RCTs) have documented the short- and long-term efficacy of LSVT LOUD, which trains people with PD to use their voice at a more normal loudness level while speaking at home, work, or in the community. A key to the treatment is helping people "recalibrate" their perceptions so they know how loud or soft they sound to other people and can feel comfortable using a stronger voice at a normal loudness level.

LSVT LOUD differs from traditional PD speech treatment in three ways: (1) the singular target of treatment is on voice (respiratory-laryngeal subsystem), specifically increasing amplitude of vocal motor output to override hypokinesia throughout the speech mechanism; (2) LSVT LOUD is delivered in an intensive dosage (16 individual, 1-h session in 1 month) and high effort mode with exercises aimed at maximally stimulating the nervous system and building complexity across weeks of training; and (3) LSVT LOUD addresses the sensory component of the speech disorder and includes retraining of sensory perception of normal loudness (self-monitoring) and internal cueing. In contrast, traditional speech treatment for PD, focused on multiple targets (e.g., loudness, articulation, rate), was delivered once or twice a week with limited repetitions and no focus on training effort and did not directly address sensory and cueing deficits.

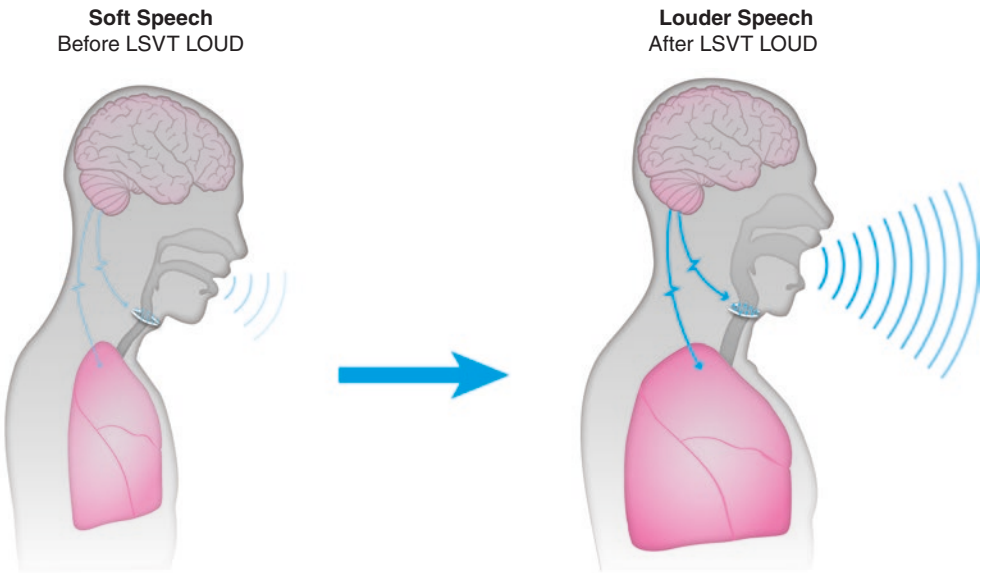

Fig. 9.1 This figure illustrates the changes from soft speech, before LSVT LOUD (left) to louder, more normal speech, after LSVT LOUD (right) observed in people with PD. (Used with permission from LSVT Global)

Treating vocal loudness has been documented to make changes across the entire speech production system and improve functional communication (Fig. 9.1).

This figure illustrates the changes from soft speech, before LSVT LOUD (left) to louder, more normal speech, after LSVT LOUD (right) observed in people with PD. Although the concept of "speak louder" may appear simple on the surface, a trained speech therapist is necessary to help people with PD improve loudness in a *healthy* way.

In addition, research has advanced insight about the underlying mechanism accompanying treatment-related change, with reports of physiologic, acoustic, perceptual, psychosocial, and neural changes posttreatment.

It is recommended that all people with PD be referred for a speech evaluation as soon as possible upon diagnosis. The evaluating therapist can establish baseline speech performance data, determine the need for treatment, and help the person with PD choose the best treatment for his or her symptoms. Speech and voice symptoms may be subtle at first, and people often fail to notice changes or deny any concerns, but we know that by diagnosis, the neuropathology exists. A speech therapist can unmask subtle and hidden deficits and educate people with PD on the best time to start therapy. That said, it is never too late for evaluation and treatment. People in later stages of PD, with atypical parkinsonism and post-deep brain stimulation surgery, can gain benefits from speech treatment as well.

There are several referral sources for finding speech therapists who are experienced in using evidence-based speech treatment for PD including the American Speech-Language-Hearing Association (ASHA), www.asha.org, and LSVT Global, www.LSVTglobal.com. Today there are over 16,000 LSVT LOUD therapists delivering this efficacious treatment in 73 countries.

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Treatment of Dysphagia in Parkinson's Disease

10

Ronald F. Pfeiffer

Case

A 72-year-old right-handed man first developed a slight shuffling quality to his gait in approximately 2012. He also began to experience some difficulty adjusting his feet when standing on the golfing tee, preparing to hit the ball. However, he did not seek any medical evaluation until 2014, at which time he was referred for neurological evaluation because of increasingly noticeable neurological dysfunction.

The neurologist initially suspected the presence of a cervical myelopathy because of the presence of neck stiffness and pain, along with brisk lower extremity reflexes and bilateral Babinski responses. X-rays of the cervical spine demonstrated multilevel degenerative changes, but an MRI was deferred because the patient was claustrophobic. The neurologist commented that the patient was not experiencing any dysphagia or choking. Baclofen produced some transient benefit but was eventually discontinued. The patient was subsequently placed on a brief trial of carbidopa/levodopa 10/100 as a diagnostic test for possible Parkinson's disease (PD), but he only took the medication at a dose of one-half tablet once or twice daily for 3–4 days before discontinuing it because of some mental "fogginess" and lack of benefit.

By mid-2015 the patient's gait dysfunction had progressed, and cervical fusion at the C3–C7 levels was undertaken. Postoperatively, the neck stiffness resolved, and there was some slight improvement in leg function. However, impairment of fine motor dexterity, particularly when performing repetitive tasks, deteriorating ability to type, and impairment of handwriting became progressively more noticeable and reduced arm swing, and slight bilateral upper extremity tremor emerged. An MRI of the brain was unremarkable. Some difficulty swallowing had become evident even prior to the neck surgery, but following surgery, the dysphagia became even more pronounced, and the patient also developed some voice hoarseness.

The patient was referred to the movement disorders clinic, and by that time, the parkinsonian features were more readily apparent, and a diagnosis of PD was made. The patient was still experiencing dysphagia and at times would choke when swallowing. Carbidopa/levodopa 25/100 was initiated, with definite improvement in motor function within 1 month. He even resumed driving, which he had given up 8 months previously. However, his dysphagia did not improve. In addition to difficulty swallowing, the patient also mentioned that he would sometimes cough up or regurgitate undigested food or pills that he had swallowed up to an hour earlier. This description raised the question of a possible Zenker's diverticulum, and the patient was referred for gastroenterology evaluation.

A fluoroscopic upper gastrointestinal radiographic study was subsequently performed and demonstrated the presence of a large, wide-mouthed Zenker's diverticulum extending from the posterior aspect of the esophagus (Fig. 10.1). The mouth of the diverticulum measured approximately 1.8 cm, beginning at the C3–C4 level. The pouch measured approximately 2.3 × 1 cm, and a large amount of retained contrast was noted within the diverticulum throughout the examination. The distal esophagus appeared unremarkable and no gastric abnormalities were identified. Endoscopic surgery was subsequently performed, and the large, wide-mouthed Zenker's diverticulum was visualized, along with a prominent cricopharyngeal bar. The diverticulum was repaired and cricopharyngeal myotomy performed without incident, with subsequent resolution of the dysphagia.

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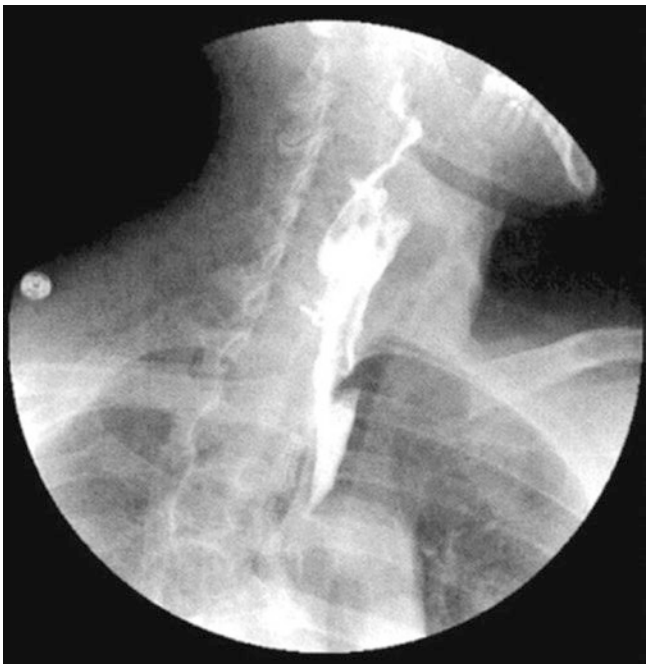

Fig. 10.1 A large, wide-mouthed Zenker's diverticulum, with a pouch measuring approximately 2.3 × 1.0 cm containing a large amount of retained contrast, extends from the posterior aspect of the esophagus

Discussion

Many patients with PD have some difficulty swallowing. The exact percentage is uncertain because large variability has been reported in different studies, probably owing to differing definitions of dysphagia and differences in the assessment tools utilized. Subjective survey studies suggest that anywhere from 30% to over 80% of persons with PD may have some awareness of swallowing impairment, whereas studies that use objective measures, such as radiographic or manometric techniques, arrive at higher figures of prevalence, often exceeding 95%. It also is evident from such studies, however, that not all individuals who have objective abnormalities involving swallowing actually experience or are aware of any difficulty swallowing. Studies even suggest that silent aspiration may be present in up to one-third of PD patients.

All three stages of swallowing – oral, pharyngeal, and esophageal – can be impaired in PD. Within the mouth, impaired function of the lips, tongue, and other oral muscles due to rigidity and bradykinesia can result in impaired bolus formation, delayed initiation of swallowing, the need for repetitive tongue pumping, and residual food being left in the mouth. In the pharyngeal phase of swallowing, pharyngeal dysmotility may lead to misdirection of swallows and residual food material being left in the vallecular and pyriform sinuses. A potentially serious complication due to these abnormalities is the development of aspiration. In fact, some studies suggest that aspiration may occur in over 50% of persons with PD. Symptoms that suggest oropharyngeal dysfunction include difficulty keeping food in the mouth, hesitation in swallowing, a sensation of food sticking in the mouth or throat, nasal regurgitation, the need for multiple attempts to successfully swallow, painful swallowing, laryngeal abnormalities such as hoarseness or a "wet" voice after eating, and symptoms of aspiration such as coughing with eating or drinking. Recurrent episodes of pneumonia might also raise the question of aspiration. Oropharyngeal abnormalities can be best visualized with a modified barium swallow (MBS) study, in which the patient is asked to swallow both solid and liquid food mixed with barium under fluoroscopy. It is important to recognize, however, that although the MBS also visualizes the cervical esophagus, it does not adequately view the entire length of the esophagus.

Esophageal abnormalities have also been described in the setting of PD and may be present in up to 85% of patients. Esophageal dysfunction in PD may include slowed esophageal transit, segmental esophageal spasm, diffuse esophageal spasm, ineffective contractions, and even aperistalsis. Achalasia has also been reported in individuals with PD. A sensation of food sticking below the clavicle is suggestive of esophageal dysfunction. It is important to remember that the MBS does not adequately visualize the entire extent of the esophagus. Therefore, if the MBS does not reveal the cause of dysphagia in a person with PD, additional investigation with a barium esophagram, which employs liquid barium rather than food substances and visualizes the entire esophagus, should be performed.

Zenker's diverticulum actually is a false diverticulum that forms in the posterior aspect of the hypopharynx, just above the cricopharyngeal muscle, which serves as the upper esophageal sphincter. The cricopharyngeal muscle normally relaxes in response to the force of a food bolus and then constricts after the bolus passes in order to prevent reflux of the bolus. Formation of a Zenker's diverticulum is believed to be the result of inadequate relaxation of the cricopharyngeal muscle, with consequent increased intraluminal pressure just above the sphincter that eventually produces the outpouching that becomes a Zenker's diverticulum. An increased frequency of Zenker's diverticulum formation has been reported in patients with PD, presumably due to cricopharyngeal muscle dysfunction and perhaps even cricopharyngeal dystonia with consequent cricopharyngeal bar formation. In one study, 22% of patients with PD who were referred for evaluation of dysphagia were found to have either a cricopharyngeal bar or a Zenker's diverticulum. Symptoms suggestive of a Zenker's diverticulum include choking on food, regurgitation of food particles minutes or even hours after swallowing, bad breath, hoarseness, and a sensation of mucous in the back of the throat. A barium esophagram is the preferred study for visualizing a Zenker's diverticulum. Diagnosis of

Zenker's diverticulum is important because treatment in the form of surgical removal or closing of the diverticulum, along with cricopharyngeal myotomy, is curative.

Although curative treatment was available in this case and may also be in other instances, such as when anterior cervical osteophytes impinge on the esophagus or when dysphagia is caused by severe gastroesophageal reflux, for most PD patients with oropharyngeal dysphagia due to rigidity and bradykinesia, curative treatment approaches are not available. Some individuals will benefit from adjustment of antiparkinson medication. For most, however, speech/swallowing therapy is the treatment of choice. Various swallowing techniques, including tilting the head, effortful swallows, and expiratory muscle strength training, may improve swallowing and reduce the risk of aspiration. Changing food viscosity by employing thickened liquids may also reduce aspiration potential. Treatment programs primarily designed to improve speech may also benefit swallowing.

Three clinical points can be made from this case. First, it is important to remember that dysphagia is a frequent gastrointestinal component of PD that may be present and pose risk to the patient even when the patient is unaware of it. Therefore, questions about its presence should be asked at every visit including to the caregiver. Second, it also is important to remember that, although dysphagia in PD most often is the consequence of impaired coordination of the oropharyngeal musculature due to rigidity and bradykinesia, other processes also may be responsible. In this case, it was a Zenker's diverticulum along with cricopharyngeal bar formation, but other processes also may be to blame, such as anterior osteophytes of the cervical spine impinging on the esophagus, severe gastrointestinal reflux, or even achalasia, in which the presence of Lewy bodies has actually been reported. The third point to remember is that the pathology producing dysphagia in PD may not always be oropharyngeal in origin, but may reside in the esophagus. In such cases, a barium esophagram may be needed to visualize the pathology.

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Rehabilitation for PD

11

Lynn Rochester

Case

An energetic and highly accomplished 51-year-old businessman was diagnosed with Parkinson's disease (PD) in 2003. He was categorised as postural instability-gait disorder phenotype and prescribed ropinirole XL, levodopa and selegiline. Within a year he was experiencing significant end-of-dose wearing off, pain, dystonia, very mild dyskinesia and incipient freezing of gait. However, over the next decade, he was able to maintain reasonable function and a demanding work schedule via regular review, optimal medication and an energetic exercise regime (gym attendance, outdoor activity such as hill walking) plus movement strategies (cues) to overcome gait dysfunction. By 2013 obsessive features of gambling were evident, and ropinirole XL was reduced but retained. The effect was positive although gambling still had to be monitored and motor deficit increased. He started to fall in 2013, mostly as a result of freezing whilst turning, and around 60% of his day was spent in the 'off' state. He intermittently experienced vivid dreams and REM sleep behaviour, but no hallucinations. He attended a 6-week rehabilitation programme focusing on treadmill training to improve falls, with little effect. Throughout this period his mood was stable, he remained motivated and his cognition was still excellent. In 2015 he was referred to physiotherapy for falls assessment because falls frequency had increased.

Physiotherapy assessment took place in the clinic. A detailed subjective assessment revealed that falls occurred mostly when he was turning and under dual-task conditions (e.g talking whilst walking or carrying objects whilst walking). His wife noted that he could be impulsive and rush. Objective examination under single-task conditions (walking, walking and turning) revealed excellent motor control. His gait was moderate to fast (around 1.3 m/s), and it appeared symmetrical and consistent. Step length was reasonable. His posture was good, and arm swing whilst slightly reduced was not asymmetrical. Bradykinesia was not evident. Similarly, clinical assessment of balance revealed no obvious impairment. He could turn 180° appropriately and modulate his gait speed on command. Reactive and anticipatory postural responses were excellent. The 'pull' test was not impaired, and there was no loss of medial-lateral control from external perturbation. He could stand on one leg for at least 30 s, tandem walk, walk in all directions, turn, negotiate obstacles, walk through narrow doorways, reach and move well outside his base of support with confidence. He did not veer, and there was no obvious start hesitation or freezing of gait.

All manoeuvres were then tested under dual-task conditions (walking whilst carrying out a simultaneous cognitive task). He was asked to walk, turn, negotiate obstacles and walk through narrow spaces whilst at the same time recite numbers backwards (in serial 7s), starting from a random number between 0 and 200. This more complex task prompted him to freeze, and in response to freezing, he lurched impulsively towards a chair for support. The threshold for effective motor control had been reached. Freezing made him vulnerable to falls, and his impulsivity was an unsafe response. Treatment focused on movement strategy training (auditory cues) delivered via a metronome set at 10% below step frequency and adapted to suit different walking conditions (slower, short bouts of walking indoors compared with faster and more sustained bouts of walking outdoors). On discussion with the medical team, his ropinirole XL was withdrawn completely. His cueing strategy was reviewed at the next appointment. Over the next 12 months, falls occurrence was reduced.

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Discussion

Falls are common in people with Parkinson's disease. Around 61% of people with PD fall each year compared with 33% older adults, with 39% of people with PD reporting recurrent falls. Interventions to reduce falls range from multicomponent falls prevention programmes to single therapies including administration of cholinesterase inhibitors. Falls prevalence nevertheless remains high. As falls become embedded with advancing disease, secondary effects such as fear of falling, loss of confidence and reduced levels of activity further complicate the issue. Falls are multifactorial with a complex pathophysiology. A recent task force identified 31 falls predictors in PD (16 disease-specific and 15 age-related) indicating the challenges associated with falls assessment which requires a nuanced but thorough approach. The strongest predictor of a future fall is a previous fall, which has obvious limited utility and cannot guide treatment. Critical to understand is the context in which falls occur, notably the environment and the activity immediately preceding the fall. Also highly relevant is the mismatch between clinical performance and free-living performance, as clearly illustrated by this case. Attentional drive, which is heightened in the clinic, exerts a powerful and positive influence on motor control, reducing falls risk.

Assessment of motor function to detect the cause of falls focuses on dynamic balance tasks, gait, complex gait activities (turning, obstacle negotiation, spatial navigation) and dual-task performance. Static balance tests are limited. Most falls occur during gait, with recent work showing the adverse effect of turning on dynamic postural responses in people with PD. Falls are also associated with freezing of gait, often provoked by turning.

In this case it was necessary to provoke freezing of gait in the clinic, from which his impulsive response was observed. For people with high level cognitive function who compensate for motor deficit (especially in the clinic where attention is primed), motor and cognitive systems must be stressed to reveal motor deficit. A common approach is to test performance under dual task. People with PD describe difficulties with dual task and studies typically highlight a slower, more variable gait in PD when distracted by a concurrent, second task. Dual-task performance is supported by cognitive processes such as executive function, working memory and attention, which are mediated via the prefrontal cortex. These processes are able to compensate for motor deficit in the early stages of PD but become impaired with advancing disease, and patients then lose the ability to compensate. Dual task is tested by asking patients to perform walking with a concurrent cognitive task such as backwards subtraction (Serial 7 or Serial 3), animal naming or verbal fluency. Despite strong clinical utility, it is important to recognise its limitations. In PD (and controls), response is highly variable and not in itself predictive of falls. Reasons for variability include differences in protocol, task difficulty, instructional set and lack of normalisation to baseline values for the cognitive task, which vary as a function of cognitive reserve.

Cognitive reserve is particularly relevant to this case. Single-task testing was insufficient to provoke loss of postural control or a near fall. Freezing of gait and impulsive behaviour was only revealed when the dual task (backwards Serial 7) was added to the motor task, which in itself was challenging. It is unusual to compensate this effectively and reflects high cognitive reserve. Dual-task interference is protected by high 'hazard estimate' which denotes the ability to recognise self-limitations and effectively estimate risk, which was evident here.

Evidence supports the use of movement strategy training (in this case auditory cues) to reduce episodes of freezing, and for this patient with intact attention, it was entirely appropriate. Impulsivity characterised his motor response, mediated at least in part by his dopamine agonist. His wife had noticed his impulsivity although he had little awareness of it. On further questioning it became apparent that this was a common feature associated with his falls. Removal of ropinirole had some impact, but as noted in the literature, it is unlikely to totally ameliorate the behaviour.

The scenario described here illustrates the advantages of a team approach to falls management in PD. Given the complexity of falls, this is the recommended approach. The cause of his impulsivity was revealed after discussion with the medical team who informed management.

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Part II

PD Non-motor

Treatment of Orthostatic Hypotension in Parkinson's Disease

12

Stephen G. Reich

Case

During a routine follow-up visit, a 72-year-old man with a 5-year history of Parkinson's disease (PD) reported having "brownouts" about once per week for the prior 3–4 months. They only occurred when upright including arising after a meal and while ascending the stairs. He never completely lost consciousness but during the spells felt "uncoordinated." His wife, a nurse, observed that during the spells, he was "out of it" and pale. During a recent appointment in radiation oncology, where he was being treated for prostate cancer, his blood pressure was found to be 116/68 supine and 79/51 standing. At that point his internist stopped his prior treatment for hypertension. He was taking carbidopa/levodopa 25/100, two tablets every 3 h and carbidopa/levodopa ER 50/200 at night for difficulty getting out of bed to go to the bathroom and also return of tremor after getting back into bed.

On examination, signs of PD included decreased voice volume, resting tremor of the left hand, and mild bradykinesia and rigidity, affecting the left limbs more than right. He had no difficulty arising from the chair. He walked slowly and did not lose his balance on the pull test. Supine BP was 110/63 and was difficult to hear after standing for 1 min, but by palpation the systolic was 72, and he simultaneously felt light-headed, akin to his "brownouts." I reviewed a number of non-pharmacologic tips [see section "Discussion"] for managing orthostatic hypotension, and because he was so symptomatic, I simultaneously began fludrocortisone 0.1 mg in the morning.

Two weeks later I heard from the patient's internist that he had his first episode of actual syncope, in contrast to the prior spells in which he never completely lost consciousness. This recent episode happened at a restaurant where he and his wife were celebrating their anniversary. Despite counseling to minimize alcohol, he had had three drinks, and during desert, without warning, he lost consciousness and became very stiff. He was assisted by a physician sitting nearby and within a few minutes made a complete recovery. At that point the fludrocortisone was increased to 0.2 mg in the morning, and the patient was again warned about use of alcohol and the need to eat smaller more frequent meals. He has subsequently had no further episodes of syncope and infrequent, short-lived "brownouts." His most recent BP was 142/60 supine and 140/70 after standing for 3 min (Tables 12.1 and 12.2).

Table 12.1 Non-pharmacologic management of orthostatic hypotension in Parkinson's disease

Reduction or elimination of medications known to lower BP (including those for PD as well as nonneurologic conditions)
Avoid large meals especially high carbohydrate meals
Eat frequent small meals
Minimize alcohol
Avoid situations that increase core body temperature such as hot environments, hot baths or showers, or saunas
Become familiar with the earliest symptoms of OH and sit or lay down immediately
Use of isometric exercise to transiently increase BP (flexing buttocks or thighs)
Increase water intake (up to 2 l per day)
Increase salt intake (equivalent 1–2 tablespoons) either by adding additional salt to food or via high-salt soups or vegetable drinks
Prop the head of the bed 30°
Use an abdominal binder
Avoid prolonged sitting or lying down
Encourage exercise (recumbent bicycle)

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Table 12.2 Pharmacotherapy for orthostatic hypotension in Parkinson's disease

Drug	Dosages	Starting dose	Maintenance dose	Side effects
Fludrocortisone	0.1 mg tablet	0.1 mg in the AM	0.2 mg in the AM	Edema, hypokalemia, supine hypertension
Midodrine	2.5, 5, 10 mg tablet	2.5 mg tid (8 am, noon, 4 pm)	5–10 mg tid	Supine hypertension, piloerection, scalp itching, urinary retention
Droxidopa	100, 200, 300 mg capsules	100 mg tid (8 am, noon, 4 pm)	300–600 mg tid	Supine hypertension, headache, dizziness, fatigue, nausea
Pyridostigmine	60 mg tablet	30 mg tid	60 mg tid	Salivation, abdominal cramps, diarrhea, sweating, urinary incontinence

Discussion

Orthostatic hypotension, defined as a BP drop of 20 mm systolic or 10 mm diastolic within 3 min of standing, is one of the most common non-motor features of PD, affecting at least 30% of patients. Yet, only about half are symptomatic emphasizing the need to routinely check for OH. Further disguising OH in PD is the fact that many affected patients do not have the traditional symptoms of orthostatic lightheadedness, near-fainting, or actual syncope. Instead they may experience orthostatic pain across the shoulders (coat-hanger pain) or low back pain, fatigue, shortness of breath (with exertion), visual blurring, or mental fogginess. Orthostatic hypotension may contribute to falls in PD, and there is emerging evidence that it is also a risk factor for cognitive impairment. It is important to be aware of OH, even if asymptomatic, as its presence might influence the choice of PD medication and provides an opportunity to counsel the patient about situations in which it may become symptomatic.

If OH is symptomatic, then the first step in treatment is a careful review of all of the patient's medications to see which may be causal or at least contributing—and this includes PD medications, especially dopamine agonists. It is often possible to stop or reduce medications used to treat hypertension. The next step is to provide education to the patient about situations that can exacerbate OH and to utilize non-pharmacologic therapies. Orthostatic hypotension is worsened after a meal, especially a high carbohydrate or hot meal, and patients should be counseled to eat smaller, more frequent meals. They should get up slowly after a meal and at other times, especially after sitting or lying down for prolonged periods (which should be avoided). Hot baths, showers, saunas, and hot climates should be avoided as they may cause peripheral vasodilation. Straining at stool decreases venous return thus lowering BP so constipation and firm stools should be treated. Ascending stairs can also precipitate OH, and patients should go slowly holding on to the banister. Patients (and caregivers) often become very sensitized to the presence of OH and should be counseled to sit or lay down immediately at the first sign, and if not able to do so, then an isometric exercise such as squeezing the fists or tightening the buttocks or thighs can transiently raise BP.

The next step in the management of OH is non-pharmacologic as there are many ways to raise BP and avoid OH that do not require medication. The first is to increase salt and water intake, unless there is a contraindication such as congestive heart failure or renal insufficiency. Since OH tends to be worse in the morning, I advise patients to have a full glass of cold water upon awakening and to the degree possible, try to drink at least 1–2 l of water per day. This is challenging since PD patients with OH are also often already struggling with urinary frequency, urgency, and incontinence and therefore are purposely limiting fluid. Extra salt (the equivalent of 1–2 teaspoons) can be added to meals, or salt tablets can be employed, but for many patients, this is easiest accomplished by eating salty soups or drinking salty liquids such as certain vegetable juices. Sugary drinks should be avoided as carbohydrates may lower BP, and similarly alcohol should be used judiciously with special caution if taken with a meal.

A common recommendation given to patients with OH is to use elastic stockings. If you have ever observed a patient with PD, try to put these on, and then the uselessness of this recommendation becomes readily apparent. The knee-high support hose are not sufficiently effective at increasing venous return, and the waist-high stockings are nearly impossible for most patients with PD, including their caregiver, to put on, are often uncomfortable and hot. As an alternative, an abdominal binder is easier to put on and off and can be helpful to raise BP by increasing splanchnic venous return. Propping the head of the bed about 30° may improve BP by attenuating nocturnal diuresis, and it is also helpful for supine hypertension which may accompany OH even when not being treated with medication.

One especially challenging problem in treating OH is encouraging patients who are poorly tolerant of being upright to avoid prolonged lying down or sitting. Although exercise can lower BP, in the balance, it has a net positive effect as long as precautions are taken and patients stay well-hydrated

before, during, and after exercising. For those who cannot exercise while standing, such as walking, then a recumbent bicycle is a good option as are chair or pool exercises.

For many PD patients with OH, the initial approach to treatment, including elimination of as many medications as possible, recognition of circumstances to avoid, and utilizing the non-pharmacologic recommendations above, is not enough to improve BP and symptoms. For the remainder, the next step is pharmacologic therapy, and the three mainstays include the volume expander fludrocortisone and two vasoconstrictors, midodrine and droxidopa, and there are others. Despite widespread use, the evidence base for the use of these drugs for treating OH in PD is limited, and as such, the order and combination of therapies must be individualized, and it is often a matter of trial and error balancing the beneficial versus the deleterious effects. I often start with fludrocortisone since is it is easy to titrate and generally well-tolerated. It should be avoided if there is congestive heart failure or renal insufficiency. The starting dose is 0.1 mg in the morning and can be increased to 0.2 mg, also once in the morning as higher doses rarely offer additional benefit and increase the risk of hypokalemia, which must be monitored, especially in patients who are also using extra salt. Fludrocortisone, like midodrine and droxidopa, can cause supine hypertension, and this is discussed below.

If there is benefit from fludrocortisone but the patient remains symptomatic (and I follow symptoms more than relying just on BP readings), then a second agent can be added. If there is no clinical benefit from fludrocortisone, then it should be replaced by another agent. The choices of a second agent include midodrine, droxidopa, or pyridostigmine. The latter is an acetylcholinesterase inhibitor well known to neurologists for treating myasthenia. For OH, it works by enhancing transmission at sympathetic ganglia which, like the neuromuscular junction, also uses acetylcholine as the neurotransmitter. When there is peripheral sympathetic denervation, as there is in PD, this may be less effective, and in general, pyridostigmine has a very modest symptomatic effect but a potential advantage in that it does not cause supine hypertension. The starting dose is 30 mg tid increasing to 60 mg tid. Side effects are those expected with enhanced cholinergic transmission and include increased salivation, diarrhea, abdominal cramps, sweating, and urinary incontinence, which may limit its tolerance.

Usually more effective than pyridostigmine are the peripheral vasoconstrictors midodrine and droxidopa. Midodrine is started at 2.5 mg tid but should be taken during the first half of the day (approximately 8 am, noon, and 4 pm) to avoid supine hypertension overnight. The dose can be escalated gradually, based on assessment of both BP readings (supine and standing) and symptoms to as much as 10 mg tid. Side effects include piloerection, scalp itching, and, rarely, urinary retention. An alternative to midodrine is droxidopa which is converted to norepinephrine. The starting dose is 100 mg tid, at the same time recommended for midodrine as it can also cause supine hypertension. Again, using a combination of BP readings and clinical response, the dose can be escalated gradually to 600 mg tid. Additional side effects include headache, nausea, dizziness, and fatigue.

For patients who remain symptomatic despite optimizing pharmacotherapy with the above agents (alone or in combination), the likelihood of another agent offering significant improvement is remote. The list of second-line agents, most of which I have not used, includes indomethacin, methylphenidate, yohimbine, desmopressin, octreotide, and atomoxetine.

As mentioned above, supine hypertension often complicates treatment of OH, but it is worth noting that it can occur even without treatment. It is not clear at what point, if ever, it should be treated, and in general, for most patients, the consequences of OH are more concerning than supine hypertension. Some simple measures to treat it include avoiding pharmacotherapy of OH within 5 h of bedtime, having patients prop up the head of the bed, and taking a carbohydrate snack before bed. Personally, I practically never treat supine hypertension, but if thought to be necessary, then recommended medications include captopril, clonidine, hydralazine, losartan, or nitroglycerine patch, near bedtime. My concern is exacerbating OH when patients awaken to urinate or get out of bed first thing in the morning. The management of supine hypertension does emphasize that in treating OH, while the BP results are of course very important, they have to be viewed in the context of symptoms. For instance, if the patient still has OH despite treatment, but their symptoms are under acceptable control, then I'm hesitant to increase or add additional therapy to treat just the BP.

Through the combined use of non-pharmacologic and pharmacologic therapies, most PD patients with OH can be helped. For some though, OH remains frustratingly resistant to treatment; in that circumstance, and in all PD patients with OH, it is worth considering whether they may instead have multiple system atrophy. The high prevalence and symptomatic consequences of OH in PD necessitate routine check of supine and standing BP. You will be surprised to see how often OH is detected.

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Treatment of Constipation in Parkinson's Disease

13

Leslie Cloud

Case

A 71-year-old man with idiopathic Parkinson's disease (PD) for 2 years presented with a chief complaint of constipation, which was present for the past 5 years and had worsened significantly during the previous 6 months. He was having one bowel movement per week that was hard and painful to pass. He was up to date on his age-appropriate health screening, including colonoscopies, which had always been unremarkable except for the presence of internal hemorrhoids. His medical history was otherwise only significant for well-controlled depression, which was treated with doxepin 150 mg po qhs. His daily medications otherwise included carbidopa/levodopa 25/100 mg, two tablets TID, and a multivitamin with iron. For his constipation, he had tried prune juice and psyllium powder intermittently with no relief. When questioned about his diet and lifestyle, it was discovered that he was drinking very little water (less than 1 L daily) and his diet was deficient in fiber. He did not exercise. Neurological exam was significant for mild right-sided rigidity and bradykinesia. There was no tremor. Gait was normal, but right arm swing was diminished. Abdominal exam revealed hypoactive bowel sounds and mild distension but no tenderness to palpation.

Initial recommendations included increasing water intake to 2.5 L/day, increasing dietary fiber intake to the recommended daily allowance for men over 70 (30 g/day), and adding regular exercise to his lifestyle. His doxepin was switched to citalopram 20 mg daily to avoid the possible contribution of doxepin to his constipation. His multivitamin was switched to one that did not contain iron for the same reason. If ineffective, he was advised to add over-the-counter docusate sodium 100 mg bid to soften stools and psyllium (up to 5.1 g po bid) to facilitate more regular bowel movements. He returned for follow-up 4 months after initiating all of the above changes, except the addition of docusate and psyllium daily, and was happy to report an improvement in his bowel movement frequency to 3–4 times per week. Stools were also less hard and painful to pass. He did, however, still experience occasional constipation when he was not compliant with the daily water and fiber intake suggested. In those circumstances, he used the docusate and psyllium daily for a few days until his bowel movements returned to normal. His depression had not worsened due to the change in his antidepressant therapy. He was pleased with these results.

Discussion

Chronic constipation is most commonly defined by Rome III criteria, which require the presence of two or more of the following symptoms during at least 25% of defecations over at least 3 months: straining, lumpy or hard stools, feelings of incomplete evacuation, sensations of anorectal obstruction, use of manual maneuvers to facilitate elimination, and having less than three bowel movements per week. Chronic constipation occurs in more than half of Parkinson's disease (PD) patients due to slow transit through the colon combined with dyssynergic defecation, which is discussed in more detail below. As seen in the above case, constipation may predate the onset of the motor symptoms of the disease by many years. The mechanisms underlying the slowed transit through the colon in PD are unknown. While constipation is a common adverse effect of many PD medications such as anticholinergics and dopamine agonists, it often occurs independent of these drugs. Recent research has focused on the presence of alpha-synuclein histopathology in the enteric nervous system (ENS) of PD patients; however, the presence of this alpha-synuclein histopathology is now known to be equally prevalent in the ENS of PD patients and controls. Furthermore, its presence has never been correlated with gastrointestinal symptoms in PD. Reduced bowel sounds

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may be found on exam, a finding thought to reflect the underlying hypomotility. No additional workup is needed in patients who are up to date on age-appropriate health screening including colonoscopy, provided that there are no red flags in the history such as weight loss, bloody stool, anemia, pencil thin stools, or severe abdominal pain.

In addition to having a negative impact on quality of life, severe constipation can be associated with serious and even life-threatening complications such as megacolon, intestinal pseudo-obstruction, and even bowel perforation in rare cases. Chronic constipation may also negatively impact PD medication absorption. For example, there have been case reports of chronic constipation and intestinal pseudo-obstruction triggering parkinsonism hyperpyrexia syndrome, which is a neuroleptic malignant-like syndrome that occurs in the context of levodopa withdrawal in PD. It is therefore important for providers to screen patients for constipation and treat it effectively.

Unfortunately, there is a dearth of level I evidence to guide the management of constipation in PD. Most experts advise that treatment should always begin with a conservative, non-pharmacological approach. Careful scrutiny of the medication list to identify and eliminate medications that may be contributing to the problem is essential. Counseling patients on the recommended daily allowances for fiber and water is also helpful since many adults often do not meet these recommendations. Men under 51 years of age should consume 38 g/day of fiber, while those older than 51 should consume 30 g/day. Women younger than 51 years old require 25 g/day of fiber, while women over 51 need 21 g/day. Both men and women should drink at least two liters of water daily, and active individuals may require more. Increasing daily physical activity levels is also helpful.

If additional pharmacotherapy is required, psyllium, alone or in combination with a stool softener such as docusate sodium, is a safe and effective initial regimen for daily use. If more aggressive therapy is required, polyethylene glycol is an osmotic laxative that is safe and effective in PD patients. It can be used daily or on an as needed basis. Lubiprostone, a chloride channel activator, has also been found to be safe and effective for the short-term treatment of constipation in PD. However, it may not be well-tolerated in individuals with comorbid gastroparesis due to its tendency to cause nausea as a side effect. Table 13.1 summarizes the pharmacological treatment options for constipation in PD that are supported by level I evidence, including mechanisms of action, doses, and side effects. For patients who have constipation that is refractory to the above measures, referral to gastroenterology is strongly advised to rule out other causes of chronic constipation and to seek expert advice on management.

In addition to slow transit through the colon, some patients may also have dyssynergic defecation, which is experienced as excessive straining, pain, or a feeling of incomplete evacuation during defecation. Defecation is a complex process that requires coordinated action of multiple muscle groups. Muscles that maintain fecal continence must relax, while those that increase intra-abdominal pressure must contract. Multiple abnormalities in this complex process have been described in PD patients, including paradoxical contraction of the puborectalis muscle and external anal sphincter during defecation. While dyssynergic defecation can be formally evaluated and diagnosed using defecography and/or anorectal manometry, these tests are rarely used in clinical practice. Unfortunately, no treatments for dyssynergic defecation have been rigorously studied in PD; however, it has been reported to improve after subcutaneous injection with apomorphine, ultrasound-guided botulinum toxin injections into the affected musculature, and biofeedback techniques.

Table 13.1 Pharmacological treatment of constipation in PD

Medication	Class	Dose	Side effects/cautions	Evidence
Psyllium	Bulk forming laxative	5.1 g 2×/day	Gastrointestinal obstruction if not taken with adequate liquid; avoid in gastroparesis	Randomized single-blind trial (7 patients)
Polyethylene glycol	Osmotic laxative	Up to 17 g daily	Electrolyte abnormalities with chronic use; caution in those with underlying cardiac and renal dysfunction	Randomized double-blind controlled trial (57 patients)
Lubiprostone	Chloride channel activator	24 μg 2×/day	Nausea, allergic reactions, hypotension	Randomized controlled trial (54 patients)

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Treatment of Urinary and Sexual Dysfunction in Parkinson's Disease

14

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Case

This patient is a 72-year-old man with Parkinson's disease (PD) diagnosed 3 years earlier who complains of daily urinary urgency with urinary incontinence several times per week, nocturia twice nightly, and erectile dysfunction. His past medical history includes depression, hypertension, hypercholesterolemia, benign prostatic enlargement (BPE), and constipation. Current medications include carbidopa/levodopa 25/100 mg two tablets three times daily, lisinopril 20 mg daily, atorvastatin 10 mg daily, escitalopram 10 mg daily, and polyethylene glycol as needed for constipation.

On exam, his Hoehn and Yahr stage is 2, and he has normal gait speed with decreased arm swing on the right. His Mini-Cog is normal with 2 out of 3 recall and a normal clock draw test. Blood pressure is 115/68 while sitting. On rectal exam he has an enlarged prostate without tenderness to palpation or nodules. He is able to perform an isolated pelvic floor muscle contraction without abdominal muscle recruitment on exam. A post-void residual assessment immediately after voiding by bladder ultrasound reveals 55 mL of urine in the bladder. His goals for treatment include improved symptoms without adding multiple medications.

Discussion

Up to two-thirds of persons with PD report bothersome urinary symptoms. The symptoms that comprise overactive bladder syndrome, such as urinary urgency (sudden need to void that is difficult to defer), nocturia (getting up at night from sleep to void), daytime frequency (voiding more than 8 times during the day), and urgency urinary incontinence, are most common. Urinary symptoms in PD may be due to dopaminergic alterations leading to decreased inhibition of the pontine micturition center and resulting detrusor (bladder muscle) hyperactivity. Alpha-synuclein pathology could also lead to decreased cortical integration of sensory afferent signals related to bladder fullness. Because PD is more common among older adults, many persons will have multiple chronic conditions, which could impact urinary symptoms, such as constipation, sleep disorders, and BPE in men. Thus, the treatment approach for urinary symptoms is usually multicomponent.

Quality indicators for PD care recommend at least an annual assessment of autonomic symptoms. "Are you having any trouble with your bladder?" is an appropriate screening question. If urinary symptoms are present, additional questions about urinary frequency, incomplete emptying, nocturia, and associated symptoms of incontinence are helpful to determine next steps in the assessment and an initial management strategy. Querying about the timing and type of fluid intake may provide clues to associated factors and potential areas for lifestyle modification. A voiding diary, including fluid intake (type and amount), is a valuable tool in guiding lifestyle and behavioral strategies. Patients and caregivers may benefit from this self-monitoring tool as they gain insight regarding factors contributing to UI, constipation, and nocturia.

In the setting of new urinary symptoms, a urinalysis should be considered to assess for infection or abnormal cells such as microscopic hematuria (defined as more than five red blood cells/high powered field on two consecutive urinalyses without evidence of infection). If a urine culture is obtained, clinicians should consider that asymptomatic bacteriuria occurs in up to 20% of older women and 15% of older men. Diagnosis of a urinary tract infection requires new symptoms such as urgency, dysuria, or suprapubic pain and culture of one bacterial species in a quantitative count of at least 10^5 CFU/mL in women and 10^3 CFU/mL in men.

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Serum prostate-specific antigen (PSA) is not routinely recommended in the assessment of men with lower urinary tract symptoms. In 2018, the PSA received a D recommendation (harms outweigh benefits) from the United States Preventive Services Task Force (USPSTF) for men age 70 years and older. Both the American Urological Association and the USPSTF recommend shared decision-making among men who are at average risk between the ages of 55–69 years old in order to determine a man's values and preferences for PSA testing.

A focused physical exam serves to direct therapeutic decision-making. Assessment of cognitive function and mobility are important as those with significant impairment in either domain often benefit from interventions that involve a caregiver. Suprapubic fullness, dullness to percussion, or palpation causing leakage or a strong urge to void suggests a need for further evaluation of an elevated bladder post-void residual (PVR). During the pelvic exam, it is important to assess skin integrity, which can be compromised with chronic wetness, and to determine if atrophic vaginitis is present in women. The rectal exam is essential to assess for stool impaction and to evaluate prostate size in men. The pelvic and rectal exams also provide an opportunity to teach pelvic floor muscle exercises, if needed. Lower extremity edema may contribute to nighttime urinary symptoms as dependent, interstitial fluid is recirculated during recumbency, resulting in atrial natriuretic peptide release and solute diuresis. Lower extremity edema can be a side effect of some medications frequently used in the setting of PD including dopamine agonists and amantadine or mineralocorticoids used for orthostatic hypotension.

Among patients who have symptoms suggestive of urinary retention, it is important to determine if residual urine is present immediately post-void by bladder ultrasound. While there is no evidence to suggest a specific cut point defining an elevated PVR, greater than 300 mL should prompt the provider to order a serum creatinine to evaluate for renal impairment. Persistent elevation in PVR > 200 mL may require clean intermittent self-catheterization.

After a focused history and physical exam, careful medication review, and goal setting with the patient and caregiver, practitioners have access to a wide range of treatment options for urinary symptoms. Lifestyle and behavioral strategies are side effect-free and should be the initial management direction. With regard to fluid management, it is important to maintain an intake of 6–8 oz. glasses of fluid daily in order to prevent concentrated urine, which is irritating to the bladder, and to promote regularity of bowel movements. Avoiding fluids within 2–3 h of bedtime may be reasonable among those who complain of nocturia. Choosing fluids with less potential to irritate the bladder (such as decaffeinated beverages) may be beneficial.

Preliminary evidence suggests pelvic floor muscle exercise-based behavioral therapy is effective in persons with PD and incontinence. For urgency-related symptoms, patients are taught an urge suppression strategy in which they use rapid pelvic floor muscle contraction as part of an adaptive strategy to suppress urgency and prevent UI when the urge to void suddenly strikes. During the urge suppression strategy, patients are taught to selectively and rapidly contract and relax the muscles of the pelvic floor (levator ani), which leads to bladder relaxation. Practicing pelvic floor muscle exercises allows patients to strengthen their muscles and to master the motor skill. Typical recommendations for a home pelvic floor muscle exercise regimen are to perform 45 pelvic floor muscle exercises daily divided into 3 sets of 15 contractions/relaxations. For patients with significant cognitive impairment, prompted voiding is a caregiver-based strategy in which the patient is encouraged to go to the bathroom to void at regular intervals. Importantly, it is more effective to merely suggest that it is time to void and encourage the care recipient to attempt voiding rather than ask if the care recipient feels the need to void. Some patients or caregivers may prefer containment strategies with absorptive undergarments, but these should not be the initial response to the presence of incontinence. External collection devices may also be considered in men, but they do pose some increased risk of urinary tract infections, although less than indwelling catheters. Use of a barrier cream and treatment of fungal infections, if they occur, should also be discussed. In women who have atrophic vaginitis, low-dose topical estrogen reduces urgency, frequency, and incontinence. Among women who have a contraindication to topical estrogen, personal lubricants may be an alternative to reduce skin irritation.

Drug therapy for urinary problems should be considered for persistent symptoms after a trial of lifestyle and behavioral therapy (Table 14.1). Antimuscarinic bladder relaxants reduce the action of acetylcholine to influence detrusor muscle contraction by competitively binding muscarinic receptors; however, they also may reduce afferent sensory signaling from bladder C-fibers and Aδ-fibers. Because antimuscarinic agents vary in their affinity for the bladder muscarinic receptor subtypes and in lipophilicity, which impacts their likelihood to cross the blood brain barrier, there is additional concern about the potential for cognitive adverse effects. While further studies regarding effects on cognition are needed, all antimuscarinic drugs are associated with the side effects of dry mouth and constipation. Beta-3 receptor agonists are another medication class that lead to bladder smooth muscle relaxation. Currently, there is one FDA-approved medication in this class, mirabegron. Beta-3-agonists avoid the anticholinergic side effects associated with antimuscarinic bladder relaxants. Mirabegron is not recommended in persons with uncontrolled hypertension or

Table 14.1 Drugs commonly used in the USA to treat urinary incontinence

Drugs	Dosages	Mechanisms of action	Type of incontinence	Potential adverse effects
Bladder relaxants	In general, reduced dosages for renal and hepatic impairment	Increase bladder capacity, diminish involuntary bladder contractions	Urgency or mixed with urgency predominant	
Darifenacin (Enablex)	7.5–15 mg qd			Anticholinergic, lower dose if reduced hepatic function
Fesoterodine (Toviaz)	4–8 mg qd			Anticholinergic
Mirabegron (Myrbetriq)	25–50 mg qd			Beta-3-agonist, max 25 mg/day with CrCl 15–20, reduced hepatic function (hypertension, tachycardia)
Oxybutynin (Ditropan, immediate release, available as generic)	2.5–5.0 mg tid			Anticholinergic (dry mouth, blurry vision, elevated intraocular pressure, delirium, constipation)
Oxybutynin (extended release) (Ditropan XL)	5–30 mg qd (most often 10 mg qd)			Above, but with less dry mouth
Patch (Oxytrol)	3.9 mg qd	Patch applied twice weekly		Above, but with less dry mouth, available over the counter
Oxybutynin gel (Gelnique)	3% pump or 10% gel packet	One application daily		Above, but with less dry mouth
Solifenacin (Vesicare)	5–10 mg qd			Anticholinergic, lower for severe renal impairment or reduced hepatic function
Tolterodine (Detrol)	1–2 mg bid			Anticholinergic, lower dose for severe renal impairment or reduced hepatic function
Tolterodine (Detrol LA)	4 mg qd			Above, but with less dry mouth
Trospium chloride (Sanctura)	20 mg bid			Anticholinergic, 20 mg once daily qhs with CrCl <30 or in patients >75 yo
Trospium chloride (Sanctura XR)	60 mg qam			Avoid in severe renal impairment or reduced hepatic function
Vaginal estrogen				
Topical	0.5–1.0 g per application	Strengthen periurethral tissues	Urge associated with atrophic vaginitis	
Vaginal ring (Estring) (estradiol acetate)	One ring every 3 months			
Alpha adrenergic antagonist				
Doxazosin (available as generic, or Cardura)	1–8 mg qhs (higher dose typically necessary for urinary symptoms associated with prostatic enlargement)	Relax smooth muscle of urethra and prostatic capsule	Urge incontinence associated with prostatic enlargement	Postural hypotension, dizziness, lowers blood pressure
Terazosin (available as generic, or Hytrin)	1–20 mg qhs (at least 10 mg dose typically necessary for urinary symptoms associated with prostatic enlargement)			Same as above
Prazosin (Minipress)	1–2 mg bid			Same as above
Alfuzosin (Uroxatral)	10 mg qhs			Less effects on blood pressure

(continued)

Table 14.1 (continued)

Drugs	Dosages	Mechanisms of action	Type of incontinence	Potential adverse effects
Silodosin (Rapaflo)	8 mg qd			Less effects on blood pressure, CrCl 30–50 use 4 mg qd
Tamsulosin (Flomax)	0.4–0.8 mg qd			Less effects on blood pressure (when used at 0.8 mg dose, greater blood pressure effects)
Phosphodiesterase inhibitor			Urge incontinence associated with prostatic enlargement with or without erectile dysfunction	
Tadalafil	5 mg daily	Inhibits PDE type 5, enhancing effects of nitric oxide-activated increases in cGMP		Orthostatic hypotension, flushing, headache (contraindicated with terazosin/doxazosin/prazosin)
Other phosphodiesterase inhibitors given daily may be effective				
5-alpha reductase inhibitor		Inhibits type II 5-alpha-reductase, interfering with conversion of testosterone to 5-alpha-dihydrotestosterone	Prostate enlargement on exam or PSA > 1.5 ng/mL	
Finasteride	5 mg daily			Sexual dysfunction, gynecomastia, decreased overall risk of prostate cancer with increased risk of high-grade prostate cancer
Dutasteride	0.5 mg daily	Inhibits type I and II 5-alpha-reductase, inhibiting conversion of testosterone to dihydrotestosterone		Sexual dysfunction, decreased overall risk of prostate cancer with increased risk of high-grade prostate cancer

Adapted from Talebreza S, editor. Geriatrics evaluation and management tools: lower urinary tract symptoms in men and urinary incontinence, New York: American Geriatrics Society; 2015 with permission from the American Geriatrics Society

in those with significant arrhythmias. In the setting of persons with PD and orthostatic hypotension, the potential to increase blood pressure could be favorable.

In men who have concomitant benign prostatic enlargement (BPE), alpha-blockers may be useful as first-line therapy or in combination with bladder relaxant therapy. Even with selective alpha-1-adrenergic receptor antagonists (e.g., tamsulosin, silodosin), significant orthostasis can still occur in up to 1 in 12 men without neurologic disease. If the patient's blood pressure is low normal (< 110/70) and the patient is already taking antihypertensive therapy, as in the case presented, it is reasonable to hold antihypertensive therapy during the initiation of even a prostate-selective alpha-antagonist. 5α-Reductase inhibitors can be considered in men with an enlarged prostate on exam or a PSA > 1.5 ng/mL to reduce the incidence of surgical treatment for lower urinary tract symptoms associated with BPE and emergent treatment for acute urinary retention. Daily type 5 phosphodiesterase inhibitors (PDE5i) such as tadalafil are another option for men with BPE-related lower urinary tract symptoms who are not candidates for alpha-blocker therapy or as add-on therapy to selective alpha-blockers. PDE5i's may be associated with increased risk of hypotension, however, could be useful in men with concomitant erectile dysfunction.

When lifestyle, behavioral, and drug therapies have not adequately addressed the patient's goals of care, there are surgical and device options to consider. It is unclear exactly how neuromodulation affects urgency urinary symptoms, but it is hypothesized that stimulation of afferent fibers from the bladder leads to central inhibition of bladder motor neurons, resulting in less detrusor hyperactivity. Percutaneous tibial nerve stimulation is minimally invasive and requires weekly visits to the clinic for up to 12 weeks, which could be burdensome. Sacral neuromodulation with an implanted stimulator device is another option, although long-term response in the setting of a neurodegenerative disease is largely unknown.

Cystoscopic injection of *botulinum* toxin for urgency UI secondary to overactive bladder received approval in the USA with a recommended total intravesical dosage of 200 units. Urinary retention requiring intermittent catheterization for up to 3 months could occur and is more likely if an elevated PVR is present prior to the injection. Repeat injections are typically required every 6–12 months. Prostate reduction procedures should be consider in men with persistent symptoms because of the availability of newer, less invasive procedures for reducing prostate size. Evidence suggests that preoperative urodynamic assessment to confirm bladder outlet obstruction and consultation with a neurologist specializing in movement disorders to confirm the diagnosis of PD improves the potential for successful outcomes after transurethral resection of the prostate.

Similar to the treatment approach for urinary symptoms, a multicomponent approach should be considered to address erectile dysfunction. Careful medication review for drugs that may impact sexual function such as antidepressants and antihypertensive medications may reveal opportunities for alternative therapies without sexual side effects. In the presence of decreased libido, exploring options for optimizing situational factors to promote intimacy and timing during "on" periods with regard to PD symptoms in order to enhance sexual function is important. Referral to a sex therapist for the person with PD and their partner may be helpful. Limited evidence suggests PDE5i are effective for erectile dysfunction in men with PD and no significant cardiovascular disease. PDE5i should be used with caution in men with a history of orthostatic hypotension. Men using a PDE5i should be counseled about the timing of sexual activity as relates to onset and duration of action of these drugs.

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Treatment of Drenching Sweats in Parkinson's Disease

15

Stewart A. Factor

Case 1

This patient is a 79-year-old man who was diagnosed with Parkinson's disease (PD) 3 years earlier. Problems include mild cognitive impairment, tremor of the left hand present nearly all the time, micrographia, nocturnal calf and thigh cramps, urinary frequency causing fragmented sleep, rhinorrhea, and obstructive sleep apnea using CPAP. He has difficulty getting up from a chair but no freezing or falling. He is independent on activities of daily living, but buttons are challenging. He still works part time in real estate. He has no motor fluctuations or dyskinesia. A main complaint during a visit at the end of February in Atlanta was drenching sweats. These would occur primarily at night and force him to change his pajamas. They lasted up to 20 min but were regular in occurrence and troublesome. However, by the end of June, these episodes spontaneously stopped.

Case 2

This patient is a 50-year-old man with PD diagnosed at age 44. Initial features were primarily akinesia and rigidity although a prominent jaw tremor developed in his second year of disease; tremor did not occur elsewhere. He was treated with carbidopa/levodopa after 1 year of symptoms and was remarkably responsive. Six months after initiating levodopa, he developed end-of-dose wearing off and 6 months after that, dyskinesia. He experienced no problems with gait and balance. The "off" times were treated with the addition of entacapone and selegiline. His fluctuations and dyskinesia were reasonably controlled with this regimen where he had <25% of his time "off" and 25% with mild dyskinesia.

Although he never sweated much, in the last 6 months, he started experiencing drenching sweats that first occurred in springtime with mild exertion. More recently it was apparent that the sweating was occurring during "off" times.

Discussion

Autonomic dysfunction is well known to occur in PD, impacting perhaps 50% of patients. The most common symptoms relate to urinary or bowel changes or orthostatic hypotension, and these are covered in other chapters. Excessive sweating is another troublesome autonomic feature that relates to abnormal reflex vasodilation in the skin. Studies examining vascular tone in PD patients and autonomic dysfunction have demonstrated that vasodilatation predicted the occurrence of either sweating or anhidrosis. This is reflected in the poor temperature tolerance that occurs in PD where they complain of being cold when ambient temperature is warm and vice versa. Altered sweating appears to occur in two forms that related to dopaminergic innervation and the other being non-dopaminergic. It is important to determine the temporal pattern of sweating and relationship to timing of levodopa to differentiate the two. Since sweat glands are stimulated by sympathetic cholinergic, adrenergic, and noradrenergic pathways, these represent the major non-dopaminergic types.

Overall, 10–30% of PD patients experience hyperhidrosis. Some studies suggest it is more common in younger women with PD. Some patients will be experiencing anhidrosis when sudden episodes of hyperhidrosis occur. The presence of drenching sweats tends to correlate with severity of PD. The dopaminergic type of hyperhidrosis is illustrated in case 2 where sweating occurs in the off state. The non-dopaminergic type (case 1) is more frequently nocturnal and, although autonomic in nature, may not correlate with other autonomic symptoms. It relates mostly to diminished cholinergic innervation and

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decreased activation of the sudomotor skin reflex response of the sweat glands and, mostly in the limbs, particularly hands and feet. In both cases this syndrome is characterized more by sweating on the face, head, and trunk. The axial features are thought by some to be a compensatory phenomenon for reduced sympathetic function in the extremities.

Treatment options are limited. In some patients hyperhidrosis is a mere annoyance, and in that case just education and reassurance is all that is needed. If they have the non-dopaminergic type, this may not be continuous and can run its course as seen in case 1. It appears to me that this occurs during the times of year when environmental temperatures vary more, like in the spring and fall. Once summer or winter occur, the sweating usually decreases or stops altogether as in case 1. But if the hyperhidrosis is distressing, then medical therapy may be needed. For the dopaminergic type that occurs during off times, treatment of the end-of-dose wearing off is the best strategy. This includes long-acting formulations of dopamine agonists or levodopa at night. See chapter "Medical Therapy for Fluctuations in Parkinson's Disease" for treatment of fluctuations. For the non-dopaminergic type, the logical choice is an anticholinergic agent such as trihexyphenidyl or benztropine. While these can be well tolerated by younger patients, they are problematic for the elderly because of memory loss and hallucinations. Other problems include dry mouth, dry eyes, constipation, and urinary frequency, urgency, and incontinence. Some authors have suggested oxybutynin or tolterodine because of presumed fewer CNS side effects. I have recommended amantadine in some of my older patients with hyperhidrosis which is better tolerated. It has anticholinergic effects but to a lesser extent than other anticholinergics. In those patients with underlying anhidrosis with episodic hyperhidrosis, anticholinergics may not be the best choice. Since noradrenergic innervation changes may also play a role in hyperhidrosis, trying serotonin and norepinephrine reuptake inhibitors (SNRIs) may be beneficial. Some have also suggested β-adrenergic blockers. There is no evidence for any of these agents in the treatment of drenching sweats. For less frequent focal hyperhidrosis, topical agents such as aluminum chloride hexahydrate (10–12% axilla, 20% palmar-plantar, 10% craniofacial) or Glycopyrrolate (0.5–4% topical preparations) have been recommended. Localized botulinum toxin injections may also help. Because of the episodic and generalized nature of the drenching sweats, I have not had the occasion where I felt a need to utilize these options.

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Treatment of Drooling in Parkinson's Disease

16

Stephen Grill

Case

The patient presented at age 54 with an 8-year history of Parkinson's disease (PD). She had a difficult time tolerating levodopa in the past due to nausea and underwent a right pallidotomy 2 years previously. She was on ropinirole (20 mg/day) which inadequately treated her PD. At the time of the visit, she had moderate drooling during the daytime. She underwent deep brain stimulation (DBS) surgery placing a left subthalamic nucleus lead at age 57 because of severe rigidity and bradykinesia. The drooling was not helped by DBS.

The drooling gradually worsened to the point that it was constant, and she required the use of a towel to keep saliva from getting on her clothes. This was bothersome and embarrassing to her to the point that she would not go out in public. She also developed dysphagia in part because she was not able to control her saliva. She was treated initially with atropine sulfate 1% solution (an ophthalmic preparation) placing one drop under her tongue as needed several times during the day. This was not very effective and she did not like the taste of the drops. Subsequently, she underwent botulinum toxin injections targeting the parotid and submandibular glands, using rimabotulinumtoxinB. This produced dramatic improvement which she judged as a 70% reduction in her drooling. She no longer required a towel to control the saliva flow and was more comfortable going out in public. She undergoes these treatments about every 3 months.

Discussion

Normal salivation produces up to 1.5 l per day and is important in providing lubrication of the oropharynx, having antibacterial effects, enhancing the taste of foods, and in beginning the breakdown of sugars and fats. Of the three major salivary glands, the submandibular is responsible for the basal rate of salivary flow, while the parotid glands respond to stimulation by increasing the salivary flow up to 20 times. The sublingual glands are the smallest of the three major glands.

Sialorrhea is a condition of increased salivary flow that is associated with a number of conditions such as inflammation of the mouth and can also be medication-induced (e.g., clozapine). Drooling, on the other hand, is when saliva flows out of the mouth. People with sialorrhea do not necessarily drool if they are able to swallow the saliva in time. Problems with saliva control in persons with PD (and other parkinsonian syndromes such as progressive supranuclear palsy, dementia with Lewy bodies, cortico-basal syndrome, and multiple system atrophy) are common occurring in up to 70% of patients.

Drooling in PD is considered a non-motor symptom. Patients with PD do not actually have increased production of saliva, and in fact saliva production is thought to be reduced or normal although the excretion speed may be increased. Instead, the problem stems from not swallowing saliva appropriately. This could be due to oropharyngeal bradykinesia, dysphagia, or to simply "not remembering to swallow." Drooling is worse in PD patients when they are in an "off" state. Some studies indicate a correlation between dysphagia and drooling. The stooped posture, neck flexion, and unintended mouth opening as part of hypomimia may also contribute to the inability to keep the saliva from spilling out. Xerostomia (dry mouth) on the other hand occurs in about 50% of PD patients and may occur even in patients with drooling.

The degree to which a patient's life is affected by drooling depends largely on its severity. Drooling is most often a

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social embarrassment and inconvenience. However, the embarrassment can lead to reduction in social activities and even social isolation as in this patient. It may also increase demands on the caregiver, and caregiving partners may also experience the social embarrassment. Drooling can have more serious medical consequences including an increased risk for aspiration pneumonia as well as negative effects on oral hygiene. Patients with PD who drool appear to have a worse quality of life in specific domains with increased difficulty speaking, eating, and in social interactions. In my experience, most PD patients do endorse that they experience some excessive drooling, but it is only patients with severely increased drooling who are very troubled and desire treatment.

A stepped approach to the treatment of drooling is recommended. This includes conservative measures, pharmacologic agents, and injections of the salivary glands with botulinum toxin. The first step should be to review the patient's medications for ones that may exacerbate drooling such as cholinesterase inhibitors and clozapine (may be seen in up to 30% of patients) and to use alternatives if possible. Since drooling is worse in the "off" state, efforts should be made to reduce the amount of time the patient is in the off state with levodopa and other dopaminergic drugs. Agents such as anticholinergics, including trihexyphenidyl, benztropine, and amantadine, which may be used to treat motor symptoms cause dry mouth and hence may be useful. Encouraging patients to consciously swallow more frequently is rarely helpful. Many patients seem to benefit from sugarless candy or chewing sugarless gum, and this is easy to try. The use of auditory cues at regular intervals to remind patients to swallow may reduce drooling, but the effects diminish with time, and it requires great self-motivation. On the other hand, an explanation of the problem and that drooling may improve with more frequent swallowing should be done so patients can at least make that effort.

Pharmacologic agents can be effective for treating drooling. The salivary glands are innervated by cholinergic receptors, particularly of subtype M3, and therefore blocking cholinergic receptors with anticholinergic agents can be helpful. Unfortunately, there are frequent side effects with oral anticholinergic agents including confusion, hallucinations, urinary retention, drowsiness, blurred vision, and constipation. Since those symptoms are frequent in patients with PD anyway, oral anticholinergic agents such as glycopyrrolate are generally not well tolerated.

Sublingual atropine drops (a 1% ophthalmic solution) may be effective in treating drooling and have better tolerability than traditional anticholinergics, although adverse events of delirium and hallucinations have been reported. In my practice, when there is a need to treat drooling, this is generally the first choice because of its ease of use, effectiveness, relatively good side effect profile, and low cost. Frequently, however, patients do not like the taste, as in the case above, and that can limit its use. Patients are instructed to place one drop of the solution under the tongue 3–4 times per day and to refrain from swallowing it, so that it can work locally on the submandibular glands, which are more responsible for the basal rate of secretion compared to the parotid glands. If one drop is ineffective, patients may try two drops. Patients are cautioned against using it to the point of drying out the mouth as that can increase the risk of carries and gum disease. Patients may need a caregiver to accurately deliver the drops for them to avoid overdosage.

If sublingual atropine drops are not effective or tolerated, the next step is to consider injection of botulinum toxin targeting the parotid and submandibular glands. The main advantage of this treatment is that the toxin is delivered directly to each gland, and so there are relatively few systemic side effects. The most common adverse event is dry mouth but that can usually be avoided by starting low and using the minimum effective dose. Off-label use of both botulinum toxin types A and B are effective in treating drooling in Parkinsonian syndromes. I use mostly botulinum toxin B (rimabotulinumtoxinB) starting with 250–500 units to each submandibular gland and 1000 units to each parotid gland using anatomical landmarks to target the glands (see Fig. 16.1). Effective starting doses when using onabotulinumtoxinA or incobotuolinumtoxinA are 15–20 units per each parotid gland and 5 units to each submandibular gland. When using abobotulinumtoxinA, initial effective doses are 50–100 units to each parotid and 25–50 units to each submandibular gland. These injections are done at approximately 3 month intervals in most patients. Although there are reports of better targeting of the glands using ultrasound guidance, I do not consider it necessary. Currently, use of botulinum toxin injections may be limited due to insurance coverage; incobotulinum toxin A is recently approved by the FDA for this indication (Fig. 16.1a, b).

Surgical resection of the salivary glands may be performed in extreme cases where patients have severe dysphagia and are unable to control their saliva to the point of having recurrent aspiration pneumonia. Such patients are generally receiving their nutrition through a feeding tube. I have successfully managed only one patient with this option.

The extent to which drooling diminishes quality of life of an individual and whether there is a risk for aspiration pneumonia determines whether treatment is indicated and how aggressive the treatment should be. Drooling in PD should not be ignored since many patients are distressed about it, it

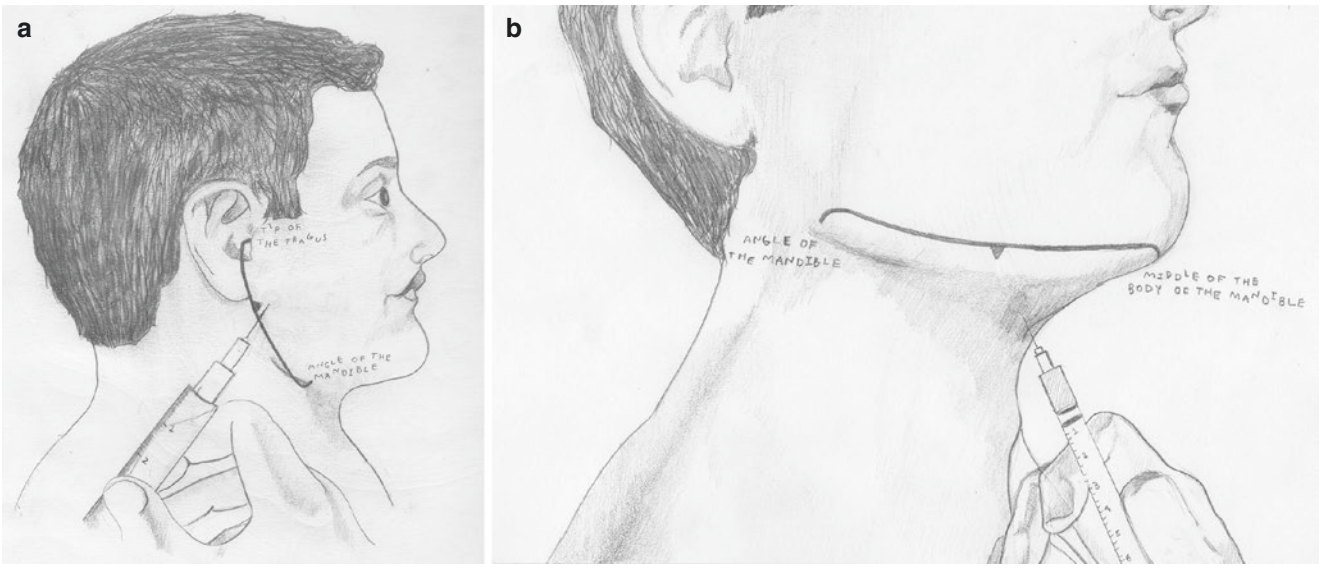

Fig. 16.1 (**a**) Injection of parotid gland. The injection site is at the midline between the tip of the tragus and the angle of the mandible to a depth of about 1 cm. (**b**) Injection of submandibular gland. The injection site is about 1 cm medial to the midline between the angle of the mandible and the middle of the body of the mandible, to a depth of about 1 cm (drawings by Gabriella Grill)

may lead to medical complications, and there are simple and effective treatments.

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Treatment of Pain in Parkinson's Disease

17

Vicki L. Shanker

Case

The patient is a 66-year-old man who was diagnosed with Parkinson's disease (PD) when he was 58 years old. He has a history of prostate cancer, hypertension, coronary artery disease, depression, and anxiety. He presented to the office after 6 weeks of severe (10/10) right foot and calf pain. The pain was muscular and did not have a neuropathic quality (i.e., electrical, burning, tingling). The pain was present all day, for most days of the week, and he did not notice any relationship between the pain and the timing of his medications or whether he was "on" or "off". It worsened with walking, and as a result, he had significantly decreased his physical activity. He had not noticed erythema or swelling of the foot. He denied any trauma to his back, leg, or foot.

He previously saw a podiatrist who prescribed meloxicam and gave him a steroid injection without benefit. He subsequently saw an orthopedist whose examination documented tenderness at the right posterior tibial tendon; X-rays showed ankle osteoarthritis, and he was referred to an orthopedist specializing in foot and ankle problems.

His PD history was pertinent for initiating levodopa therapy 3 years after symptom onset. He did not tolerate trials of various dopamine agonists or amantadine. A trial of Rytary increased dyskinesias. His disease course was notable for the development of dyskinesias and increasing "off" time. His medications included 1300 mg of levodopa in divided doses, entacapone, and rasagiline.

The first neurological examination after the onset of foot pain was during a planned visit to assess the patient "off" and "on" medication in consideration for deep brain stimulation. During the "off" examination, there was significant, painful dystonic toe extension and limited range of motion of the right foot (Fig. 17.1). There was right-sided rigidity and bradykinesia. He needed assistance to stand, had a shuffling gait requiring a walker, and postural instability. After receiving levodopa, all symptoms improved including the foot pain and dystonia; he had dyskinesias on the right side, was able to stand independently, did not require a walker, and his pull test was negative.

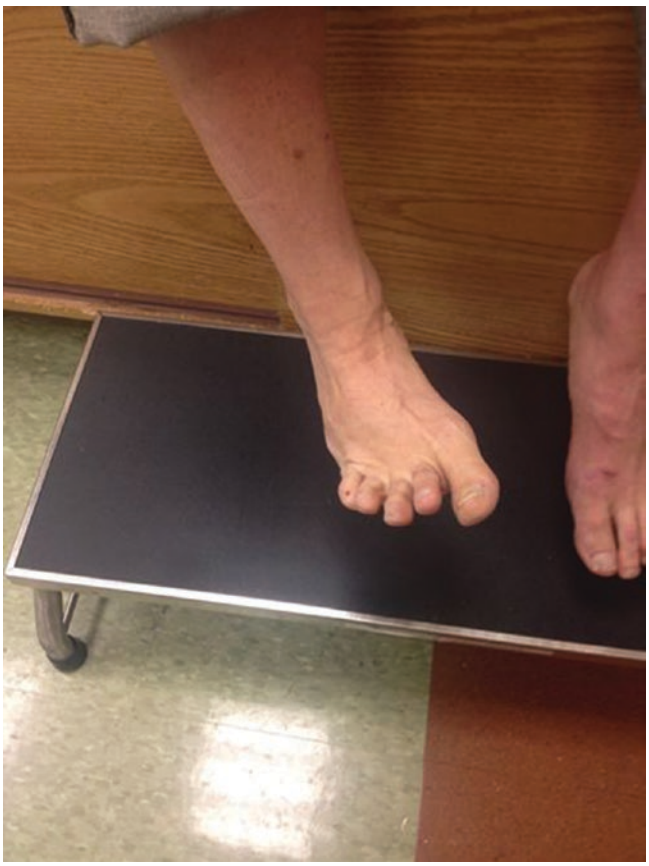

Fig. 17.1 This demonstrates the patient's painful off-period foot dystonia with extension of the toes

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Discussion

Although the traditional motor symptoms and signs of PD are well-recognized, equally common and disabling are a wide variety of non-motor features including psychiatric symptoms, autonomic disturbances, gastrointestinal difficulties, cognitive impairments, and sleep disorders.

Pain is also a common but often under-recognized non-motor complaint in PD. Studies have demonstrated that up to 2/3 of people with PD have pain; the lower limbs are the most common location, and musculoskeletal pain is the most frequent pain quality. This is followed by dystonic, radicular, and central neuropathic pain.

Musculoskeletal pain may be characterized as joint pain, muscle cramping, or muscle tightness. The shoulder is a common site of musculoskeletal pain. When affected, it is referred to as "frozen shoulder," periarthritis, or adhesive capsulitis. Patients with "frozen shoulder" experience an acute onset of pain followed by progressive restriction of range of motion in the joint. The majority of patients experience this symptom within the 2 years prior to the onset of PD motor symptoms or simultaneously with motor onset, and a frozen shoulder may be the first manifestation of PD. Pain ultimately dissipates, and the shoulder has limited range of motion. Hips, knees, and ankles are also common sites for joint pain. The neck, arms, paraspinal, and calf muscles are common locations of muscle pain.

Musculoskeletal pain is often associated with the rigidity seen in Parkinson's disease. When patients have significant rigidity on exam, increasing current medication or adding a second Parkinson's disease medication should be considered. Physical therapy and/or exercise may also improve symptoms and are usually incorporated into the treatment plan. Pre- or comorbid rheumatologic and orthopedic disease can contribute to pain. The use of nonsteroid anti-inflammatory drugs (NSAIDs), acetaminophen, and mild opioids (i.e., tramadol) are treatment options when these comorbid conditions are present.

Dystonic pain results from the involuntary patterned muscle contractions which cause posturing or tremor in the affected area(s). Dystonia may be an initial presentation of Parkinson's disease, especially in patients with young onset PD ($\leq$50 years old). The feet are a common area of involvement; the back and shoulders may also be affected. In undiagnosed patients, these symptoms often lead to evaluation by specialists such as podiatrists and orthopedists. PD patients often report dystonic pain during "off" periods, when medication is not adequately treating symptoms. Common "off" times are early morning and end of dose. Dystonia can also manifest during peak medication dosing.

Because treatment is different for "on" time and "off" time painful dystonia, it is important to carefully document onset of dystonic symptoms in relation to time of day and time of each medication dose. When patients are unsure regarding the relationship of medication and symptoms, they should be encouraged to keep calendars of their symptoms or to come into the office where they can be observed during "on" and "off" periods. In our case, the patient was asked to withhold his morning dose and was allowed to take it after observation of the "off" state. When painful dystonia is an "off" phenomenon, treatment should focus on strategies to increase "on" time. This may include increased frequency of levodopa or using extended release levodopa capsules, adding an *MAO-B* inhibitor, dopamine agonist, or entacapone. The fast-acting injectable dopamine agonist apomorphine can be used as well. When painful dystonia occurs during "on" periods, levodopa reduction is attempted but often challenging as lowering doses may worsen parkinsonism. Amantadine can be tried as it has antidyskinetic properties. Although there are no *FDA*-approved oral drugs for dystonia, baclofen, benzodiazepines, and anticholinergic medications are reported to successfully treat some cases of both "on" and "off" dystonia. When medication therapy fails, botulinum toxin injection, under guidance from electromyography and/or ultrasound, is a very good option for painful, focal limb dystonia. Surgical interventions, including duodenal continuous infusion of levodopa and deep brain stimulation of the subthalamic nucleus or globus pallidus, also improve "off" dystonia.

Radicular and neuropathic pain is often described as burning, tingling, electrical, or as a "pins and needles" sensation in the distribution of a root or nerve. Although radicular pain is not directly due to Parkinson's disease, radicular back pain is more frequently present in PD patients than in age-matched controls. In these patients, the clinical examination may reveal numbness or weakness in the distribution of the affected nerve or root. Neuropathy is common in Parkinson's disease, but attribution to PD itself is largely a matter of excluding more likely causes. The disease itself may contribute to neuropathy as there is evidence that even drug naïve patients have small nerve fiber deterioration and evidence of α-synuclein deposition in the peripheral nervous system. Levodopa use may contribute to lower B12 and B6 levels; studies have found elevated levels of serum methylmalonic acid in patients with Parkinson's disease; there may also be direct neurotoxicity from levodopa associated with an axonal sensory neuropathy.

Additional work-up for radicular pain, including *MRI* spine imaging and electromyography, is often needed. A typical serum screen (e.g., B12, TSH, HgA1C) should be performed for patients with neuropathic complaints. When warranted, vitamin B deficiencies can be treated with oral supplementation or intramuscular injections. There are a variety of oral medications that are useful for neuropathic pain including antidepressants (e.g., nortriptyline, amitriptyline, duloxetine) and antiepileptics (e.g., pregabalin,

gabapentin). NSAIDs and steroids can be used for acute pain as well as a short course of opioid medications. Occupational and physical therapy can often improve pain symptoms. When there are nerve or root entrapments, surgical decompression may be necessary.

Central nerve pain (CNP) is described as a continuous aching, burning, or cramping sensation. On surveys, up to 30% of Parkinson's patients have reported complex pain that is categorized as CNP. This pain is often described as "bizarre" in the literature. The pain distribution can include the face, head, pharynx, epigastrium, abdomen, pelvis, rectum, and genitalia. It is often bilateral and asymmetric, with greater intensity on the most affected motor side in Parkinson's disease. It may be more common during "off" periods. As the name implies, it is thought to be caused by PD itself, but other sources of the pain must be excluded. Treatment is often challenging, and many of the strategies discussed above are used to treat CNP. Since symptoms are sometimes associated with "off" time, strategies to increase "on" time may be helpful. Analgesics, opioids, tricyclic antidepressant, selective serotonin and norepinephrine reuptake inhibitor (SNRI) medications, and atypical antipsychotics (e.g., clozapine) are sometimes helpful. There are some reports of improved central pain after subthalamic nucleus DBS.

Regardless of the etiology of the pain, a multidisciplinary approach to pain management is typically the most effective in Parkinson's patients. Physical therapy and exercise (e.g., stretching, range of motion, aerobic activity) improve both physical symptoms of Parkinson's disease and improve comorbid psychological symptoms such as depression and anxiety. When appropriate, psychiatric intervention can be helpful as comorbid depression, and anxiety may lower pain thresholds. Although evidence-based support is weak, some patients report clinical benefit from complementary therapies such as massage and acupuncture.

Many patients express interest in using cannabis to treat pain associated with Parkinson's disease. In 2014 an open-label observational study reported improved pain in 20 patients who smoked marijuana. The pain in this trial was not characterized. In the same year, the American Academy of Neurology published the results of a systematic review looking at the role of medical marijuana on various neurological diseases. There were no reviewed papers addressing the use of cannabis for pain in PD. There was one class I study suggesting that oral cannabis extract (OCE) is probably ineffective for treating levodopa-induced dyskinesias in patients with Parkinson's disease. The only focal dystonia mentioned in the review was cervical dystonia, and there was no conclusive data that medical marijuana improved this condition. Of note, two class I studies supported the use of OCE in central pain associated with multiple sclerosis, and further research should explore the role of OCE in central pain in Parkinson's disease.

When a patient with PD complains of pain, a thorough history, examination, and targeted work-up are needed to identify the cause of the pain. Often the pain is not due to PD although PD places patients at increased risk for other conditions that can cause pain, such as osteoporosis leading to spontaneous fractures. When an alternative cause of the pain is not apparent, then the pain may be due to PD, and as discussed above, it is important to assess whether there is any relationship between the pain and the time of day or timing of levodopa and if there are associated findings such as dystonia. Pain that fluctuates with levodopa, either at peak dose or when "off", is a strong clue that it is PD related.

In the case of this patient, despite his complaint of continuous pain, the "on" and "off" examination in the office revealed the pain was mostly associated with "off" dystonia. The patient was not able to tolerate strategies used to increase "on" time as he developed either side effects or worsening dyskinesias. His internist prescribed an opioid that produced lethargy; trials of baclofen and diazepam were unsuccessful in managing the pain. Botulinum toxin injections were discussed, but the patient chose to defer injections as he expressed concern regarding possible weakness, and he was on schedule to have deep brain stimulation surgery. Although the subthalamic nuclei (STN) were initially targeted, the surgeon found the anatomy unsuitable for lead placement during the surgery and subsequently placed the leads in bilateral globus pallidus interni (GPi). The patient returned 4 weeks later and reported the dystonia in the foot, and associated pain, had completely resolved.

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Treatment of Fatigue in Parkinson's Disease

18

Umer Akbar and Joseph H. Friedman

Case 1

A 68-year-old man with a 5-year history of PD, mildly affected and still working a full 8-h day as an accountant, reports feeling so tired at the end of the workday that he has to lie down on his sofa as soon as he returns home, but he does not fall asleep. He stays there until bedtime. He is not depressed, he sleeps well at night, and he has no other medical conditions to explain his fatigue. He has no energy or time to begin a physical therapy program. His only PD medication is L-Dopa.

He is started on methylphenidate 5 mg bid, taken on arising and in the early afternoon. This is increased by 5 mg bid weekly and on reaching 15 mg bid reports significant improvement although not complete resolution.

Case 2

A 75-year-old woman with stage 3 PD reports severe fatigue that keeps her from many activities. She also has difficulty sleeping at night and isn't sure whether she has both fatigue and excessive sleepiness or just sleepiness. Her Epworth Sleepiness Score is very high. She takes trazodone 200 mg qHS for sleep and admits feeling depressed. She takes carbidopa/levodopa 25/100 three times daily and many other medications for diabetes, hypertension, and mild congestive heart failure.

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Discussion

It has been almost 200 years since James Parkinson first published his observations of the condition that now holds his eponym, but only within the past 20 years has the field recognized fatigue as a major component of disability. Despite two decades of research, no consensus definition exists, and the tools of measuring fatigue are not always concordant. Several factors contribute to the challenge of studying fatigue in PD. Fatigue is a subjective symptom – without an objective qualitative measure – and it can be comorbid with other features that are commonly present in PD. Some tools used to measure fatigue rely on the patient's performance of activities of daily living (ADLs). But there is great variability among individuals' daily activities and their expectations to complete those tasks.

Although PD patients experience physical fatigue due to their motor symptoms and the loss of muscle strength with repeated use, the subjective sensation of fatigue – or central fatigue – is the focus of this chapter. Central fatigue is loosely defined as the inability to initiate or sustain a task in the absence of a physical impediment.

Due to the lack of a standardized definition of fatigue, the reported prevalence varies from 33% to 58%. More than half of the subjects in one study considered fatigue as one of the three most disabling symptoms, and two-thirds reported the fatigue to be different compared to that noted before PD onset. Central fatigue has been associated with depression but not motor dysfunction, suggesting that fatigue is not a result of physical impairment from PD symptoms. Several studies demonstrated that fatigue occurs independently of motor dysfunction, including a clinical trial (ELLDOPA) in which one-third of newly diagnosed patients without treatment, dementia or depression reported fatigue. While fatigue is thought to be comorbid with other behavioral disturbances, a Norwegian study showed that fatigue was just as prevalent in patients with depression, dementia, and sleep problems as in subjects without these comorbidities. In a Dutch study,

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over a half of subjects reported fatigue to be just as severe as their other PD symptoms, and 15% rated fatigue as their most disabling symptom. A Norwegian 8-year follow-up study showed that severity and incidence of fatigue increased in their PD cohort over time, while an American study showed no increase in incidence but worsening severity of fatigue in a 9-year follow-up of the same cohort. Fatigue was found to affect nondepressed, nondemented, and nonsleepy PD patients as much as those with these problems.

Although motor symptoms are more likely to trigger a consultation with a physician, non-motor symptoms are often under-recognized, and even underreported, despite being more disabling. In a self-report survey completed prior to their routine clinic encounter with the neurologist, 42% of PD patients reported significant fatigue, while the neurologists diagnosed the problem in only 14%. Compared to other non-motor symptoms, the concordance of patient's report and clinician's diagnosis was lowest for fatigue (25%).

Fatigue Severity Scale (FSS) is the most widely used scale for the assessment of fatigue and was rated as "recommended" for screening and severity assessment by the MDS Task Force. FSS is a 9-item questionnaire in which patients rate on a 7-point scale how strongly they agree with statements about the impact of fatigue on various domains of function. Parkinson's Fatigue Scale (PFS) has 16 statements, which originated from experiences of patients with fatigue, that are rated on a 5-point scale. PFS was "recommended" for screening and "suggested" for fatigue severity. Multidimensional Fatigue Inventory (MFI) is a 20-item assessment on a 7-point scale regarding feelings of effort and capacity. The MFI was rated "suggested" for screening and "recommended" for severity rating.

The pathophysiology of central fatigue in PD is unknown, just as it is in virtually every other medical disorder. Dopaminergic deficit results in some motor symptoms of PD, and treatment with levodopa alleviates these symptoms but not fatigue, suggesting that pathogenesis of fatigue is not directly related to dopamine deficiency. Physiological studies have shown increased cortical excitability with motor fatigue but with no correlation to subjective complaints of fatigue. Inflammatory markers like C-reactive protein and cytokines are potential biomarkers of central fatigue, but further studies are required to confirm these findings. SPECT scan studies have failed to differentiate fatigued and non-fatigued PD patients. Using positron emission tomography (PET) imaging, serotonin transporter binding in the caudate, putamen, ventral striatum, insula, and thalamus was found to be decreased in the fatigued patients compared to non-fatigued PD patients in a single study.

Specific treatment for fatigue in PD is lacking. In fact, treatments effective for fatigue outside of PD have not shown definitive benefit in PD fatigue. Although one randomized controlled trial of methylphenidate showed clinically and statistically significant improvement in PD fatigue compared to baseline, it did not show a difference compared to placebo, and the aggregate of stimulant studies have not shown a benefit. Post hoc analysis of a rasagiline study showed a statistically significant difference in treated patients, but the improvement was negligible clinically. Nonpharmacological options include exercise, increased physical activity, massage therapy, and scheduling of daily activities. Before treatment is considered, other medical conditions associated with fatigue should be excluded (e.g., hypothyroidism, hypotestosteronism, etc.), fatigue-inducing medications should be minimized, and comorbid behavioral disturbances (e.g., depression, anxiety, apathy, poor sleep) should be assessed.

Case 1 Comments

No intervention has been shown to improve fatigue in PD. We try low dose stimulants, having seen some success, but it is unclear whether the result is "real" or placebo. Since fatigue differs from somnolence, modafinil has, not surprisingly, been shown to be ineffective for fatigue. Stimulants, in low doses, are being increasingly used by geriatric psychiatrists to enhance mood, and increase energy, and appear to be safe when cardiac and uncontrolled hypertensives are excluded. In our extensive experience over many years, we have not yet seen a patient with typical "drug seeking behavior." As with all symptomatic medications, the stimulant should be stopped if not effective.

Case 2 Comments

She is not started on a stimulant. She has contraindications and it is not clear that she suffers from fatigue and, even if she does, that it is due to her PD. We would recommend having her cardiologist optimize CHF treatment, if not already accomplished. We would recommend that she begin a physical therapy program in addition to a slowly increasing exercise regimen. She should also address her sleep issues, followed by treatment of the depression, if still needed. There is no need to make more than one change at a time. Fatigue is not life threatening, and changes in one problem area may produce benefits in other areas, making further medication changes unnecessary.

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Treatment of Diplopia in Parkinson's Disease

19

Stephen G. Reich

Case

A 78-year-old man with a 15-year history of Parkinson's disease (PD) complained of several months of intermittent double vision when reading, when watching television, and when working on the computer. The diplopia was horizontal and he noticed that it was easier to read if he closed one eye. On examination, there was hypomimia and moderate hypophonia. He scored 23/30 on the Montreal Cognitive Assessment (MOCA). He had to push off the armrests to arise from a chair. He walked with a walker and lost his balance on the pull test. There were a rest tremor in both hands and the jaw, moderate bradykinesia, and rigidity. On ocular examination, there was no actual ptosis although he did have redundant eyelid tissue. Visual acuity with glasses was 20/30 on the right and 20/25 on the left with normal visual fields, equal and reactive pupils, and normal discs. Aside from mild conjugate limitation of upward gaze, there was no ophthalmoparesis. With the alternate cover test, there was an exophoria. He was unable to converge and noticed diplopia when attempting to do so (see Video 1). He was referred to a neuro-ophthalmologist who confirmed the above findings and prescribed a base in prism for his reading glasses. This was somewhat helpful, but he found it more useful to simply put masking tape over one of the lenses of his reading glasses.

Discussion

Diplopia is experienced by at least 20% of people with PD yet is an under-recognized sensory symptom and just one of a broad array of visual and ocular motor symptoms and signs in PD (Table 19.1). A complete review of the spectrum of visual and ocular motor abnormalities in PD is beyond the scope of this chapter, and instead, here I focus on convergence insufficiently (CI) which is the usual cause of diplopia in PD. The typical history from the patient with CI is horizontal diplopia which is worse at near and goes away when viewing out of one eye. Some patients with symptomatic CI do not experience or at least recognize double vision (particularly if objects are only slightly displaced) but instead complain of blurred vision or non-specific difficulty seeing/reading, and this history should also prompt consideration of CI.

The evaluation of the PD patient with diplopia necessitates a broad approach to ocular symptoms and signs with, of course, consideration of disorders not associated with PD such as cataracts, glaucoma, and alternative causes of diplopia. Ocular features of PD that may contribute to impaired vision include dry eye, blepharitis, blepharospasm, and eyelid opening apraxia. Impaired contrast sensitivity and color discrimination occur in PD but typically do not cause diplopia nor do the saccadic abnormalities that have been reported, such as impaired predictive saccades. Higher-order impairments of visual processing and visuospatial dysfunction may occur in PD and interfere with visual processing despite normal visual and ocular motor function. Hallucinations and illusions are common in PD, and while they may be visually distracting, they are not causes of diplopia (see Chap. 29). Medications for PD may contribute to diplopia and impaired vision by interfering with accommodation (anticholinergics) or causing somnolence (especially dopamine agonists). Some patients notice that diplopia, even when due to CI, may fluctuate with the timing of levodopa (if not noticed, ask if this happens), typically worse in the off state, and in that case, attempts to smooth out fluctuations may be useful.

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Table 19.1 Ocular and ocular motor disorders in Parkinson's disease

Ocular
Dry eyes
Blepharitis
Impaired contrast sensitivity
Impaired color discrimination
Visual spatial impairment
Hallucinations and illusions
Ocular motor
Conjugate limitation of upward gaze
Saccadic intrusions
Saccadic pursuit
Impaired convergence
Hypometric saccades
Inaccurate and delayed visually guided saccades
Impaired self-generated saccades
Impaired memory-guided saccades
Impaired antisaccades
Eyelid
Decreased blink rate
Eyelid retraction
Lid lag
Eyelid opening apraxia
Blepharospasm
Myerson's sign (glabellar)

Although visual symptoms due to PD tend to correlate with duration and severity of disease, that is not always the case and may be present early in the course.

The evaluation of the PD patient who complains of diplopia should first make sure that there are no signs aside from what is expected with CI and second confirm the presence of impaired convergence, which, when symptomatic, is typically associated with an exophoria. As for the former, this should include checking visual acuity, fields, pupils, discs, and eyelid function. If diplopia is due to CI, there should be no ophthalmoparesis with the exception that conjugate limitation of upward gaze is common in PD. Otherwise, limited movement in one or both eyes suggests an alternative cause such as myasthenia gravis, thyroid eye disease, or a cranial neuropathy, among others. Although saccades are often hypometric in PD, there is no actual slowing of saccades and if present (especially if vertical), suggests the patient may have progressive supranuclear palsy. The alternate cover test, in which an occluder is moved back and forth from eye to eye while the patient fixates, often demonstrates an exodeviation in PD patients with diplopia. As one eye is covered, the other eye adducts to fixate, and this pattern alternates as the occluder rod is moved back and forth. A vertical separation during the alternate cover test requires further evaluation. The next step is to test that convergence is in fact impaired, and while the degree of impairment can be quantified by an ophthalmologist, this can usually be demonstrated convincingly at the bedside.

When diplopia is PD due to CI, the only abnormalities expected on examination include impaired convergence with an exodeviation at near, almost always combined with an exophoria seen on the alternate cover test. Anything other than these findings suggests the patient may have an alternative cause of diplopia necessitating a referral to an ophthalmologist or neuroophthalmologist.

Once the diagnosis of CI is made, there are several treatment options. For the patient with only occasional diplopia, no intervention may be necessary. Since CI is typically a problem with near vision, patients may benefit from having separate glasses for near and distance vision, rather than using bifocals or progressive lenses. A base in prism may help. Additional low-tech suggestions include closing one eye when diplopia occurs, using an eye patch, or occluding one of the lenses of reading glasses with masking tape. Patients should be encouraged to have adequate lighting while reading, to consider an e-reader with the ability to increase the font size, and if tremor interferes with holding reading material, it should be placed on a surface, book, or music stand. Comorbid conditions that may affect vision such as dry eyes should be treated along with ensuring proper refraction.

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Treatment of Insomnia in Parkinson's Disease

20

Donald L. Bliwise

Case

This patient was a 68-year-old woman with a 3-year history of idiopathic Parkinson's disease (PD) who had a body mass index (BMI) of 28 (overweight). Her daytime motor symptoms were relatively well controlled on only modest doses of anti-Parkinsonian medication (carbidopa/levodopa, 25/100 TID). She also had mild and well-controlled hypertension and hypothyroidism. She was treated for all of her conditions by her primary care physician (PCP) but was sent for overnight polysomnography (NPSG) by her PCP because her husband noted that she snored. The PCP was also concerned that the possible sleep apnea was hastening disease progression and complicating treatment of her PD. She presented in Sleep Clinic as follow-up to this testing. The NPSG report is summarized in Table 20.1. History-taking in the Sleep Clinic revealed that snoring was a longstanding issue (at least a decade prior to diagnosis of PD). Furthermore, the patient's own concerns focused largely on the poor quality and interrupted nature of her nocturnal sleep. She complained of awakening frequently during the night for no apparent reason (c.f., awakenings due to urinary urgency). She was not drowsy during the daytime (Epworth Sleepiness Scale was 3 out of possible 24), nor did she (or her husband) report dream enactment suggestive of REM behavior disorder. She did not report symptoms suggestive of restless legs syndrome, nor did her husband report that she kicked her legs during the night.

Inspection of the NPSG results (Table 20.1) are revealing in several respects. First, with regard to the snoring, the patient evidences only very mild sleep apnea (respiratory disturbance index of 17.2; apnea-hypopnea index [AHI] of 5.8) with very little hypoxic burden (0.7%: % of time below saturation of SaO2 of 88%). A sufficient quantity of REM sleep was seen to allow determination of dream enactment, but there is no evidence of absence of REM atonia (i.e., normal REM atonia was present). Subjective estimates made by the patient of her own time to fall asleep and the duration of her sleep generally were confirmed objectively via NPSG. Although she reported no RLS, her NPSG showed some evidence of periodic leg movements in sleep (PLMS) occurring at a rate of 9.2 per hour. Perhaps the most mundane finding in the NPSG, but the one that most closely captures the patient's own concerns, was that her sleep efficiency (the proportion of time in bed asleep by NPSG criteria) was relatively poor, at 65.6%.

Discussion

The NPSG report is as revealing for what it did not show as was for what it did show. Although the basis for the initial referral for the NPSG by the patient's PCP was snoring and concerns over the possibility that sleep apnea was worsening her PD, her results (Table 20.1) showed only a relatively mild case of sleep disordered breathing, not atypical for a woman of this age. In fact, most studies have shown that PD patients as a group do not have higher rates of sleep apnea than age-matched control populations, despite some early literature raising the possibility of upper airway motor control abnormalities in at least some PD patients. Necessity for treatment of sleep apnea (customarily with nasal continuous positive airway pressure, CPAP) remains a clinical judgment at this time, though many studies suggest that morbidities in the cardiovascular domain become manifest only when the apnea-hypopnea index (AHI) exceeds 30 events per hour or higher. In elderly women, even levels in excess of this do not confer higher mortality risk. Therefore, the decision to pursue treatment for sleep apnea in a PD patient should be dictated by presenting complaint and the relative likelihood that the condition might be contributing to pre-existing cardiovascular or metabolic disease. Although theoretically

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Table 20.1 Nocturnal polysomnography (NPSG) results on case presented

Total sleep time (TST) (mins)	241.0
Sleep latency (SL) (mins)	17.5
Sleep efficiency (%) (total sleep duration/time in bed × 100)	65.6
N1 (% of TST)	24.7
N2 (% of TST)	62.1
N3 (% of TST)	1.3
REM (% of TST)	11.9
Respiratory disturbance index (RDI) (events per sleep hour)	17.2
Apnea-hypopnea index (AHI) (events per sleep hour)	5.8
Periodic leg movements in sleep index (PLMSI) (events per sleep hour)	9.2
Hypoxic burden (% of TST with SaO2 < 88%)	0.7
Subjective TST (hours)	3
Subjective SL (minutes)	30

N1%, N2%, and N3% refer to the percentage of the total amount of sleep (TST) occupied by each of those stages. RDI, AHI, and PLMSI are measures of the severity of sleep apnea (AHI, RDI) and periodic leg movements in sleep (PLMSI), presented as rates of events occurring per hour of sleep

possible that severe nocturnal hypoxic burden could also hasten progression in motor symptoms in PD cases, there are no published data to support such an assertion. A more substantial hypoxic burden in this patient might raise suspicion further in that regard, but this patient showed minimal desaturation during sleep. If treatment was pursued, the two most likely treatments would be nasal continuous positive airway pressure (CPAP) or oral appliance therapy (OAT). If the NPSG report had suggested that the patient showed a positional dependence in her OSA, then simple avoidance of supine sleeping position would also become a viable treatment.

The patient's NPSG also showed evidence of PLMS, which have been shown in some genetic studies to be an objective indicator for RLS. However, PLMS may occur in the absence of RLS symptoms and often represent an "incidental" finding on NPSG. An association between RLS in PD (i.e., as would be suggested by a higher prevalence of this condition in PD) remains a controversial finding, with some studies suggesting an association and others not (see Chap. 79). Apart from RLS, however, the prevalence of PLMS has been shown to be higher in PD than in age-matched controls. Whether this translates into a need to treat these movements in this case remains uncertain. In non-PD patients, possible associations between PLMS (without RLS) and insomnia complaints more often than not have been inconclusive, but it is conceivable that this woman's leg kicking (though not corroborated by her husband, who is a sound sleeper himself) could be the source of her poor and fragmented sleep. Dopamine agonist class medications (ropinirole, pramipexole, rotigotine) have been shown to decrease the quantity of leg kicks during sleep. Although she is treated exclusively with carbidopa/levodopa at this point, initiation of evening dosing (about 2 h before bedtime) of such an agonist (e.g., 0.25–0.50 mg pramipexole) might be considered. The dopamine agonist class also has the advantage of inducing some sleepiness, which might serve to improve her sleep as well. Alternatively, the more newly approved prodrug formulation of gabapentin (gabapentin enacarbil) has been shown to decrease PLMS and could be used at 600 mg or 1200 mg. The advantage of this formulation over regular gabapentin is its more stable biological availability after ingestion.

Without concurrent daytime sleepiness (see Chap. 23) or reported dream enactment (see Chap. 24) treatments, targeting these conditions would not be warranted in this case.

After full consideration of all the foregoing possibilities, what remains is that the patient is presenting poor sleep, likely as a consequence of her Parkinsonism, and her self-perceptions are indeed corroborated by the NPSG findings. Figure 20.1 shows a frequency distribution of the sleep efficiency metric (SE %) as recorded in our sleep lab in 275 PD patients. The mean value (< 70%) suggests characteristically highly disturbed sleep for this patient group. Even considering the well-known "first-night effect" of patients in the sleep lab for the first night (where SE values in the 80–85% range are typical), this frequency distribution indicates that PD patients as a group are much worse than this. To this extent, the patient's low SE is not at all surprising.

Approaches to insomnia in all patient groups generally resolve into non-pharmacologic and pharmacologic options. Non-pharmacologic treatments are often subsumed under the broad rubric of Cognitive Behavioral Therapy for Insomnia (CBT-I). Although CBT-I has been shown to successfully treat insomnia across a broad range of conditions (e.g., young/elderly, with and without comorbid pain, with and without comorbid depression), there are no large-scale trials that suggested its utility for insomnia in PD. Nevertheless, the basic concepts of CBT-I can always be attempted initially in such patients before moving to pharmacologic interventions. Key components include restriction of all daytime sleep opportunities; arising from bed if being unable to sleep during night and moving into a different room; avoidance of caffeine, alcohol, and tobacco in the evening and near bedtime; enhanced exposure to daylight (particularly during morning hours); increased levels of physical activity of any kind (e.g., even simple walking) during daytime; avoidance of electronics (particularly typical blue wavelength light) in the evening; and delaying customary bedtime 1–2 h and arising from bed the same time every morning. When presented as a package, these multi-faceted components often tend to stabilize the sleep/wake rhythm and enhance the homeostatic pressure for sleep. Unfortunately, for many patients with PD, they do not work.

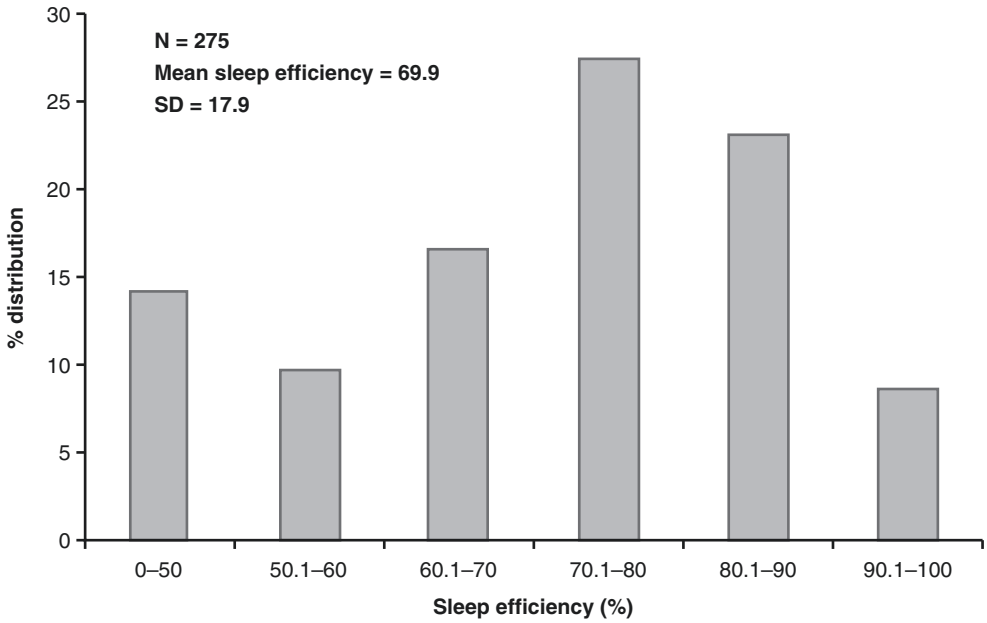

Fig. 20.1 Relative frequency distribution of sleep efficiency (defined as total sleep time divided by time in bed × 100) for 275 Parkinson's disease patients undergoing initial night of nocturnal polysomnography. Mean and standard deviation were 69.6 and 17.9, respectively

Table 20.2 Listing of US Food and Drug Administration-approved medications with sedative/hypnotic indication (shown by chemical name, mechanism of action, half-life [in hours], and available dose range [in mg])

Medication	Mechanism	Half-life (hours)	Dose range (mg)
Flurazepam	GABA agonist	48–120	15–30
Temazepam	GABA agonist	8–20	15–30
Triazolam	GABA agonist	2–6	0.125–0.25
Estazolam	GABA agonist	8–24	1–2
Quazepam	GABA agonist	48–120	7.5–15
Zolpidem	Site-specific GABA agonist	1.5–2.4	5 (women); 10 (men)
Zaleplon	Site-specific GABA agonist	1	5–10
Eszopiclone	Site-specific GABA agonist	5–7	2–3 mg
Zolpidem—continuous release	Site-specific GABA agonist	1.5–2.4 (as extended release)	6.25–12.5 mg
Ramelteon	Melatonin agonist	1.5–5	8 mg
Suvorexant	Orexin antagonist	10–12 h	5–20 mg

GABA gamma-aminobutyric acid

The broad range of pharmacologic options for inducing and/or maintaining sleep are shown in Table 20.2. Traditional benzodiazepine class drugs are generally out of favor because of their long half-life, though for very anxious patients, they may still play a role. More site-specific gamma-aminobutyric acid (GABA) agonists that have sites of action limited to subcomponents of the GABA receptor (the so-called z-drug) are used more frequently at this time. They have a broad range of half-lives, with some short-acting medications having utility for only middle-of-night administration (e.g., zaleplon, sublingual zolpidem at 3.5 mg), some being more effective when dosed at the beginning of the night for both trouble falling asleep and staying sleep (e.g., eszopiclone), and others (e.g., zolpidem) having intermediate half-life dosing advantages. Most traditional benzodiazepines and "z-drug" have been associated with a higher incidence of adverse events such as falls, confusion, disorientation, next-day drowsiness, and, on relatively rare occasions, abnormal behaviors during the overnight period. These are not inevitable, and many patients derive benefit from judicious use (i.e., not taking the drug every night, allowing for sufficient time in bed for drugs with longer half-lives, avoidance of concurrent use of this class with alcohol or opioid medication). Over-the-counter (OTC) melatonin and the prescription melatonin agonist, ramelteon, have shown a very mixed pattern of efficacy across a broad range of worldwide clinical trials. Although seemingly harmless, within the United States, OTC melatonin is considered a dietary supplement and falls under food law, rather than drug law, and published studies suggesting inconsistency in potency and purity of various commercially available products might be the basis for some concern. Finally, the relatively newly approved hypocretin/orexin antagonist, suvorexant, with a half-life approaching 12 h may also be worthy of consideration for start-of-night dosing in patients who can spend at least 8 h in bed. Although a few studies have suggested lower than normal levels of hypocretin/orexin in the cerebrospinal fluid of PD patients (thereby implying caution with use of a medication functioning as an antagonist for this wake-promoting peptide), not all studies concur with this finding. In our clinical experience, suvorexant, dosed at 20 mg HS, is a reasonable choice of a sedative/hypnotic medication with few demonstrated tolerance and withdrawal effects when used in a PD population. No formal clinical

trials have tested it specifically in PD patients. There is scant evidence that low-dose antidepressant medication (e.g., trazodone at 50 mg, mirtazapine 7.5–15 mg) has any benefit for the sleep disturbance in PD patients, and use of typical or atypical antipsychotic medications as de facto hypnotics in this population is strongly cautioned.

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Treatment of Daytime Sleepiness in Parkinson's Disease

21

Lynn Marie Trotti

Case

A 60-year-old man with a 3-year history of PD presented to the Sleep Clinic with a chief complaint of waking unrefreshed. Daytime sleepiness required him to nap once or twice a day, for up to 60 min at a time. Epworth Sleepiness Scale score was 15/24 (normal <11). He habitually went to bed at 10:30 pm, fell asleep in "less than 1 minute" by his estimation, woke briefly once or twice per night, and got out of bed for the day at 6:30. His wife noticed occasional snoring but no witnessed apneas. He underwent polysomnography, which showed no significant sleep apnea (apnea-hypopnea index = 4.4), a total sleep time of 396 min, a sleep efficiency of 86%, and no periodic limb movements or REM sleep without atonia. His next-day multiple sleep latency test demonstrated a mean sleep latency of 1.6 min with all five naps containing REM sleep. Modafinil was recommended to the patient to treat sleepiness, but he decided to continue naps rather than take medication for this symptom.

Discussion

Daytime sleepiness is common and may be problematic in patients with Parkinson's disease (PD). In severe cases, daytime sleepiness is a major impediment to quality of life, limiting a patient's ability to work, engage in social activities, and drive. While both sleepiness and fatigue are common in patients with PD, they respond differently to treatment, and it is therefore important to draw the distinction between sleepiness, i.e., an increased propensity to sleep, and fatigue, i.e., a weariness or difficulty remaining on task.

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Several PD-specific sleep scales are well-validated and screen for multiple sleep symptoms; our clinic routinely uses the Parkinson's Disease Sleep Scale. For the quantification of subjective sleepiness, the Epworth sleepiness scale is most commonly used (Fig. 21.1). It is not specific to Parkinson's disease but has been validated in this population. It asks patients to rate their likelihood of dozing off in eight routine situations on a 0–3 scale, yielding a total score from 0 to 24; scores greater than 10 are indicative of excessive sleepiness. Caregiver-completed Epworth scales may be quite different than patient-completed scales, suggesting that some patients underestimate their daytime sleep. Daytime sleepiness in some cases is intrinsic to PD, occurring in patients with sufficient duration of sleep, no comorbid sleep disorders, and no soporific medications. Indeed, prospective studies have repeatedly demonstrated that people who are sleepy have a higher rate than those who are not sleepy of developing PD over the next 4–12 years, suggesting that sleepiness, like constipation, is an early but non-specific symptom of the developing neurodegenerative disease. However, the clinical evaluation of a PD patient with sleepiness must include an assessment for treatable conditions that may be contributing to sleepiness. Assessment of sleep timing and duration allows for the identification of behaviorally induced insufficient sleep syndrome (i.e., not devoting enough hours to sleep) and insomnia (i.e., the inability to sleep even in the presence of adequate opportunity to sleep). For patients with PD, nocturnal motor dysfunction can substantially interfere with sleep, and any history of waking with "off" symptoms, dyskinesias, and limited bed mobility should be assessed. The evaluation of sleep timing and quality should ideally involve both the patient and a bedpartner.

Medications are a common cause of daytime sleepiness. Dopamine agonists, in particular, are a major cause of sleepiness in patients with PD, with an odds ratio of approximately 3.5 for sleepiness compared to placebo in clinical trials of patients with early PD. However, levodopa may be less sedating, and so we recommend a transition from dopamine

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THE EPWORTH SLEEPINESS SCALE

Name: _____

Today's date: _____ Your age (years): _____

Your sex (male = M; female = F): _____

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you have not done some of these things recently try to work out how they would have affected you.
Use the following scale to choose the *most appropriate number* for each situation:

0 = would *never* doze
1 = *slight* change of dozing
2 = *moderate* change of dozing
3 = *high* chance of dozing

Situation	Chance of dozing
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theater or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

Thank you for your cooperation

Fig. 21.1 The Epworth Sleepiness Scale. (Reprinted from Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):549–5. with permission from the American Academy of Sleep Medicine)

agonists to levodopa whenever possible in patients with problematic sleepiness. Both sleepiness and insomnia may be considered relative contraindications to use of dopamine agonists. Other medications that are implicated in sleepiness, which should be withdrawn or minimized, include antihistamines, benzodiazepines, and sedating antidepressants (e.g., trazodone and mirtazapine).

In patients with problematic daytime sleepiness that is not due to a readily identifiable cause (such as medications, short sleep duration, or insomnia), overnight polysomnography is generally indicated. Current evidence suggests that patients with PD are no more likely than age-matched controls to demonstrate obstructive sleep apnea, but this remains a common disorder in the PD population that should be investigated in patients with sleepiness.

Daytime sleepiness can be objectively quantified in the sleep laboratory, most commonly with the multiple sleep latency test (MSLT). This test involves five daytime nap opportunities in which the patient is asked to fall asleep while undergoing polysomnographic monitoring. Patients who fall asleep quickly (i.e., in less than 8 min, on average, across the five naps) are considered to have objective evidence for sleepiness. In PD patients, even shorter mean sleep latencies of <5 min are seen in 20–40% of unselected patients. The MSLT also quantifies the number of naps during which REM sleep occurs (known as a "sleep-onset REM periods"). The combination of a mean sleep latency <8 min and two or more sleep-onset REM periods is the MSLT diagnostic criteria for narcolepsy, and this pattern is seen not uncommonly in patients with PD. In the case above, a diagnosis of narcolepsy due to a medical disorder (i.e., PD) was rendered. However, unlike the nocturnal polysomnogram, which is important to identify potentially treatable comorbid conditions, the daytime test is focused on quantifying sleepiness itself and as a result does not generally change management in a patient who is already reporting problematic sleepiness. Thus, the MSLT may present more of a burden for a PD patient than potential benefit and is not necessarily performed in every sleepy PD patient. The exception is that an MSLT demonstrating narcolepsy (due to PD) may be useful in advocating for insurance coverage of wake-promoting medications.

Offending medications, comorbid sleep disorders, and problems of insufficient nocturnal sleep duration (including

due to depression or anxiety) should be corrected when present. However, persistent sleepiness after treatment of these issues is not uncommon and likely reflects the intrinsic association between PD and sleepiness. When behavioral approaches to sleepiness treatment are desired, the role of naps will depend on the clinical context. For patients who have daytime sleepiness and no difficulty sleeping at night, napping can be a very useful treatment strategy (although napping sometimes has to be normalized for people who erroneously associate daytime sleep with laziness). For people who are sleepy but also have insomnia, naps are generally not recommended, because sleep during the day reduces the homeostatic drive to sleep at night, worsening insomnia. However, in our experience, patients with PD often find daytime naps to be unavoidable, either because of the severity of sleepiness or because of a need for a "break" from motor dysfunction. In such cases, if insomnia is present, we focus on trying to keep the duration of scheduled naps as short as feasible and, ideally, limited to relatively early in the day. Caffeine presents similar challenges. Although a recent clinical trial did not show an intention-to-treat benefit of caffeine for PD sleepiness, individual patients' experience with caffeine certainly encourages them to continue its use for sleepiness, and increasing evidence suggests that caffeine may be beneficial for PD motor symptoms. Yet, for patients who are prone to insomnia, who also have daytime sleepiness, caffeine may worsen sleep disruption. Cessation of caffeine use after noon may be a useful compromise in these patients.

There are no medications that are FDA-approved specifically for the treatment of sleepiness associated with Parkinson's disease. However, the wake-promoting agent modafinil, which is FDA-approved for narcolepsy, sleep apnea-related sleepiness, and shift work sleep disorder, has been tested in multiple randomized controlled trials of patients with Parkinson's disease and sleepiness. Each of the studies was relatively small, and the combined number of patients included in all the PD modafinil trials barely exceeds 100. Despite this, meta-analysis does confirm a benefit of modafinil on subjective sleepiness in PD patients, although of a somewhat smaller magnitude than that seen in modafinil studies of other populations. This is concordant with the clinical observation of a relative modest, although clinically significant, benefit of modafinil on sleepiness in PD patients. No changes in objective measures of sleepiness were found in these studies. It is unclear if this represents type 2 error or a true disconnect between subjective and objective sleepiness, but patients should be counseled to continue to exercise caution, even on modafinil, when driving and performing other safety critical tasks. Modafinil is typically started as 100 mg in the morning and titrated by 100 mg every week to a maximum of 200 mg in the morning and 200 mg with lunch. Armodafinil, the R-enantiomer of racemic modafinil, has not been tested in PD but would be expected to be similarly useful. Traditional amphetamine-based psychostimulants have historically been used in patients with PD. Their increased risk of cardiovascular side effects and dependence compared to modafinil keep these medications from being routinely used in PD patients, but in carefully selected patients, they may provide benefit.

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Treatment of REM Sleep Behavior Disorder in Parkinson's Disease

22

Ronald B. Postuma

Case

A 63-year-old man came in at the request of his wife. Five years earlier he began yelling in his sleep, and 3 years ago, he began to thrash out and kick. In retrospect his wife mentioned that he had similar movements for as long as they were married, but these were rare. On one recent occasion, he fell out of bed, and on several nights, he has struck his wife. He has little recall of these events, but if he is woken from an episode, he recalls a dream that matched the movements. If woken, he quickly returns to normal alertness, and apologizes for his behavior. There is no sleep walking, he does not snore, and his wife has noticed no apnea episodes.

He has no other defined medical conditions. However, despite taking early retirement to travel, he has been less interested in doing so. He has occasional constipation, and his wife notices that he detects odors in the room less often than she does. Although cognition is relatively good, he occasionally has trouble following a very complex conversation, something that is new for him.

Examination was normal except for a subtle decreased facial expression and borderline slowing of fine finger movements. Blood pressure was 138/82 lying and 120/78 standing after 1 min. Montreal Cognitive Assessment was 26/30 – he lost points for cube drawing and Trail Making B and recalled 3/5 words. On olfactory testing, he demonstrated hyposmia.

We made a clinical diagnosis of probable RBD, and a polysomnogram was completed. This documented clear loss of REM atonia. Of his REM periods measured on surface EMG at mentalis, 58% had tonic REM and 45% had phasic bursts. Melatonin was tried with no success. A low-dose clonazepam 0.5 mg at bedtime reduced movements, with some mild somnolence.

He continued to follow with us in the clinic. Over the next 4 years, bradykinesia became gradually more prominent, although rigidity remained equivocal. Quantitative motor testing demonstrated gradual decline. Four years after presentation, his spouse noticed more severe cognitive problems that were affecting quality of life and notably fluctuating. MoCA had declined to 22/30, and MMSE was 25/30. Examination now revealed unequivocal rigidity. A diagnosis of parkinsonism and dementia was made. He had a marked improvement of cognition with donepezil that lasted for 1–2 years and a moderate improvement of motor features with levodopa.

Discussion

This case demonstrates several of the classic elements of RBD. His dream enactment is very typical of most idiopathic RBD patients seen in clinics. Review of systems disclosed some subtle abnormalities, but nothing easily definable as being due to neurodegenerative disease. However, on long-term follow-up, he developed an overlapping syndrome of dementia with Lewy bodies (DLB) and Parkinson's disease (PD). This is quite typical; in the longest-term studies, more than 80% of idiopathic RBD patients eventually developed a neurodegenerative synucleinopathy. Within established neurodegenerative synucleinopathies, approximately 35–50% of PD patients and 75% of DLB patients have RBD.

The most important differential diagnoses of RBD are non-REM parasomnias (sleep walking, sleep talking, etc.), obstructive sleep apnea, non-dream enactment movements like periodic leg movements of sleep, and much less commonly narcolepsy and nocturnal epilepsy. Several elements are used in diagnosis:

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1. History – When taking a history of dream enactment, focus on:
   (a) Duration of symptoms – Most classic RBD has its onset around age 50–70 years. A history of lifelong movements of similar severity may suggest non-REM parasomnia, apnea, or narcolepsy.
   (b) Concurrence with dream content – Although not always available (patients do not always recall dreams), most patients will recognize a correlation between movements and dreams, for at least some episodes.
   (c) Sleep walking – Although RBD patients may take a step or two out of bed, any prolonged walking is unlikely to be RBD. However, this is frequent in non-REM parasomnia.
   (d) Nature of sleep talking – Although all kinds of vocalizations can occur during RBD, if the spouse hears a prolonged one-sided conversation (i.e. like listening to half of telephone conversation), long duration of talking, or singing, RBD is more likely.
   (e) Response when confronted – Most of the time, RBD patients will not respond during an episode, unless they are wakened (in which case the episode stops quickly). This is in contrast to non-REM parasomnia, in which patients may talk back but remain confused/partially aroused.
   (f) Interaction with the environment – Although RBD patients may grab something in the immediate vicinity, any deliberate interaction with the environment (e.g., opening doors, reaching for things with eyes open) is more typical of a non-REM parasomnia.
   (g) Snoring/apnea – Any loud snoring or prolonged apnea with gasps raises the possibility that episodes are apnea with associated confusional arousals.
   (h) Confounding medications – Look for antidepressants, as they commonly trigger RBD. If there is a clear onset with new prescription of antidepressants, risk of neurodegeneration may be less (although it is still substantially elevated compared to the general population). Stopping antidepressants often reduces RBD, although often only partially.
   (i) Symptoms of neurodegenerative synucleinopathies – Even without a documented neurodegenerative disease diagnosis, most idiopathic RBD patients over 50 years old are actually in prodromal stages of neurodegenerative synucleinopathy (i.e., PD, DLB, or multiple system atrophy). These have a diverse array of potential symptoms. The commonest symptoms I see are constipation, bladder urgency, decreased olfaction, subtle apathy (usually noticed only by spouses), and subtle cognitive changes. Most patients are not aware of any motor changes (even if mild abnormalities are present on examination).
2. Examination – The examination of an RBD patient should focus upon signs of neurodegeneration. The commonest motor abnormality seen is subtle bradykinesia, especially in facial expression and slowed movements of fingers/hands. I often observe equivocal rigidity in the dominant hand with activation, but this is difficult to define as clearly abnormal. Cognitive testing with bedside examinations (we use the Montreal Cognitive Assessment, (MoCA)) often shows subtle changes. For the MoCA, focus especially on the top 5 visuospatial/executive points, and the delayed recall, since these are usually the first to be affected. Among the more specialized bedside tests, olfaction is particularly useful; about 60% of RBD patients have olfactory loss, and this strongly predicts outcome.
3. Confirming the diagnosis – Unless the patient already has a defined neurodegenerative syndrome, polysomnogram should be performed if possible. Even after expert interview, a diagnosis of probable idiopathic RBD will be wrong 15–35% of the time. Given the considerable implications of an idiopathic RBD diagnosis for the patient's future, this error rate is too high. Moreover, obstructive sleep apnea, a major alternative diagnosis, is treatable. On the other hand, if patients already have PD or DLB, a careful sleep expert interview documenting likely RBD will be correct >90% of the time; in this case, empirical treatment (or observation if symptoms are mild) may be warranted. To help in diagnosis, there are several questionnaires that can be used. Among those with high specificity are the Innsbruck Questionnaire and the RBD-HK.

For polysomnographic diagnosis, it is not essential to observe dream enactment; rather, the focus should be on documenting loss of the normal REM atonia. Various algorithms and diagnostic cutoffs have been prepared for this. Methods are being developed to automatically detect REM atonia loss; if artifacts (arousals, electrode displacement, etc.) are first ruled out manually (i.e., visually), these may be quite reliable. For manual measurement, various algorithms have been developed. We assess both tonic and phasic activities, and cutoffs in our laboratory are 30% and 15%, respectively. Another good method is the SINNBAR method which combines tonic and phasic activities together, and an 18% cutoff in mentalis is reliably specific (adding assessment of finger flexors can increase sensitivity further).

Treatment includes non-pharmacologic and pharmacologic approaches including:

(a) Counseling – Among patients with established PD or DLB, simple symptomatic discussion likely suffices. It is probable that RBD within PD/DLB is associated with a worse prognosis, on average. However, because prognosis still varies considerably, I usually do not directly discuss this unless asked. For patients with idiopathic RBD, one needs to provide at least a minimal counseling of neurodegenerative risk. However, this should vary according to the individual. At minimum, I generally tell patients that RBD can be associated with other neurologic problems in the future, so we should follow their condition carefully together. After that, the discussion is highly tailored to the amount of information that patients want to have (the desire "not to know" is difficult for patients to communicate, so be sensitive and alert to this possibility). If patients ask what they can do to prevent disease, I usually suggest regular and relatively vigorous exercise (given that evidence for other measures remains very limited, I do not generally recommend other specific treatments or lifestyle changes). As part of the more detailed discussions, I often also stress the treatability of PD and the possibility that disease-modifying agents may not be far off.

(b) Symptomatic treatment – The first step is to decide whether any treatment is required at all. Unless dream enactment is extreme, RBD itself does not disrupt sleep very much. Patients may obviously arouse from an episode, but most fall asleep again quite readily (note that dozens of arousals normally can occur per night, even in patients without RBD). This means that symptoms of somnolence or insomnia are not indications to treat RBD. Rather, the primary indication for medical treatment of RBD itself is safety or sleep disruption of others.

If symptoms are very mild, no medications may be needed. However, bed safety should be ensured. If patients are already sleeping alone, even moderately severe RBD can be tolerated as long as the bed is low to the floor and no sharp/breakable objects are nearby. Of the medical treatments, I usually start with melatonin 3–6 mg at bedtime. Overall, this seems to be less reliably effective than clonazepam, but also has fewer side effects. Clonazepam 0.5 mg, titrating up to a maximum of 2 mg at bedtime, is usually effective. However, given that patients are at risk of cognitive impairment, somnolence and falls, this needs to be used with caution. I have often noted that symptoms of RBD often improve when levodopa or dopamine agonists are used for the first time in PD convertors (in which case trials of withdrawal of clonazepam or melatonin may be warranted). Stopping antidepressants can often help, although mild symptoms often persist. Paradoxically, in patients who already have RBD, antidepressants sometimes reduce episode frequency (because they reduce the amount of REM sleep).

(c) Follow-up – All patients with a diagnosis of idiopathic RBD should be periodically followed by a neurologist. I typically follow patients annually, unless motor/cognitive testing shows borderline results and likely conversion is in the near future. Patients often do not notice motor changes, so rely upon objective examination for this. As part of the follow-up, screen also for non-motor symptoms such as constipation, depression, etc.; even if neurodegenerative disease conversion has not occurred, symptomatic treatment of non-motor problems can improve quality of life.

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Treatment of Mild Cognitive Impairment in Parkinson's Disease

23

Melissa J. Armstrong

Case

A 68-year-old attorney with a 5-year history of Parkinson's disease (PD) presented for routine follow-up. He was a partner in his law firm and continued to practice. During the history he admitted that he was finding work increasingly challenging, more from a mental than physical standpoint. While he still responded well to levodopa/carbidopa motorically, he noticed that he was having increased difficulty framing his opening arguments during cases, particularly when he needed to make changes spontaneously. He also noticed more difficulty paying close attention in court and organizing his large workload. He did not think that any of his cases had suffered, but he was concerned that others in his office might start to notice that he was not performing at his prior level. He was debating changing his role or retiring. His medications included carbidopa/levodopa 25/100 mg, two tablets four times/day, pramipexole 0.5 mg three times/day, and medication for hypertension and hypercholesterolemia. He had no sleep complaints. He scored 26/30 points on the Montreal Cognitive Assessment (MoCA), losing 1 point for a minor error on the clock hands, 1 point for digit span backward, 1 point for sentence repetition (adding the word "the"), and 1 point for delayed recall (improving with a category cue). The history and cognitive screening suggested mild difficulties with attention and executive/visuospatial tasks as can be seen in PD, and his score of 26/30 on the MoCA was at the suggested cutoff for PD-MCI (cutoffs of ≤25 and ≤26 have each been recommended). The pros and cons of proceeding with formal neuropsychological testing were discussed, and he chose to defer testing. The suspicion of PD-MCI was discussed and the potential implications of this for long-term employment, including the likelihood of progression of his cognitive symptoms. He was encouraged to remain physically and mentally active and informed that there are no proven pharmacologic treatments for PD-MCI.

Discussion

Definitions "Mild cognitive impairment" (MCI) is a term that entered the medical lexicon in the 1990s. The term was initially used exclusively in the context of memory concerns, indicating the presence of memory impairment beyond what one would expect from normal aging but not meeting criteria for dementia. MCI in this "conventional" context is a risk factor for future Alzheimer's dementia, but many individuals with amnestic MCI do not progress to dementia in long-term follow-up.

The concept of MCI was first applied to PD in the mid-2000s and quickly gained acceptance within the field of movement disorders. Initial criteria for Parkinson's disease-mild cognitive impairment (PD-MCI) mimicked those proposed for conventional MCI, requiring a cognitive complaint from the patient or a close contact, evidence of cognitive deterioration in at least one of five cognitive domains (frontal/executive, amnestic, visuospatial, attention, language), and absence of significant functional decline. A Movement Disorder Society (MDS) Task Force published diagnostic criteria for PD-MCI in 2012 (Table 23.1).

A diagnosis of PD-MCI (and MCI in general) can be further classified by the type of MCI, including (1) single domain versus multiple-domain MCI (based on the number of domains demonstrating impairment) and (2) amnestic versus non-amnestic MCI (based on whether one of the impaired domains is memory).

Epidemiology PD-MCI is common in PD, with prevalence estimates varying by the criteria used. In early cross-sectional series, approximately one quarter of all non-demented patients with PD met criteria for PD-MCI. In more recent

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Table 23.1 Summary of Movement Disorder Society Task Force criteria for diagnosing PD-MCI

(1) Diagnosis of idiopathic PD; (2) gradual cognitive decline reported by the patient, close contact, or clinician; (3) cognitive deficits on testing; (4) retained functional independence (subtle difficulty on complex functional tasks allowed); (5) absence of dementia or other explanations for cognitive impairments (e.g., stroke, depression, medication side effects)	
PD-MCI Level I (abbreviated assessment) 1. Impairment on a global cognitive scale validated for use in PD 2. Impairment on at least two tests when a limited neuropsychological testing battery is performed (i.e., battery is insufficient for Level II assessment)	*PD-MCI Level II (comprehensive assessment)* 1. Neuropsychological testing includes at least two tests within each of five cognitive domains (executive, visuospatial, attention and working memory, memory, language) 2. Impairment on at least two tests (either within the same domain or in different domains), where impairment is defined in one of three ways: (a) Performance 1–2 SDs below norms (b) Significant decline from premorbid estimates (c) Significant decline present on serial examinations

Adapted from: Litvan I, Goldman JG, Tröster AI, Schmand BA, Weintraub D, Petersen RC, et al. Diagnostic criteria for mild cognitive impairment in Parkinson's disease: Movement Disorder Society Task Force guidelines. Mov Disord. 2012;27(3):349–56. With permission from John Wiley and Sons

PD-MCI Parkinson's disease-mild cognitive impairment, *PD* Parkinson's disease, *SD* standard deviation

cross-sectional series using the MDS Task Force criteria, approximately 20–35% of non-demented PD patients met criteria for PD-MCI. However, Task Force criteria require evidence of cognitive impairment on testing as compared to population norms, which may underestimate declines in patients with PD and high levels of education. If diagnosing PD-MCI by considering a decline from estimated premorbid functioning, the prevalence of PD-MCI was as high as 80% in a highly educated cohort. PD-MCI is also common in newly diagnosed incident PD cases, with a reported frequency of over 40% using MDS Level II criteria. PD-MCI is more common with increasing age, longer PD duration, more severe motor impairments, and the presence of depression.

The most commonly identified PD-MCI subtypes vary between and also within studies, reflecting considerations such as the specific neuropsychological testing performed and the cutoffs used (e.g., 1 versus 1.5 SD below the norm). Numerous studies suggest that executive and visuospatial impairments are the most common deficits seen in PD-MCI, but other studies describe memory as the most commonly impacted domain. Of the five domains considered in the MDS criteria – frontal/executive, amnestic, visuospatial, attention, and language – it is clear that the first four are the most commonly involved in PD. True language deficits are relatively uncommon in PD, though "tip of the tongue" difficulties (where patients describe knowing what they want to say but having difficulty retrieving the correct word from memory in the moment) are a frequent complaint. Most patients with PD-MCI meet criteria for multidomain impairment.

Diagnosis Given the frequency of cognitive impairment in PD – both PD-MCI and PD dementia (PDD) – clinicians should be alert for development of this complication. The American Academy of Neurology updated quality measurement set recommends screening for cognitive impairment in PD at least annually using one of several tools, overlapping with tools recommended by the MDS Task Force. Screening tests mentioned in both publications include the MoCA, the Parkinson's Disease – Cognitive Rating Scale (PD-CRS), the Dementia Rating Scale (DRS, with the MDS Task Force mentioning the Mattis Dementia Rating Scale [MDRS] and the AAN measure set mentioning the DRS-2), and the Scales for Outcomes of Parkinson's Disease – Cognition (SCOPA-Cog). The MoCA is generally considered superior to the Mini-Mental State Examination (MMSE) for screening in PD given greater coverage of executive-visuospatial tasks with the MoCA and a ceiling effect with the MMSE. Studies have suggested cutoff scores of ≤25 or ≤26 for screening for PD-MCI using the MoCA.

Clinicians vary on approaches to ordering neuropsychological testing to further evaluate cognition in patients with PD and early cognitive complaints. Reasons to order formal neuropsychological testing include better assessment of highly educated individuals for whom screening tests may miss cognitive changes, establishing a baseline to which to compare future assessments, identifying weaknesses that might impact employment, and/or further investigating the overall profile in patients with an unusual cognitive presentation (e.g., to evaluate for the possibility of alternate or comorbid diagnoses). The MDS Task Force for PD-MCI provides examples of what tests could be considered when a formal neuropsychological evaluation is performed; follow-up work suggests that using a neuropsychological battery with two tests per domain is both practical and sufficient (Table 23.2). While most applications of MCI criteria use a cutoff score of 1.5 SD below appropriate norms to suggest

Table 23.2 Suggested neuropsychological battery for diagnosing PD-MCI by MDS Task Force criteria

Domain	Neuropsychological tests
Executive function	1. Clock drawing 2. Trail Making Test – B
Visuospatial	1. Judgment of Line Orientation 2. Intersecting pentagons
Attention/working memory	1. Symbol Digit Modalities Test 2. Trail Making Test – A
Memory	1. Free and Cued Selective Reminding Test 2. Figural memory learning and delayed recall
Language	1. Boston Naming Test 2. Category fluency: animal naming

Based on results from: Goldman JG, Holden S, Ouyang B, Bernard B, Goetz CG, Stebbins GT. Diagnosing PD-MCI by MDS Task Force criteria: how many and which neuropsychological tests? Mov Disord. 2015;30(3):402–406

PD-MCI Parkinson's disease-mild cognitive impairment, *MDS* Movement Disorder Society

cognitive impairment, research suggests that a cutoff of 2 SD may have better sensitivity and specificity when using MDS Level II criteria for PD-MCI. It is unlikely that many neuropsychologists have implemented this during interpretation in routine clinical practice, but it should be kept in mind when clinicians are reviewing neuropsychological testing results.

Prognosis In both conventionally defined MCI and PD-MCI, there are three trajectories for the prognosis: persistence in the MCI state, progression to dementia, or reverting to normal cognition. As many as 20% of people classified as PD-MCI using MDS PD-MCI Level I criteria revert to normal cognition on follow-up assessment; less than 10% revert to normal using Level II criteria. "Reverting" to normal is likely an artifact of applying PD-MCI criteria rather than a true improvement in an individual's underlying state. It could also reflect a change in medication (e.g., cessation of cognitive-impairing medications like anticholinergics) or successful treatment of sleep disturbance or depression. In patients with conventionally defined MCI, there is some evidence that individuals who revert to normal cognition on follow-up testing have an intermediate risk of dementia between those with persistent MCI and those who never received an MCI diagnosis, but this is not well-studied in Parkinson's disease.

In stark contrast to conventionally defined MCI, which is a risk factor for dementia but with which most patients will not become demented, PD-MCI is considered a transitional cognitive state to dementia. In a recent longitudinal study, all incident cases of PD-MCI progressed to dementia within 5 years of PD-MCI diagnosis using MDS Level I criteria. This is not surprising given that most individuals with PD will develop dementia if they live long enough with the disease.

Treatment Treating individuals with PD-MCI starts with addressing modifiable risk factors, including weaning medications with cognitive side effects such as anticholinergics. While not proven to help individuals with PD-MCI, addressing sleep disturbances such as obstructive sleep apnea (linked to dementia) and/or decreased sleep efficiency (associated with impairments in working memory) is an important element of overall care. Treating depression and anxiety is important for quality of life in PD in general and also has potential cognitive implications.

There are no current proven cognitive-enhancing pharmacologic strategies for treating PD-MCI. Recent trials of rasagiline and rivastigmine showed no evidence of cognitive improvement in PD-MCI. Cognitive training in patients with mild-moderate PD may have modest cognitive benefits but this has not been studied specifically in PD-MCI. Similarly, physical exercise programs may improve cognition in PD, particularly executive function, but specific evidence for PD-MCI is lacking. Given existing research, maintaining physical and mental activity in PD-MCI is prudent, particularly given other known benefits of physical exercise in PD. Several pharmacologic and non-pharmacologic studies for PD-MCI are underway and clinicians can refer interested patients to www.clinicaltrials.gov for available opportunities.

Prognostic counseling for patients with PD-MCI and their families is critical but also delicate. While research shows that some individuals with PD-MCI will "revert" to normal on follow-up testing, the general trend for cognition in PD is that of gradual decline, with most if not all patients with PD-MCI transitioning to PDD in subsequent years. Implications for employment and long-term planning are highly patient-specific, and discussions will be tailored to individual scenarios.

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Treatment of Dementia in Parkinson's Disease

24

Jennifer G. Goldman

Case

This patient is a 75-year-old man who had Parkinson's disease (PD) for about 8 years. His PD symptoms began with a rest tremor in his right hand, which later progressed to involve his right leg as well as left hand. He noted slowness, stiffness, micrographia, and a shuffling gait. He was treated with carbidopa/levodopa with doses increased over the years to a total of 800 mg/day. He developed wearing off as his disease progressed for which entacapone 200 mg was added to each carbidopa/levodopa dose. More recently, he developed peak-dose dyskinesias and was treated with amantadine 100 mg three times daily.

Over the last 3 years, he reported a decline in his thinking and that his "memory was bad." He found that it was more difficult to come up with the words that he wanted to say. He also seemed to have a harder time keeping up with his hobbies and learning how to work new appliances at home. His wife noticed that he was getting confused with directions when driving and when leaving a tip at a restaurant. He made occasional errors in paying their bills and in setting up his medication pill containers, and as a result his wife has now taken charge of these tasks. In addition, his wife felt that he was not as motivated to participate in activities and stopped going to his exercise class since he wanted to sleep much of the afternoon. More recently, he experienced occasional hallucinations seeing people outside the kitchen window.

His medical history was significant for benign prostate hyperplasia, orthostatic hypotension, depression, and osteoarthritis. Medications at his visit included carbidopa/levodopa 25/100–2 tablets four times daily, entacapone 200 mg four times daily, amantadine 100 mg three times daily, sertraline 100 mg daily, tamsulosin 0.4 mg daily, and tramadol 50 mg as needed. On examination, his sitting blood pressure was 118/70 with pulse 76, which dropped to 96/60 with pulse 78 when standing. Neuropsychological evaluation revealed impairment on tests of global cognition (Montreal Cognitive Assessment [MoCA] total score of 23/30) and moderate deficits on tests of attention, executive function, verbal fluency, visuospatial function, and delayed recall with better performance on recognition. He had moderate bradykinesia, rest tremor, and rigidity, worse on his right than left side. He had difficulty arising from a seated position and moderately flexed posture. He took small, shuffling steps, with start hesitation and intermittent freezing. Postural instability was present on the pull test. The rest of the neurological exam was normal.

Discussion

Dementia is a frequent complication of long-standing PD. Cross-sectional prevalence estimates of PDD are about 40% of PD, and several longitudinal studies reveal that up to 80% of PD patients ultimately develop dementia after 8 or more years of disease. PDD has been defined as a syndrome with an insidious onset, impairment in more than one cognitive domain, and having a significant impact on activities of daily living. In contrast to the dementia associated with Alzheimer's disease (AD), PDD, as defined by the Movement Disorder Society (MDS) Task Force criteria by Emre et al. in 2007, does not necessarily require that memory is impaired. Rather, PDD can manifest with impairment in non-memory cognitive domains (e.g., executive function, attention, language, visuospatial function), though declarative memory functions can be affected. Executive function, visuospatial function, and memory are among the most commonly affected cognitive areas in PDD. Symptoms of PDD reported by the patients and/or caregivers and recognized by the clinician and/or neuropsychologist include slowed thinking, trouble with paying attention and

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concentration, problems with multitasking or planning, difficulty switching tasks or starting new ones, forgetfulness or short-term memory problems, or difficulty with one's sense of direction. While language (i.e., confrontational naming) is generally less affected, PD patients often report difficulty finding the "right words." As in this patient, behavioral issues can frequently be found in PDD. These neuropsychiatric complications include psychosis, sleep disturbances (especially daytime sleepiness), and mood disturbances. This patient had a history of depression and was treated with an antidepressant (sertraline). In addition, he was noted to have apathy, was sleepy during the daytime, and had visual hallucinations. Unfortunately, PDD is generally associated with poor outcomes, negatively impacting patients' quality of life, contributing to morbidity and mortality, and increasing nursing home placement. Furthermore, PDD is associated with high rates of caregiver stress and burden. This case illustrates that his wife needed to take on additional responsibilities (paying the bills, managing medications) as the patient had increasing cognitive difficulties. These factors are frequently associated with increased caregiver strain.

Many demographic, clinical, and biomarker features have been assessed as potential risk factors for developing PDD, though some findings vary across studies. The most consistently reported risk factors for PDD in longitudinal studies include older age; more severe parkinsonism, especially with postural instability and gait disturbance; mild cognitive impairment at baseline; and cognitive deficits especially affecting visuospatial, memory, and language functions. Other features have been inconsistently reported including older age at PD onset, male gender, lower education, and presence of depression or hallucinations. Certain mutations or variants in the GBA, MAPT, or APOE epsilon e4 genes may also confer increased PDD risk. Other biomarkers such as brain atrophy patterns on MRI scans or abnormal perfusion, metabolism, or blood flow on PET or SPECT scans; cerebrospinal levels of alpha-synuclein, amyloid-beta, and tau proteins; or changes on electroencephalograms may be associated with PDD risk but await additional study.

Cognitive function in PD can be examined in numerous ways, ranging from "bedside" tests by the clinician to formal evaluations by a neuropsychologist. It is important to have an informant provide commentary on the patient's current and past cognitive functions, especially if there is concern for mild cognitive impairment or dementia. Cognition in PD can be assessed by tests of global cognitive performance (e.g., Mini-Mental State Examination, MoCA, Mattis Dementia Rating Scale, PD – Cognitive Rating Scale, Scales for Outcomes of Parkinson's Disease – Cognition, among others) and with tests targeting individual cognitive domains and functions (e.g., orientation, attention, working memory, processing speed, executive function, memory, language, abstract reasoning, visuospatial abilities, and praxis). Cognitive tests vary in their sensitivity to PD cognitive deficits and optimal use (e.g., screening, response to change or intervention). To date, there is no consensus regarding specific neuropsychological test batteries, or even global tests, though reviews and literature provide recommendations for global and domain-specific tests. A key feature of dementia is that the cognitive deficits have a significant impact on the person's daily life functioning. Several reasons make it challenging to assess the functional impact of cognitive deficits in PD; these factors include difficulty in separating cognitive from motor and other non-motor deficits in PD, recognizing changes in a person who is highly functioning or alternatively who is not very active functionally, and a paucity of functional outcome instruments specific for PD. One simple test to assess decline in cognitive function and its impact on daily life was proposed by Dubois et al. in 2007. The test included a "bedside" assessment of whether the person with PD could describe his or her medication regimen, spontaneously and clearly including the drugs, doses, and timing of treatment. Conferring with the PD patient's caregiver also provides information on whether the patient can safely and reliably take his or her medications without supervision in daily life. This patient was having trouble handling his medications, and his wife had to assume these responsibilities.

For an overview of the diagnosis and management of PDD, see Fig. 24.1. In the evaluation for acute or new onset cognitive issues in PD, one should exclude infections (e.g., urinary tract infection, pneumonia), metabolic derangements, dehydration, new neurological problems (e.g., stroke, subdural hematoma, especially in the setting of PD falls), new medical problems (e.g., B12 deficiency, thyroid disorders), or medication effects (e.g., pain, bladder, sedating medications). It is important to inquire about other comorbid neuropsychiatric problems including poor nighttime sleep, excessive daytime sleepiness, psychosis, depression, anxiety, and apathy, which may influence cognitive function and are frequent comorbidities in PDD. These neuropsychiatric symptoms may require medication treatments of their own, which in turn may have some benefit for the cognitive symptoms. Orthostatic hypotension is common in PD, particularly as the disease advances and with increasing doses of dopaminergic therapy, and may require intervention. Low blood pressure, or drops in blood pressure, can contribute to symptoms of cognitive slowing or "fogginess," sleepiness, and fatigue. In addition, careful review of medication lists should be undertaken including examining PD medications with anticholinergics, dopamine agonists, and amantadine (especially with its renal clearance) being a concern, as well as centrally acting medications for pain, bladder control, or other reasons. These medications may need to be stopped or reduced as they can contribute to impaired cognitive function.

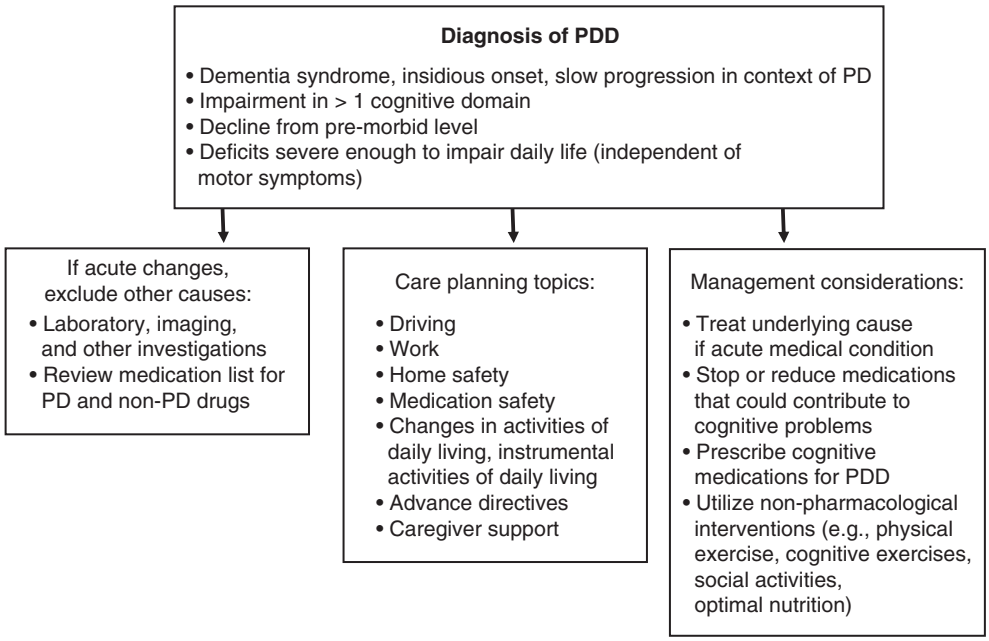

Fig. 24.1 Overview of the diagnosis and management of PDD

Table 24.1 Drug dosing

	Approximate maximum daily dose	Frequency
Rivastigmine oral	12 mg/day	Twice daily
Rivastigmine patch	13.3 mg/day	Daily
Donepezil	10 mg/day	Daily
Galantamine	24 mg/day	Twice daily
Memantine	20 mg/day	Twice daily

In the patient presented here, one may need to check renal function as amantadine is cleared by the kidneys, and increased amantadine levels can contribute to confusion, cognitive impairment, and psychosis. Moreover, the patient should minimize his pain medications, including tramadol, and consider low-potency, non-central nervous system-acting medications such as nonsteroidal anti-inflammatories. Discussions regarding driving, home safety issues, and medication management are also essential.

The medications considered for treating PDD are rooted in drugs developed for AD such as cholinesterase inhibitors (e.g., rivastigmine, donepezil, galantamine) and the NMDA antagonist, memantine due to the cholinergic deficits associated with neuropathology in AD and PDD (Table 24.1). To date, only rivastigmine has been approved by the US Food and Drug Administration (FDA) for the treatment of mild to moderate PDD based on a randomized, double-blind, placebo-controlled 24-week trial of over 500 mild-moderate PDD subjects who showed a modest but statistically significant improvement on the AD Assessment Scale – Cognitive (ADAS-Cog). Rivastigmine received this FDA indication in 2006. It inhibits both butyrylcholinesterase and acetylcholinesterase, unlike donepezil, which selectively inhibits acetylcholinesterase, and is available in two formulations (oral pills or a transdermal patch). Donepezil also was studied in a large double-blind, placebo-controlled trial, with a similar number of subjects as the rivastigmine PDD trial. The ADAS-Cog demonstrated similar effects at 24 weeks, after removing a treatment-by-country interaction, and there was also improvement on the clinician's interview-based impression of change plus caregiver input at 10 mg daily. Side effects with cholinesterase inhibitors include nausea and gastrointestinal problems (less so with the transdermal formulation of rivastigmine), increased tremor and parkinsonism, and bradycardia and syncope. These side effects are of particular relevance to PD patients who may already have gastrointestinal problems, tremor, and low blood pressure or orthostatic hypotension at their baseline. Clinical effects of cholinesterase inhibitors on cognitive functions in PDD, however, are modest, at best. In the 2006 American Academy of Neurology (AAN) Practice Parameters, rivastigmine and donepezil were considered Level B. After the AAN 2006 publication, one new study with galantamine was published by Litvinenko et al. in 2008. In this open-label, parallel group study, 41 PDD patients received either galantamine or their pre-existing therapy for 24 weeks. The study included a number of cognitive measures which improved in the galantamine-treated group, but a primary outcome was not specified. Based on the available cholinesterase inhibitor studies in PDD, the MDS Evidence-Based Medicine review (published in 2011 with revisions in 2012) classified these medications in terms of efficacy, safety, and practice

implications as follows: rivastigmine (efficacious, acceptable risk without specialized monitoring, and clinically useful), donepezil (insufficient evidence, acceptable risk without specialized monitoring, and possibly useful), and galantamine (insufficient evidence, acceptable risk without specialized monitoring, and investigational).

Double-blind, placebo-controlled studies with memantine in PDD reveal mixed results. In one study, memantine was studied in 72 patients with PDD or dementia with Lewy body (DLB) patients (dementia preceded the motor parkinsonism); at week 24, the primary outcome measure of clinical global impression of change demonstrated significantly greater improvement in the memantine group compared to placebo. However, in another study of 199 patients (PDD and DLB), the PDD group treated with memantine did not demonstrate significant improvement in the AD Cooperative study (ADCS)-clinical global impression of change scores compared to the placebo group. In addition, the Neuropsychiatric Inventory scores did not reveal significant improvement in the PDD memantine-treated group compared to placebo group. The MDS Evidence-Based Medicine review (2012) classified memantine in terms of efficacy, safety, and practice implications as follows: insufficient evidence, acceptable risk without specialized monitoring, and possibly useful.

Currently, medications that act on the serotonergic system are under study in PDD. One such trial is a phase II, randomized, double-blind, placebo-controlled study in PDD evaluating the safety, tolerability, and efficacy of SYN120, a dual 5-HT6/5-HT2A antagonist in patients already treated with a stable dose of a cholinesterase inhibitor (www.clinicaltrials.gov). The 5-HT6 and 5-HT2A receptors are widely distributed in brain regions involved in cognitive processes, psychosis, and mood, including the prefrontal cortex and hippocampus. Other trials in PDD include small, pilot studies of deep brain stimulation in the bilateral nucleus basalis of Meynert, a site implicated in attention, learning, and memory and affected in AD and dementia in PDD patients (www.clinicaltrials.gov). There is a growing interest in non-pharmacological strategies for treating PDD and cognitive impairment. These strategies include physical exercise, cognitive training, music and art therapy, and certain nutritional intake or types of foods. To date, many studies are open-label pilot studies, small trials, or limited randomized controlled trials. Larger and more rigorous studies are needed and will contribute to our ability to provide evidence-based recommendations.

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Treatment of Anxiety in Parkinson's Disease

25

Adriana P. Hermida

Case

The patient is a 68-year-old woman with a history of Parkinson's disease (PD) since the age of 49. Deep brain stimulation (DBS) therapy in the internal globus pallidus (GPi) was bilaterally implanted at the age of 62. She was referred to the geriatric psychiatry outpatient service for the management of her anxiety disorder. At the time of the evaluation, the patient was experiencing debilitating anxiety symptoms which included a sense of losing control, palpitations, difficulty breathing, fear that she was choking, feeling like she could not move, intense anxiety, a feeling of "going crazy," and an intense fear of dying. These symptoms were episodic and intense in nature with no identified triggers. They generated frequent phone calls (5–10 times per day) to 911. She was taken to the emergency room on several occasions where a cardiovascular work-up was negative. At the time of the consult, the patient was taking carbidopa/levodopa 25 mg/100 mg QID and clonazepam 1 mg four times per day. She would not leave the house due to a fear of being alone and having a "heart attack." At the time of the psychiatric evaluation, it was identified that her symptoms coincided with the wearing-off periods of carbidopa/levodopa. The initial step taken was to increase the frequency of carbidopa/levodopa dosing along with the addition of an extended release dose at bedtime. This strategy only provided partial relief. Escitalopram 10 mg per day was added to target the ongoing anxiety, which was eventually titrated to 20 mg per day. Due to the risks associated with benzodiazepines in the elderly and the partial improvement with escitalopram, clonazepam was slowly decreased to 0.5 QID, but the patient was still having anxiety symptoms, and the calls continued to 911 though with less frequency. Mirtazapine 15 mg at bedtime was added as an antidepressant augmentation strategy, which resulted in partial improvement. Escitalopram was tapered and venlafaxine was slowly titrated over 4 weeks to 225 mg per day. This led to improvement in anxiety symptoms, allowing for a further taper of clonazepam to 0.25 mg in AM, 0.25 mg at noon and 0.5 mg at bedtime. She was referred to weekly sessions of cognitive behavioral therapy (CBT) and some sessions of mindfulness-based cognitive therapy (MBCT), which helped significantly. She was then able to decrease her clonazepam to 0.25 mg twice per day. Her calls to 911 subsided, and she started to leave the house without fear of dying. Her quality of life drastically improved. Future plans include discontinuing the clonazepam and continuing psychotherapy.

Discussion

Anxiety disorders are common in PD, with reports on the prevalence in the literature ranging from 6% to 55%. According to a recent systematic review, the average point prevalence of anxiety disorders in PD is 31%. Up to 55% of patients have significant anxiety symptoms that impact quality of life, but do not meet criteria for a defined diagnosis. This discrepancy could be explained by the fact that most anxiety rating scales are not applicable for patients with PD. Some anxiety disorders in PD occur with a fluctuating nature not captured by available scales. The positive predictive values of these scales are suggested to be low in PD and likely contribute to poor diagnostic accuracy. Additionally, some studies have not included the differential diagnoses included in the anxiety spectrum, such as specific phobias, social phobia, agoraphobia, substance−/medication-induced anxiety disorders, or anxiety disorders due to another medical condition. This could easily lead to an underestimation of the true prevalence of anxiety disorders in PD.

Some studies have reported that the severity of PD symptoms, not the duration of illness, is positively associated with

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anxiety. PD patients with postural instability and gait dysfunction are more likely to experience anxiety than tremor-dominant patients. Additionally, PD patients who experience an earlier onset are more likely to experience anxiety symptoms compared to those with later onset.

Comorbid anxiety with depression has been observed in 14–55% of patients with PD. Menza and colleagues reported a depressive disorder in 92% of PD patients diagnosed with an anxiety disorder, and an anxiety disorder was present in 67% of depressed PD patients. These disorders are highly comorbid and the treatment approach is similar. Both disorders have been reported as potentially prodromal to the motor aspects of PD with some studies reporting the presence of anxiety and depression up to 10 years prior to the formal diagnosis of PD.

Generalized anxiety disorder (GAD) is the most frequent anxiety disorder in PD. According to the *Diagnostic and Statistical Manual of Mental Disorders (DSM)-5* definition, GAD includes excessive anxiety and worry (apprehensive expectation) relating to various activities. The symptoms must last 6 or more months and be present for the majority of that time period. The symptoms are difficult to control and are associated with three or more of the following symptoms: restlessness or feeling keyed up, becoming easily fatigued, concentration difficulties, irritability, muscle tension, and sleep disturbances. The symptoms cause clinically significant distress, impairing functioning, and are not attributable to the physiological effects of a substance or another medical disorder.

Social phobia is the marked fear of one or more social situations where the individual can be exposed to scrutiny. A frequent fear in patients with PD is about being observed while eating or drinking in public, where their symptoms may become exposed. The patient is concerned that the symptoms of PD will result in humiliation and embarrassment. These social situations provoke fear or anxiety, often resulting in avoidance and intense fear. To meet the DSM 5 criteria for social phobia, the fear, anxiety, or avoidance must cause clinically significant distress or impairment in social, occupational, or other areas of functioning.

Anxiety not otherwise specified is now classified in the DSM-5 as either "other specified anxiety disorder" or as "unspecified anxiety disorder." The former is used when the clinician chooses to communicate the specific reason that the presentation does not meet the criteria for any specific anxiety disorder (e.g., insufficient time to meet the diagnosis). The latter is used when the anxiety symptoms do not meet the full criteria for an anxiety disorder diagnostic class, the clinician chooses not to specify a reason that the presentation does not meet criteria for a specific anxiety disorder, and/or there is insufficient information to make a more specific diagnosis.

Specific phobia is the marked fear or anxiety about a specific situation, which almost always provokes immediate fear or anxiety. The phobic situation is actively avoided or endured with intense fear, the symptoms are out of proportion to the actual danger posed by the specific situation, and they cause clinically significant distress and functional impairment. Patients with PD may present with specific phobias of falling, fear of "off" periods, and fear of immobilization (or "freezing").

Panic disorder is the recurrent unexpected presence of panic attacks, where there is a surge of intense fear or intense discomfort that reaches a peak within minutes. Four or more of the following symptoms must be present: palpitations, sweating, trembling, sensation of shortness of breath, feeling of choking, chest pain, nausea or abdominal distress, dizziness, chills or heat sensation, paresthesias, feelings of unreality, fear of losing control, or fear of dying. To meet criteria for panic disorder, panic attacks should be present with the persistent concern of either additional panic attacks, losing control, having a "heart attack," or "going crazy" as we described in our case.

Agoraphobia is marked fear or anxiety relating to at least two of the following five situations: using public transportation, being in open spaces or enclosed spaces, standing in line or in front of a crowd, or being outside the home alone. These situations are actively avoided or require the presence of a companion. It is very common for PD patients to avoid going out of their houses or being in a crowd. Increased level of dependency on others is common; however the fear of being alone or outside the house is clearly excessive when compared to a typical patient with PD.

At the time of this writing, there are no randomized controlled trials regarding anxiety in patients with PD. Most of the available data comes from studies on depression in PD that reported anxiety as a secondary outcome. Further, the treatment of anxiety in PD is also extrapolated from the treatment for the general adult population. There is limited evidence for the efficacy of SSRIs and SNRIs; however, their anxiolytic properties and safer side effect profile make them reasonable treatment options.

Patients may experience feelings of despair, hopelessness, and panic that are reduced or negligible during an "on" phase. The first step in such cases is to take a detailed history regarding the timing of the symptoms and their correlation with the wearing-off phenomena. It is common to have these symptoms as non-motor fluctuations, the most common of which is described as uncomfortable anxiety or inner jitteriness. These can be accompanied by slowed thinking, fatigue, a sense of panic, hot flashes, and akathisia. If there is a clear correlation, the initial step is to *adjust the timing and increase the frequency of the PD medications* as done in this case. It is important to keep in mind that increasing the PD medica-

tions can exacerbate other neuropsychiatric disorders such as hallucinations, delusions, dopamine dysregulation syndrome, and impulse control disorder.

If that strategy does not improve the symptoms, the next step would be adding an anxiolytic medication. See Table 25.1 for medications and doses utilized to treat anxiety in PD. An *SSRI* would be the first choice. Initiating citalopram (up to 20 mg/day in patients older than 65 due to risk of QT prolongation), escitalopram (up to 20 or 30 mg/day), or sertraline (up to 200 mg/day) with careful titration would come first. The goal is to start low and increase the dose slowly. Reaching therapeutic doses is important before determining that a medication has failed. Occasionally, SSRIs may worsen tremors and could cause hyponatremia. If there is a partial response, *augmentation* could be considered with the addition of a medication with different neurotransmitter affinity, such us mirtazapine (15–30 mg at bedtime). It is an alpha-2 adrenergic antagonist and 5HT2/5HT3 antagonist. It is important to take into consideration that lower doses of mirtazapine are generally considered more sedating than higher doses. It could also exacerbate REM sleep behavior disorder and there are rare reports of agranulocytosis. Mirtazapine at bedtime can augment an SSRI and provide additional benefits of improved sleep, improved appetite, along with a decrease in nausea and anxiety symptoms. Furthermore, some studies have shown mirtazapine to attenuate tremors and levodopa-induced dyskinesias.

When the above strategies fail, *SNRIs* such as venlafaxine (up to 300 mg/day) and duloxetine (up to 90 mg/day) should be considered as we did in the case above. Venlafaxine can increase blood pressure; duloxetine should be avoided in patients with hepatic impairment and a history of alcohol abuse. Newer SNRIs include desvenlafaxine and levomilnacipran.

Vilazodone (an SSRI that partially agonizes 5-HT1A) and vortioxetine (an SSRI with additional properties that antagonize serotonin-5-HT3 receptors and agonize 5-HT1A) have been prescribed to help anxiety symptoms in adults without PD. No studies or case reports have been published for their use in PD.

Another augmentation strategy is the addition of *buspirone*, *a* 5HT1A partial agonist (10–40 mg/day). It is an anxiolytic with delayed onset of action (approximately 2 weeks). Dosing this medication three to four times per day, an hour or two before the next PD medication dose could help ameliorate anxiety related to the wearing-off symptoms. Of note, higher doses of buspirone (100 mg/day) may worsen anxiety and parkinsonism.

Benzodiazepines (BZD), commonly used in movement disorder clinics for the treatment of REM behavior disorder and anxiety disorders, can be effective in treating anxiety and panic attacks, though long-term use may be problematic. BZD are associated with increased gait instability, falls, worsened cognitive function, and risk of tolerance and dependence. Generally, the use of BZD should be discouraged or used with caution; it is important to discuss in detail risks versus benefits with patients and families. Counseling about the potential addictive properties of these medications should always be done prior to prescribing.

Use of *non-pharmacological* therapies such as mindfulness-based cognitive therapy (MBCT) and cognitive behavioral therapy (CBT) has been shown to be effective in treating anxiety disorders in PD patients. CBT focuses on the development of personal coping strategies that target solving current problems and changing unhelpful automatic negative thoughts. While the concept of mindfulness originated from Eastern spiritual and cultural contemplative traditions (e.g., Buddhism), it has also been described in psychological terms as paying attention on purpose to the present moment with

Table 25.1 Drug therapy for anxiety in PD

Medications use to treat anxiety in PD	Approximate target daily dose	Clinical pearls
Citalopram	Max 40 mg in younger pts. max 20 mg in patients >60 y/o. Once per day	Black box warning for possible QTc prolongation
Escitalopram	20 mg per day (typically in AM)	Start 10 mg per day. Some patients need up to 30 mg
Sertraline	200 mg per day (typically in AM)	Could cause diarrhea. Titrate from 25 mg in elderly pts. Increase weekly
Mirtazapine	15–45 mg at bedtime	Lower doses are generally more sedating
Venlafaxine	Max 300 mg per day. (typically in AM)	It requires a titration Monitor BP
Desvenlafaxine	50–100 mg per day. (typically in AM)	Titration not needed It has relatively higher norepinephrine reuptake inhibition than venlafaxine Monitor BP
Duloxetine	60 mg per day. (typically in AM)	Approved also for diabetic peripheral neuropathic pain, fibromyalgia, chronic musculoskeletal pain
Vilazodone	20–40 mg per day	Give with food Increase dose no more frequently than q 7 days
Buspirone	5–10 mg BID to QID	Max 60 mg per day. Watch for serotoninergic syndrome when augmenting an SSRI

Fluoxetine may not be a good option due to drug-drug interaction as it is a potent 2D6 inhibitor

Paroxetine typically not used in elderly patients, as it is highly anticholinergic, could worsen cognitive deficits and is a potent 2D6 inhibitor

nonjudgmental attitude to one's inner and outer experience. Both mindfulness-based cognitive therapy (MBCT) and mindfulness-based stress reduction (MBSR) were developed by clinical groups to address physical and mental health issues and have been showing a positive effect in treating psychiatric comorbidities in PD. In particular, these therapies can be used for the treatment of social phobia, specific phobias, agoraphobia, and panic disorders. The combination of medications and therapy has demonstrated efficacy in the treatment of anxiety disorders in the general population. An 8-week Australian study on mindfulness training and a Belgium longitudinal single-blind randomized controlled trial on mindfulness training showed quantitative benefit in motor functioning, pain, and general improvement in neurobehavioral aspects of PD. Mindfulness offers more participation, empowering the individual to learn how to strengthen internal resources to help cope with neuropsychiatric symptoms related to PD. A body awareness training in the treatment of wearing-off-related anxiety in patients with PD (BEWARE) from the Netherlands has shown to be successful in educating patients about the motor fluctuations and the wearing-off phenomena associated with PD treatments; it has been useful in improving anxiety symptoms in patients with PD-related anxiety disorders.

It is clear that attention to recognizing and treating clinically significant anxiety in PD can greatly enhance quality of life in this population.

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Treatment of Depression in Parkinson's Disease

26

Irene Hegeman Richard

Case

A 62-year-old woman, diagnosed with Parkinson's disease (PD) about 6 years earlier, was seen in routine follow-up. Her initial symptoms were rest tremor and diminished dexterity in her right hand. She was first started on selegiline, and, about a year later, as her motor symptoms progressed and began to impact function, carbidopa/levodopa was added, which was effective and was maintained on a TID schedule for the next 2 years. At that time she began to experience wearing off so the carbidopa/levodopa schedule was modified to QID, after which amantadine was added for emerging and troublesome dyskinesias with some noted benefit.

Her spouse accompanied her to this visit. She noted some wearing off, generally about 30 min prior to her next scheduled levodopa dose. Dyskinesias were occasionally present but not troublesome. She denied any dizziness upon standing, hallucinations, or issues with gait/balance. She endorsed problems sleeping, both with falling asleep and staying asleep, fatigue, and difficulty concentrating. Her husband notes that she has been reluctant to go to the movies, which they had always enjoyed on a fairly regular basis. He also reports that she seems anxious at times and has become tearful and despondent, commenting that things seem to be in a downward spiral and she worries they are unlikely to get better. She also expressed feeling badly that she can't be like the others at her support group who remain optimistic, despite having even more severe symptoms and, in one man's case, recently suffering the loss of his spouse. She notes that she has a supportive, healthy family and friends and is financially secure, but somehow she still can't be thankful and "get over it."

On exam, she is alert and fully oriented, responds rather slowly but appropriately to questions, follows all commands, can name and repeat without difficulty, and has difficulty spelling world backward – starting "D" and then stopping and noting that she "can't do it," appearing a bit anxious and frustrated. She is able to recall 2/3 objects spontaneously at 5 min, getting the third with cues. She has moderate hypomimia and hypophonia, mild rigidity and moderately impaired finger and heel tapping bilaterally, and an intermittent resting tremor in the right upper and lower extremities. She is able to arise slowly from a seated position with arms crossed and ambulate independently, albeit slowly with diminished arm swing bilaterally and normal response to retropulsion pull testing. Overall bradykinesia is moderate.

Discussion

Given the fact that approximately 50% of patients with PD suffer from clinically significant depressive symptoms which have a major negative impact on quality of life, it is important for anyone treating patients with PD to be able to recognize the symptoms and understand the various approaches toward its treatment.

Recognizing and diagnosing depression in PD can be challenging, in large part due to the number of shared signs and symptoms. One has to be on "high alert" regarding the potential for the presence of depression in PD. Most patients do not spontaneously report a mood disorder. Some patients lack insight, while others may be concerned about the stigma associated with psychiatric symptoms. The other symptoms generally seen as part of a depressive disorder (e.g., insomnia, fatigue, decreased concentration) and signs (decreased facial expression, poverty of movement, speech with low volume and reduced inflection) may be easily attributed to the PD itself, or the medications used to treat it.

The most fruitful line of inquiry to assess depression in PD is regarding whether there is an issue with the mood

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itself. Even if someone denies feeling "depressed," it is worth probing further and providing them with alternative terms that likely represent the same phenomenon (e.g., sad, blue, down, etc.). Another core feature of depression may be anhedonia (an inability to experience pleasure), which can sometimes be tricky to pin down. There may be some overlap with apathy but a patient who is apathetic (in the absence of depression) lacks motivation but, if pushed to engage in an activity, may still enjoy it. Anhedonia should also be distinguished from simply being unable (or less apt to) participate in activities once enjoyed due to motor limitations imposed by their disease.

Ideational symptoms of depression may include feelings of hopelessness, helplessness (both of which were expressed by our patient), and suicidality. Ideational symptoms are sometimes referred to as "cognitive" symptoms but, when used in this broad sense, should not be confused with the actual impairment in cognition that patients with depression may experience. Cognitive impairment associated with depression is characterized mainly by difficulty concentrating but has significant overlap with the "frontal-subcortical" executive dysfunction that may occur in PD, even in the absence of depression. Our patient had a delayed response to questions, slightly reduced spontaneous recall but intact recognition, and difficulty concentrating (evidenced with difficulty spelling world backward, though with a likely influence of mood as evidenced by decreased effort and expressed frustration).

It is important to take a few minutes when interviewing the patient to ensure that one fully understands the nature of the "somatic" symptoms commonly associated with depression. Most of these symptoms can be due to a variety of causes that require different treatment approaches (e.g., difficulty sleeping may be due to anxiety, depression, medication side effects, nocturia, wearing off of levodopa). In our patient, it is possible that medications (selegiline and amantadine in particular) could contribute to insomnia. It is also possible that wearing off of her levodopa overnight could be associated with difficulty turning in bed or that a return of tremor after a brief arousal makes it harder to fall back to sleep. It is also possible that anxiety and depression are contributing to insomnia. The most likely scenario is that some combination of factors is responsible.

Apathy

It is important to note that, while decreased motivation and interest in activities may be a sign of depression, patients with PD can have apathy in the absence of depression. The best way to distinguish between apathy and depression is generally to ask the patient about their mood and the presence or absence of emotional distress. In depression, there is generally a negative valence to the emotional state. Patients will perceive their mood as negative in some way, generally at least somewhat distressing, even if they do not describe it as "depressed" (can ask if they are sad, blue, low, down or if they feel disconnected from others) or have other depressive cognitive content (i.e., hopelessness, helplessness, suicidal ideation). Patients with apathy in isolation will deny feeling distressed by their lack of motivation or desire. They are content with doing very little (or nothing). It is generally those around the patient who are upset by the apathetic patient's lack of motivation and/or interest. It is always good to explore symptoms further when a patient is noted to be apathetic to (1) ensure that it is not occurring in the context of a depressive disorder as this may be amenable to treatment and (2) educate caregivers that patients who experience apathy without depression (which may be associated with emerging cognitive impairment) may benefit from scheduled, structured activities. Many patients who have diminished motivation solely on the basis of apathy may be capable of participating in and even enjoying things once they become involved. At the very least, the caregivers for apathetic patients can be reassured that the patient is not likely to be experiencing the emotional distress generally associated with a depressed state.

Anxiety

Anxiety is also common in PD and can occur independently but frequently co-occurs with depressive symptoms. Our understanding of anxiety in PD, including its phenomenology, relationship to depressive symptoms and approach toward treatment is still evolving. There are no placebo-controlled clinical trials to guide the treatment of anxiety in PD. Interestingly, while both paroxetine and venlafaxine were associated with improvement on all of the depression rating scales in the clinical trial of antidepressants in PD, there was no similar improvement noted on the anxiety measure. In fact, further analyses suggest that higher baseline anxiety levels predicted poorer response to treatment of depressive symptoms.

Mood Fluctuations

Another feature of PD that makes the recognition and diagnosis of depression challenging is the frequency with which patients who are treated with dopaminergic medications experience state-related fluctuations. In addition to the classic motor fluctuations characterized by transition between "on" (i.e., optimal medication effect and mobility) and "off" (inadequate medication effect with impaired mobility), patients may also experience non-motor fluctuations, which

can include autonomic and sensory symptoms as well as changes in mood and levels of anxiety. Patients most frequently transition between normal mood and periods of dysphoria and/or anxiety with or without full-fledged panic attacks. Some patients with mood fluctuations may only experience dysphoria during their "off" state, whereas others may have a more pervasive disturbance of mood, perhaps with fluctuating severity. Mood fluctuations are frequently, but not uniformly, temporally correlated with motor fluctuations (the most common scenario being dysphoria and/or anxiety when off). It is important to ask patients about fluctuations in mood and to try to establish if there is a relationship to levodopa dosing. For patients whose dysphoria is transient and correlated with levodopa dosing, an adjustment of the antiparkinsonian medication regimen to prevent "off" time may suffice. This may include altering the frequency of levodopa dosing and/or addition of an agonist (see chapter on medical treatment of motor fluctuations). There is some evidence to suggest that pramipexole may have antidepressant efficacy above and beyond its impact on fluctuations. It is also important to realize that the diagnostic impression of a possible depressive disorder may be significantly influenced by the state of the patient at the time of the interview. Some patients undergo dramatic changes in mood states, appearing severely dysphoric and/or anxious, endorsing hopelessness and even suicidal ideation while "off" but become euthymic or even hypomanic (or at least in good spirits), and expressing optimism when "on." Such dramatic and frequent changes may leave the examiner (and the patient) scratching their heads when they continue the conversation in the alternate state, which might be in the context of follow-up call or visit, but for some patients it may happen within the same encounter.

Understanding Depression

In discussing a diagnosis of depression with a patient, it is important to provide a clear explanation of what it is and what it is not. Explain that depression is a manifestation of PD (like tremor or constipation) which can be treated. Note that it is possible to experience depression even when everything is going well (and in fact this is frequently the case). It is also important to stress that depression is not something one has to "live with" nor is it the "expected" response to being diagnosed or living with PD. Depression is not a reflection of one's character or a sign of weakness just as it is not something that one can "get over" by changing one's mindset or the power of positive thinking. One cannot will away a depressive episode any easier than one can will away motor symptoms.

Most evidence suggests that depression is primarily a consequence of the disease process itself, sometimes developing prior to the onset of motor symptoms (i.e., a "premotor" symptom). Potential factors implicated in its etiology have included dysfunction of neurotransmitters (e.g., dopamine, norepinephrine, and serotonin) and aberrant circuitry involving various brain regions. Immunological and neurotrophic hypotheses have also been suggested. This is not to say, however, that there is no relationship between "external" influences and mood. For example, it is quite possible that traumatic life events may precipitate a depressive episode in someone with a "biological" vulnerability toward depression. At this point, we don't know why some people with PD become depressed, while others do not (just as we do not know what determines side of onset or variation in motor manifestations). A better understanding of those factors that increase (or decrease) the risk of depression may shed further light on its biological underpinnings and provide guidance regarding approaches toward treatment or prevention.

Antidepressant Medications (Table 26.1)

There is now evidence that medications from several of the currently available antidepressant classes are more effective than placebo for the treatment of depression in PD. Despite their reported efficacy, the tricyclic antidepressants (TCAs) are generally not the first or second line of therapy due to concerns regarding potential cardiotoxicity and a poor side effect profile that is particularly problematic among patients with PD, including worsening of orthostatic hypotension and anticholinergic side effects such as constipation. The serotonin norepinephrine reuptake inhibitors (SNRIs) and selective serotonin reuptake inhibitors (SSRIs) are generally tried first as they are considered safer and generally better tolerated. We conducted a placebo-controlled, multicenter clinical trial of paroxetine (an SSRI) and venlafaxine extended release (an SNRI) in patients with PD and

Table 26.1 Drugs for depression in PD

SSRIs	Starting dosages (mg, once daily)	Maintenance dosage range (mg, once daily)
Paroxetine	10–20	20–40
Sertraline	25–50	50–200
Citalopram	10–20	20–40 (suggested max 20 mg age > 60)
Escitalopram	10	10–20 (suggested max 10 mg age > 60)
Fluoxetine	10–20	20–40
SNRIs		
Venlafaxine ER	37.5–75	75–225
Duloxetine	30	30–60 (can divide 60 to 30 BID)
Other		
Mirtazapine	7.5–15	15–45 (sedating, bedtime dosing suggested)

clinically significant depressive symptoms. Each of the medications was more effective than placebo (the study was not designed to see if there was differential efficacy between the two). Both medications were generally well tolerated and neither had an impact on motor function. There is currently no evidence upon which to base the choice for starting an SSRI vs. an SNRI in a given patient (nor is there necessarily a compelling rationale for choosing a particular agent within a class). However, it would seem to make sense to consider an agent from the alternate class if the first is either not effective or not well tolerated.

Of note, there is a black box warning about the use of MAO inhibitors with antidepressant medications. However, the incidences of symptoms consistent with the serotonin syndrome in patients with PD who take an MAO-B inhibitor (which, at dosages used in PD, are relatively selective) with an SSRI or SNRI appear to be extremely rare. In practice, MAO-B inhibitors (e.g., selegiline, rasagiline) are frequently co-prescribed with an SSRI or SNRI, and cases of serotonin syndrome or other serious toxicities attributable to this combination are almost nonexistent.

Bupropion is a commonly prescribed antidepressant in the general population that works via modification of dopaminergic and noradrenergic systems. Clinicians have long wondered if, because of its effects on the dopaminergic system, it may be particularly useful in the treatment of depression in PD patients. There have not, however, been any well-controlled studies designed to evaluate its effect in this regard. There are characteristics associated with bupropion that suggest it may have particular benefits for the treatment of depression in PD. For example, its effectiveness for the treatment of ADHD suggests the possibility that it may improve mild cognitive symptoms (e.g., attentional deficits) experienced by some patients with PD. It also tends to be less sedating than many other antidepressant medications, which may be helpful in patients with excessive daytime sleepiness. However, it is possible that it may influence dopaminergic function in ways that could, for example, be associated with worsened dyskinesias or hallucinations. Further study of bupropion in PD might provide information that would inform decisions regarding its potential use in this population.

Non-pharmacological Therapies

There is evidence to support the role of cognitive behavioral therapy for the treatment of depression in PD. However, it is sometimes difficult to find providers with the appropriate training in this technique, making feasibility an issue. Counseling and/or insight-oriented psychotherapy by a provider at least familiar with PD (or older adults, with and without neurodegenerative diseases) may be a helpful adjunct to pharmacotherapy (or perhaps an alternative for those reluctant to start a medication).

Other techniques such as transcranial magnetic stimulation are being studied, and preliminary reports in the literature suggest that they may be effective though access to providers with the training and equipment required to perform it will likely be an issue, at least for foreseeable future. There have been intermittent reports in the literature for years about the capacity of ECT to improve motor symptoms in addition to mood in patients with PD. The main concern is the likelihood that having PD may render one more vulnerable to the cognitive side effects (particularly delirium around the time of treatment). Our approach would be to refer patients with depression to a psychiatrist (hopefully one familiar with PD or other neurodegenerative disease) if they have severe depression or if their depressive symptoms are refractory to adequate trials of an SSRI and an SRNI. We would not object to a trial of ECT or even a mood stabilizer if deemed necessary to treat the depressive disorder. We do, however, caution against the use of any antipsychotic medications other than clozapine, quetiapine, and pimavanserin (recently approved by the FDA for the treatment of psychosis in PD) given the potential of all other agents to significantly worsen motor function.

Alternative or Augmenting Medications

As is the case of primary psychiatric populations, many patients (about 1/3 in the clinical trial of paroxetine and venlafaxine) do not respond or experience only a partial response to trials of traditional antidepressant agents.

Buspirone is an agent with both serotonergic and dopaminergic activity. It is widely used in the treatment of generalized anxiety disorder, is well tolerated in the elderly population, and can be used as an adjunctive agent for the treatment of depression. We believe that this agent is worthy of further evaluation in patients with PD. Through its action on the 5HT1A receptor, buspirone may have the added benefit of diminishing levodopa-induced dyskinesias. However, because of its effects on the dopaminergic system and weak affinity for D2 receptors, it could potentially be associated with worsening of PD motor function.

Mood-stabilizing medications such as lithium, valproic acid, or lamotrigine may also merit evaluation in patients with PD. These medications may be used to augment or as an alternative to traditional antidepressant agents for patients with refractory symptoms. However, even more compelling for patients with PD is the potential neurotrophic effects of mood stabilizers and the possibility that they may prevent or improve the neurobiological derangements responsible for loss of homeostasis associated with fluctuations. It should also be noted that lithium and valproic acid can cause

drug-induced parkinsonism and thus may worsen motor features of PD.

The off-label use of second-generation "atypical" antipsychotic monotherapy for patients devoid of psychotic features, typically for depression or anxiety, has increased among psychiatrists and even primary care providers. We routinely see patients for evaluation of PD in whom we determine the motor symptoms are at least partially related to treatment with these "atypical" antipsychotic medications. The majority of patients have a gradual improvement after discontinuation of the drugs (although there are some patients in whom, after further evaluation including dopamine transporter imaging [DaTSCAN], we surmise the drug may have unmasked underlying PD, which had presented with depression or anxiety as a premotor feature). Suffice it to say, we do not recommend the use of any antipsychotic medication for depression or any other nonpsychotic symptoms in patients with PD.

DBS

The relationship between deep brain stimulation (DBS) and depression in PD needs further clarification. There are conflicting reports about the impact of DBS (used to treat PD motor symptoms) on mood and potential differences between pallidal and subthalamic nucleus stimulation in this regard. In general, a history of depression would not preclude a patient from undergoing DBS surgery, but its treatment should be optimized prior to undergoing the procedure. The degree to which DBS may improve mood and other nonmotor fluctuations is worthy of further study.

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Treatment of Hallucinations and Delusions in Parkinson Disease

27

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Case

A 70-year-old man diagnosed with Parkinson disease (PD) 15 years earlier was brought in by his family for a follow-up visit with his neurologist. The patient's wife was concerned about visual hallucinations in the last few weeks involving seeing unfamiliar people in the house and cats running across the room, particularly at night. On several occasions, he was found to be talking alone in the room when there was no one there. This has greatly bothered his wife, although he did not seem to be frightened. Other than seeing things, he also experienced delusions. He became particularly paranoid when he saw his wife talking to someone on the phone or leaving the house. He was convinced that she was being unfaithful to him without any actual proof. He constantly worried about it and this has caused significant distress for his marriage. He has been sleeping poorly with vivid dreams at night. He denied symptoms of depression. His wife reported mild cognitive decline for the last 5 years prior to onset of hallucinations and delusions. Motorically, he has been doing relatively well on stable doses of levodopa 200 mg three times daily and extended-release ropinirole 12 mg once daily. There were no significant motor fluctuations or dyskinesia. He denied any recent change in his medical health or non-PD medications. He denied any symptoms or signs of infection. Basic laboratory workup including complete blood count (CBC), complete metabolic panel, and urinalysis was within normal range. An attempt was made to slowly taper the dopamine agonist, which made his parkinsonism worse, so the dosage was returned to previous level. His symptoms of hallucinations, paranoia, and sleep disturbance worsened. Quetiapine 25 mg in the evening was initiated to address his psychosis and sleep disturbance and subsequently titrated up to 25 mg twice a day with significant improvement in his psychotic symptoms without deterioration in his parkinsonism.

Discussion

Psychosis is one of the most clinically significant and disruptive behavioral problems in PD. The prevalence of PD psychosis (PDP) ranges from 20% to 50%. It is a common reason for nursing home placement or institutionalization in PD and is associated with increased morbidity and mortality. The characteristic features of PDP include hallucinations, illusions, and delusions. Initially, patients often describe what are called minor hallucinations. These include passage hallucinations which are fleeting shadows in the visual periphery or "sense of presence" hallucination which is a perception that another person is next to or behind the patient. Full-fledged hallucinations are typically visual in nature, usually non-threatening comprised of little children, animals, or relatives who passed away. Occasionally, they can be auditory, tactile, gustatory, or olfactory. Delusions typically are paranoid in nature, best known is the belief of spouse infidelity and abandonment. Because it is almost impossible to convince the patient that delusions are not real and any attempt to reason or argue may cause more agitation, caregivers often become overwhelmed to continue caring for their loved one. The 2007 NINDS/NIMH revised criteria for diagnosis of PDP include the presence of at least one of the following symptoms: illusions, false sense of presence, hallucinations, or delusions. The symptoms of psychosis must occur after the onset of PD and are either recurrent or continuous for at least 1 month. Such symptoms are not better accounted for by other causes of parkinsonism, such as dementia of Lewy body (DLB) or other psychiatric disorders. Level of insight, presence of dementia, and PD treatment are not required in PDP criteria.

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Although dopaminergic medications have been associated with the development of hallucinations in PD, they are not a necessary factor in the development of PDP. The current view in pathogenesis of PDP stems from a complex interaction of extrinsic and intrinsic factors. Age of onset, duration of PD, and cognitive impairment have a strong correlation with PDP. Other medications commonly used for PD patients such as amantadine and anticholinergics may contribute in the development of PDP, as well as visual processing deficits and sleep disturbance. Various scales have been developed to assess psychosis in PD such as Brief Psychiatric Rating Scale, Neuropsychiatric Inventory, and Schedule for Assessment of Positive symptoms, among others. While they may be useful outcome measures in clinical trials assessing new interventions, no individual scale captures the full clinical spectrum of PDP or reflects meaningful clinical change over time in real-life practice.

The principles of PDP management include a search for medical causes of delirium, a thorough review of PD and non-PD medications, and an initiation of psychopharmacologic treatment (Fig. 27.1). Underlying medical conditions such as systemic infections (e.g., urinary tract infection, pneumonia), metabolic and endocrine derangements (e.g., electrolyte imbalance, thyroid disease, liver or kidney dysfunction), cerebral hypoperfusion states, and psychosocial stressors can precipitate psychosis and delirium in PD patients; therefore it is important to assess for them as potential causes of psychosis. Polypharmacy is one of the strong risk factors for PD psychosis, thus it's crucial to perform a thorough review of patient's medication list. Medications such as dopaminergic replacement therapy, opiates, sedatives, anxiolytics, anticholinergics, and antidepressants are implicated in PD psychosis and may need to be reduced or stopped accordingly. Most authorities agree on a gradual tapering strategy for PD medications in the following order: anticholinergics, amantadine, monoamine oxidase B inhibitors, dopamine agonists, catechol-O-methyltransferase inhibitors, and if still needed, levodopa. One needs to be mindful of the development of dopamine agonist withdrawal syndrome and delirium following amantadine withdrawal. The immediate release formulation of levodopa is typically preferred over the controlled-release formulation in the end because of a lower risk of adverse effects with the former. For persistent and problematic psychosis, the next step is to consider adding a psychopharmacologic treatment (Table 27.1).

Pimavanserin is the first and only drug approved by the US Food and Drug Administration, April 2016, for treatment of hallucinations and delusions associated with PDP. It is a 5HT2A inverse agonist that has been shown to significantly reduce hallucinations and delusions without worsening motor symptoms in PD patients at a dose of 40 mg/day. Prior to approval of pimavanserin, clozapine and quetiapine, two atypical antipsychotic drugs, were (and still are) widely prescribed off-label in low doses for PD psychosis. Clozapine, a dibenzodiazepine derivative, selectively binds D1 mesolimbic receptors while sparing striatal D2 receptors and has a greater affinity to 5HT2A/2C receptors. Two landmark studies in 1999 on use of clozapine in PDP demonstrated significant improvement in symptoms of psychosis and improved motor function in some cases. However, clinicians tend to shy away from its use due to the need for frequent absolute neutrophil count monitoring which is weekly for the first 6 months, biweekly for the next 6 months, and monthly thereafter, to monitor for the less than 1% chance of developing agranulocytosis. Other adverse effects of clozapine include orthostatic hypotension and sedation. The effective dose of clozapine for PDP is lower than that used for treatment of schizophrenia. The initial dose is 12.5 mg once at night; if necessary, it can be gradually increased as tolerated not to exceed 75–100 mg daily; mean dose in clinical trials was 25 mg daily. Quetiapine is structurally similar to clozapine and has a greater affinity for serotonergic 5HT2 receptors than D2 receptors which confers a favorable motor profile but not as favorable as that of clozapine. There have been some conflicting data on efficacy of quetiapine in PDP, although strong evidence exists that it does not significantly worsen motor function. However, it commonly causes sedation and may worsen orthostatic hypotension. It may be initiated at 25 mg once at night or in divided doses; the dose may be adjusted gradually based on response and tolerability up to 200 mg daily; mean dose in clinical trials was ~91 mg daily. Other atypical antipsychotic medications that have dopamine blockade should be avoided in PDP treatment. Olanzapine causes significant motor function decline with inconsistent benefit in PDP. Aripiprazole has variable efficacy and tolerability in PD with higher risk of motor worsening. There are no large randomized trials examining cholinesterase inhibitors in PDP treatment, although in cognitive clinical trials on patients with dementia with Lewy bodies randomized to cholinesterase inhibitors, incidental improvement in hallucinations have been noted. We have not observed any consistent or clinically meaningful effect in reducing hallucinations in our patients.

Once hallucinations appear, they tend to become a chronic and progressive condition. Continued psychopharmacologic treatment may be necessary to maintain symptom control.

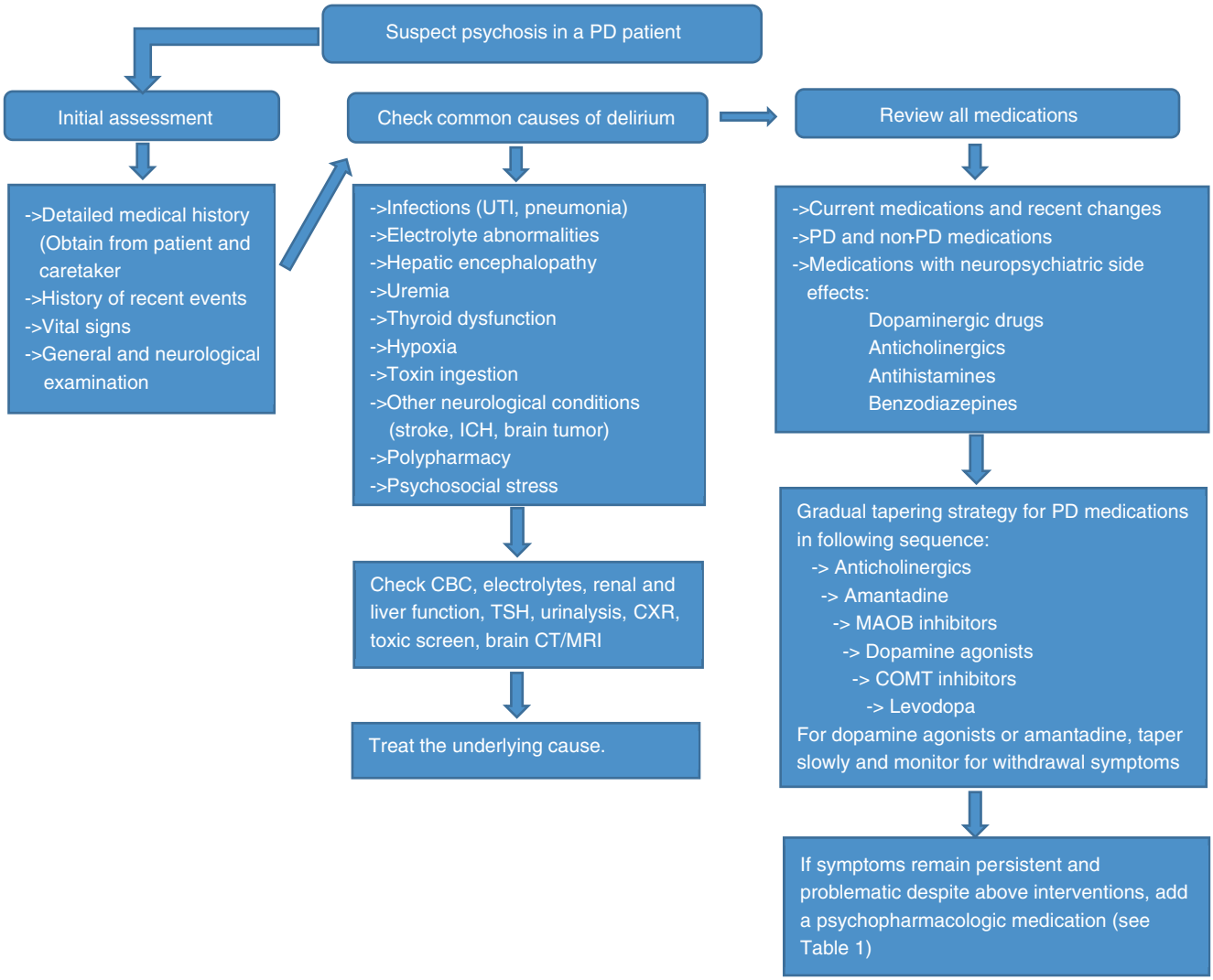

Fig. 27.1 Algorithm of psychosis evaluation in a PD patient

Table 27.1 Medications commonly used for PD psychosis

Medication	Starting dose	Titration	Max dose	Side effects and considerations
Quetiapine	12.5–25 mg at bedtime	Increase by 25 mg every few days as tolerated	200 mg daily	Monitor for worsening parkinsonism, sedation
Clozapine	12.5 mg at bedtime	Increase by 25 mg every few days as tolerated	100 mg daily	Monitor for orthostatic hypotension, agranulocytosis (1% risk) (check weekly CBC for 6 months, followed by biweekly CBCs, then monthly after 1 year)
Pimavanserin	34 mg once daily	None	34 mg once daily	Well tolerated in Phase 3 trial with no significant safety concerns or worsening motor function

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Treatment of Apathy in Parkinson's Disease

28

Sergio Starkstein and Simone Brockman

Case

A 65-year-old man who noticed resting tremor in his right hand. His handwriting had deteriorated and the tremor interfered with his ability to drink from a glass. He was referred to the Movement Disorders Clinic and diagnosed with Parkinson's disease (PD) based on the additional findings of mild rigidity and bradykinesia in the right arm and a positive levodopa test. He showed a good response to antiparkinsonian medication but 5 years later noticed the onset of parkinsonism on the left side, with frequent falls due to freezing and poor balance. The patient was an expert in fixing old watches and used to spend hours cleaning his large collection. His other pastime was meeting every Saturday with a group of friends to play bowling. On psychiatric assessment he denied symptoms of worrying or anxiety but reported moderate sadness which he related to his increasing inability to pursue his hobbies. His wife reported that he would spend hours looking at his watch collection, but would not touch them. Many of the tools used to fix the watches now lay on his worktable in disarray. He also stopped playing bowls and visiting friends, stating he was no longer interested in seeing them. Nevertheless, when pushed by his wife, he would dress himself and go to the bowling club. Once there he would meet with friends, but would rarely participate in conversations and would not play bowls, complaining of low energy. His wife reported her husband had a generalised loss of motivation and would no longer help with chores at home.

The patient was assessed at the PD clinic by a neuropsychiatrist. He reported poor motivation to perform his daily activities, incipient short-term memory loss, disinterest in his usual hobbies and daily activities, and an unwillingness to engage in social activities. His mood was flat, with no fluctuations, but he denied feeling depressed. Nevertheless, the patient reported medial insomnia and early morning awakening, poor appetite, poor energy, loss of concentration, and psychomotor retardation. He denied suicidal ideation or psychotic symptoms.

The patient was diagnosed with a major depressive episode and was started on citalopram 10 mg at night. Due to lack of efficacy, the dose was slowly titrated to 40 mg/day over a 2-month period. The patient's wife not only reported no improvement but stated that his motivation worsened and that he would rarely start a spontaneous conversation. We reviewed pharmacological options with the patient and his wife, which included, as the first step, to slowly reduce and cease citalopram over a 4-week period. We analysed the option of using a psychostimulant such as methylphenidate or atomoxetine. The latter was found to be ineffective in treating apathy in PD, and a decision was made to use the D2/D3 agonist piribedil as there is evidence of improvement of apathy with this medication. He was started on 50 mg in the morning, and the dose was increased by 50 mg every 2 weeks, until a total daily dose of 200 mg was achieved. After 2 months of treatment, he showed a moderate improvement in motivation, as manifested by working for several hours on his watch collection and requesting to meet with friends once a week. His affect was brighter and his wife reported an increased interest in helping with daily chores. There was some nausea, which was readily treated by increasing domperidone to 60 mg/day.

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Discussion

Apathy is a syndrome characterised by deficits in motivation and emotional blunting. Patients with apathy show decreased goal-directed behaviours, such as putting in less effort to perform daily life activities; decreased goal-oriented cognition, such as poor interest in learning new things; and deficits in emotional response to positive or negative events. Apathy may be present in the early stages of PD, and even among naïve patients, but is more frequent in the late stages, usually in the context of dementia. The relevance of apathy is not only expressed in the patients' poor functioning, but is also a significant predictor of decreasing response to antiparkinsonian medication, poor quality of life, dementia, and increased caregivers' emotional distress. The mechanism for apathy in PD, in the absence of depression or dementia, is unclear. Apathy may result from the withdrawal syndrome produced by the fast reduction or abrupt cessation of levodopa or dopaminergic agonists in cases of delirium, psychosis, impulse control disorder, or dopamine dysregulation syndrome.

The main challenge faced by the clinician is how to diagnose apathy in the context of PD, an illness characterised by psychomotor retardation, bradyphrenia, blunted facial expression, and increasing difficulties with daily life activities. Initially, it is important to rule out important clinical confounders, such as diminished level of consciousness, cognitive impairment, or depression. Before a diagnosis of apathy is made, patients should have a neuropsychological assessment for cognitive impairment and a psychiatric assessment for the presence of a depressive syndrome. Diminished level of consciousness may be a side effect of antiparkinsonian medication or poor night-time sleep. One of the main limitations when rating apathy in PD is the overlap with parkinsonian symptoms, and the suggestion was made to use an 'inclusive' approach (i.e. all symptoms are scored, regardless of whether they overlap with motor symptoms) to increase diagnostic sensitivity. To standardise recollection bias, it is better to assess apathy during the ON state (i.e. the state of maximal antiparkinsonian medication efficacy).

Before starting treatment for apathy, it is important to quantitate the severity of this syndrome. In a busy clinical practice, the motivation item of the MDS-UPDRS may be useful, as scores of 2 or more have good sensitivity for the presence of apathy. Patients scoring 2 or more on this item may be assessed with either the Apathy Scale or the Lille Apathy Rating Scale.

The second challenge is to how to separate apathy from depression and early dementia in a reliable way. This has great clinical relevance given the numerous, effective treatment options for depression and the poor prognosis in case of dementia. Once depression and dementia are ruled out, it is important to examine contextual factors that may underlie apathy, such as having no structured activities during the day, being unable to participate in social activities or perform basic activities of daily living due to the severity of the motor disorder, and social factors such as living alone or having no close friends. If apathy is the clinical expression of having few interesting or enjoyable activities, a referral should be made to an occupational therapist to help the patient find activities that she/he may enjoy and be able to perform without too much effort. In the case of social isolation, a social worker may help to liaise the patient with groups of people sharing similar interests or, if available, groups of patients with PD.

Another important factor to consider is the presence of diurnal somnolence. This problem may result from the many factors causing insomnia in PD, such as REM sleep behaviour disorder, nocturia, restless legs syndrome, sleep disordered breathing, and circadian rhythm disorders (see chapter "Treatment of REM Sleep Behavior Disorder in Parkinson's Disease"). It is quite common that PD patients with poor sleep will doze during the day and sit in front of the TV set for long hours. Correcting sleep problems may therefore have a positive impact on apathy.

The question whether deep brain stimulation (DBS) of the subthalamic nucleus may produce apathy is a debated issue. Recent studies estimate that about 25% of patients will develop apathy at some stage after DBS, and it is most frequent in the first 5 months post-DBS. In some patients, apathy may persist for years or even become chronic. In these cases, apathy may minimise the motor improvement obtained with DBS. The cause of post-DBS apathy remains unknown, although it may be related to the practice of reducing the dopaminergic medication immediately after surgery. A specific effect of DBS is another possibility, although it is yet not clear what are the predisposing factors to develop post-DBS apathy. A recent controlled study demonstrated that post-DBS apathy improves significantly with the D2/D3 agonist piribedil, but another controlled study showed no benefit with the use of patches of the dopaminergic agonist rotigotine.

There are few randomised controlled trials of psychoactive medication for treatment of apathy in PD. The selective norepinephrine inhibitor atomoxetine showed no efficacy to improve depression or apathy in PD. Whereas our patient

improved after being started on piribedil, it is important to note that the benefit of this medication was demonstrated in post-DBS apathy, and the benefit of this medication remains unknown in non-DBS patients. Until a drug is demonstrated to effectively treat apathy in PD, the focus should be on improving co-morbid depression, alleviating cognitive impairments, and working on relevant contextual factors.

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Treatment of Impulse Control Disorders and Dopamine Agonist Withdrawal Syndrome in Parkinson's Disease

29

Melissa J. Nirenberg

Case

A 71-year-old woman with REM sleep behavior disorder and a 12-year history of Parkinson's disease (PD) presented to an outside movement disorders specialist for ongoing management. Her motor symptoms were well controlled on pramipexole monotherapy (4.5 mg/day), allowing her to function independently, work full time, and play tennis. She reported a number of impulsive-compulsive behaviors that were not bothersome to her, but had become increasingly concerning to her family. These included compulsive eating (of sweets), exercise (using Wii Fit; playing tennis and table tennis), Internet use (playing bridge, using Facebook), and gardening (pulling weeds for hours). She was unable to stop these behaviors even when they caused injury or interfered with her social relationships or responsibilities. She had not reported these symptoms to her prior neurologist and was unaware that they were potential complications of dopamine agonist (DA) therapy.

Given the presence of impulse control disorders (ICDs), the patient's new neurologist advised her to add carbidopa/levodopa 25/100 mg (to control her motor symptoms) and then gradually taper pramipexole (from 1.5 mg three times daily to 1.5 mg–1.5 mg-0.75 mg). Soon after initiating these medication changes, the patient's ICDs remitted, but she developed intractable anorexia, nausea, and vomiting that resulted in an 18 lb. weight loss over a 9-week period. These gastrointestinal symptoms were initially thought to be a side effect of levodopa, but were refractory to supplementary carbidopa, trimethobenzamide, ondansetron, or domperidone. Extensive workup for potential infection, gastrointestinal disorder, or other medical etiologies for her symptoms was unrevealing.

Nine weeks later, the patient presented to our center because of ongoing gastrointestinal symptoms and apparent difficulty tolerating dopaminergic medications. On further questioning, she reported that she had also been experiencing marked fatigue, severe anxiety, panic attacks/hyperventilation, depressive symptoms, dysphoria, crying spells, frustration, social withdrawal, and marked orthostatic lightheadedness. These symptoms occurred throughout the day and did not vary in relationship to her medication timing. In contrast, her motor symptoms remained well controlled on carbidopa/levodopa 25/100 mg three times daily, with no fluctuations.

On examination, she had symptomatic orthostatic hypotension (blood pressure 124/84, pulse 60 seated; blood pressure 96/69, pulse 68 standing) and moderate parkinsonism, with a modified Hoehn and Yahr scale score of 2. Review of her symptom diary showed that she tolerated the addition of levodopa well, with improvement in her motor symptoms and no side effects. It was not until 2 weeks later, when she reduced the dosage of pramipexole from 1.5 mg three times daily (4.5 mg/day total) to 1.5–1.5-0.75 mg (4.25 mg/day total), that she developed this cluster of severe nonmotor symptoms. These symptoms progressively worsened as she continued to slowly taper and then discontinue pramipexole. Numerous medication changes were made in an attempt to alleviate her symptoms, including adjustments in levodopa and other dopaminergic medications and trials of numerous pharmacological and non-pharmacological interventions including clonazepam, metoprolol, selective serotonin reuptake inhibitors, bupropion, antiemetics, biofeedback, and exercise.

Based on the time course, characteristic symptoms, and lack of response to levodopa or other medications, she was suspected to have dopamine agonist withdrawal syndrome (DAWS). This diagnosis was confirmed when her symptoms responded to the resumption of a very low dose of pramipexole (0.125 mg three times daily). After restarting low-dose

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pramipexole, she experienced dramatic, nearly immediate improvement in all of her nonmotor symptoms and was able to resume normal activities and exercise. In her words, "I don't have that awful feeling like I'm in another world…like when you see people go cold turkey from drugs in a movie or something.…[I am] no longer crying all day." Her ICDs initially remitted on this very low dose of pramipexole, but about a year later resurfaced, prompting further attempts to taper pramipexole. These attempts were unsuccessful, however, due to severe, intolerable DAWS symptoms. Seven years later, she remained on pramipexole 0.375 mg/day with ongoing ICDs affecting her daily life and interpersonal relationships.

Discussion

ICDs are a relatively common side effect of DA use, with a prevalence of over 17% in DA-treated PD patients, and an estimated cumulative incidence of ~30-50% after several years of DA therapy. While other dopaminergic medications have also been associated with ICDs, DAs are the major cause. The most common DA-related ICDs include compulsive eating, compulsive shopping/buying, pathological gambling, and hypersexuality. Numerous other types of ICDs have been reported; it is also common for patients to present with two or more concurrent ICDs. The consequences of ICDs can be very serious, including devastating financial losses, unsafe sexual behavior, obesity, and divorce. Risk factors for ICDs include male sex, younger age, younger age at PD onset, cigarette smoking, a history of pre-PD ICDs, or a family history of gambling problems. Some studies have shown that higher DA dosage, greater cumulative exposure to DAs, or concomitant levodopa use may be risk factors for ICDs, but others have not demonstrated such relationships.

The pathophysiology of ICDs has been attributed to excess stimulation of D3 dopamine receptors, which are disproportionately expressed in mesocorticolimbic dopaminergic neurons (in the reward/addiction pathways), versus the nigrostriatal dopaminergic neurons (in the motor pathways) that are predominantly affected in PD. DAs such as pramipexole, ropinirole, and rotigotine all have high D3 receptor binding. This disproportionate activation of dopaminergic neurons in the mesocorticolimbic system is thought to lead to an "overdose" of relatively intact reward pathways, leading to uncontrolled "behavioral addictions."

As illustrated in this case, the diagnosis of ICDs is often delayed for months to years. This is likely due to multiple factors such as embarrassment, reduced insight, or lack of sufficient vigilance. For this reason, it is critical for providers to assess patients for ICD risk factors and obtain informed consent prior to initiating DA therapy, and to actively seek information about potential ICDs from patients, family members, and other informants at each subsequent patient contact. Before initiating DA therapy, it can be helpful to identify the patient's hobbies, tendencies, or "vices" (e.g., overeating when under stress, weekly use of scratch off lottery tickets), to help direct the clinical interview at subsequent visits. Patients with subsyndromal ICDs (ICD-like behaviors that are not causing secondary consequences) should have particularly close monitoring if they choose to continue DA treatment, because it is common for these behaviors to change from normal to maladaptive and difficult to determine when this has occurred.

Once ICDs have been identified, the only known effective treatment is to slowly taper and then discontinue DA therapy and substitute levodopa or other dopaminergic medications to control motor and nonmotor symptoms. Continuing the DA at a lower dose may transiently alleviate the problem, but ICDs can recur even with very low doses of DA, as demonstrated in this case. ICDs are a class effect of DAs, so switching to a comparable dosage of a different DA will not alleviate the problem. Some preliminary evidence suggests a possible benefit from cognitive behavioral therapy for ICDs, but further research is needed. There is conflicting data about the relationship between amantadine use and ICDs – one small crossover study suggested a potential benefit of amantadine for ICDs, but a much larger cross-sectional study showed that ICDs were more common in amantadine-treated patients.

About 20% of patients who attempt to taper a DA – and about one-third who taper because of ICDs (including the subject in this case) – develop dopamine agonist withdrawal syndrome (DAWS). DAWS is a severe, stereotyped nonmotor drug withdrawal syndrome that resembles that of cocaine and other psychostimulants. Features include prominent psychiatric symptoms (anxiety, panic attacks, dysphoria, depressive symptoms, confusion, psychosis, apathy, suicidal ideation), autonomic symptoms (orthostatic hypotension, diaphoresis), gastrointestinal symptoms (anorexia, nausea, vomiting), disturbances of sleep/energy (hypersomnia, insomnia, fatigue), and drug cravings. While some of the symptoms of DAWS are similar to those of undermedication or wearing off, the major difference is that none of the symptoms of DAWS respond to levodopa or other dopaminergic medications (other than DAs). Moreover, symptomatic treatment with numerous other therapies including antidepressants, anxiolytics, antiemetics, and non-pharmacological treatments is also ineffective. Secondary consequences of DAWS can include job loss, inability to perform activities of daily living, difficulty with interpersonal relationships, divorce, or suicidality.

One misconception about DAWS is that it only occurs when a DA is tapered too rapidly. While DAs should always be tapered very slowly, it is important to note that DAWS can occur even with an extremely slow taper. The onset of DAWS may be with the very first decrease in DA dosage or may be

delayed until the DA has been completely discontinued. Some patients who develop DAWS have relatively mild and transient withdrawal symptoms and can tolerate a very gradual DA taper. Others, as demonstrated in this case, are never able to get through the severe withdrawal symptoms, require chronic DA therapy, and therefore may experience permanent ICDs.

Given the lack of adequate treatments for ICDs and DAWS, prevention is crucial. Judicious use and conservative dosing of DAs and avoidance of the use of DAs in high-risk patients may help to reduce the risk of ICDs. Similarly, discontinuation of DAs at the first sign of ICDs may reduce the risk of DAWS. Involvement of family and other close outside observers in surveillance for ICDs and DAWS is critical to facilitate the early identification of these problems and minimize their secondary consequences.

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Treatment of Dopamine Dysregulation Syndrome and Impulse Control Disorders in Parkinson's Disease

30

Mark Stacy

Case Report

This patient was a 52-year-old right-handed woman who presented with her family for evaluation of stiffness and slowness. Her initial symptoms had begun 2 years earlier when she first noticed difficulty using her right hand while she was brushing her teeth and washing her hair. In the year prior to presentation, she developed short shuffling steps and a tendency to lean forward with ambulation. She also reported micrographia and increasing difficulty with her work as a hairdresser. Her past medical history included difficulty with anxiety which was previously treated with escitalopram, but that was discontinued.

Vital Signs: Blood pressure 122/76, pulse 62, respirations 12, weight 122.4 pounds. *Physical examination* identified only abnormalities suggestive of parkinsonism: mild hypophonia and hypomimia and moderate rigidity in the neck and right upper and mild in the right lower extremity. She had a mild scoliosis with convexity to the left and some posturing of her right arm with ambulation. She also had micrographia. Because she needed to return to work, she was initiated on carbidopa/levodopa 25/100, 3 tablets daily.

At follow-up 4 months later, on only two carbidopa/levodopa per day, she was much improved and had returned to work. She had also gained 3 pounds. However, 10 months after her initial presentation, she was no longer able to work in the beauty salon; she noticed wearing off on three carbidopa/levodopa tablets daily and had gained more than 6 pounds. Her wearing off symptoms consisted of declining mobility, limb pain, and an urge to defecate. At the next follow-up visit, she reported increasing anxiety and some symptoms of depression, as well as weight gain to 132 pounds.

She was restarted on escitalopram and encouraged to increase carbidopa/levodopa to 4 daily. At her evaluation 3.5 years after diagnosis, she weighed 134 pounds, reported severe limb pain and sweating with wearing off, and had only 2 h of benefit with each levodopa dose. Ropinirole 8 mg per day and clonazepam 1 mg at bedtime were added to her regimen.

After 4.5 years of levodopa and 4 months on ropinirole, the patient presented to the clinic with dyskinesias, anxiety, and jitteriness but denied ICD symptoms or hallucinations. Her ropinirole was changed to 16 mg daily and levodopa reduced to 500 mg per day from a high of 800 mg per day. This leads to a marked increase in anxiety, restlessness, panic, shortness of breath, and dyskinesias. Deep brain stimulation surgery was offered but declined, and she was converted from ropinirole xl to rotigotine patch (8 mg) in hopes that the wearing off symptoms of anxiety and panic would improve.

She contacted the office 2 weeks later by email with a report that the rotigotine 4 mg patch did not work as well as ropinirole, and she preferred to go to a higher dosage. She had also increased her carbidopa/levodopa and wanted to increase her clonazepam during the day. These changes lead to a phone call from her daughter with reports of chest pain, bloating feeling in her stomach, and feeling uptight. The patient underwent cardiology evaluation at a local emergency department. Her daughter also had discovered that the patient had increased doses of carbidopa/levodopa, now 7–10 tablets daily, was no longer eating, and had lost 8 pounds. While she complained of nausea, the daughter confided that she seemed somewhat obsessive about avoiding food. She also became resistant to making the long drive to the neurology clinic and preferred to remain at home.

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The next 2 years of management focused on attempts to titrate levodopa and ropinirole to maximize her mobility and minimize her dyskinesias and non-motor symptoms of anxiety and obsessionality about food and medication and to stabilize her mood. Eight years after the diagnosis of PD, the patient was willing to consider DBS as an intervention.

Four weeks after the surgery, she reported fewer symptoms of anxiety and panic and so began reducing medications on her own. This, in turn, leads to recurrence of panic, some visuo-perceptual disturbances and a new fear of falling, abdominal burning, and distension and dysuria. The family also reported that these symptoms seemed to worsen as the ropinirole was reduced. Reinstitution of this agent at 8 mg per day resulted in an improvement in her symptoms of panic, and the abdominal pain improved. A slow taper of ropinirole was instituted, and her weight began to increase.

She did well until her husband was hospitalized for a medical illness, and she was not able to manage her medications on her own. She told her daughters that every time her husband coughed, a demon was speaking and began behaving aggressively toward him. She was found to have a urinary tract infection but also had begun taking levodopa with much greater frequency. In addition, the family acknowledged increasing difficulties with memory for family and for everyday activities in the home. Her symptoms of psychosis improved with antibiotic therapy and levodopa dose reduction. However, she began to suspect a caregiver had begun an affair with her husband.

Six months later, now completely off dopamine agonists, she was again hospitalized for assistance with a delusion of spousal infidelity and auditory hallucinations. Quetiapine increasing to 150 mg per day did not improve psychosis, but did cause drowsiness. A change to pimavanserin eliminated the drowsiness and improved her psychosis. However, 9 years after diagnosis, she requires vigilant management of her medications, significant assistance with activities of daily living, and frequent redirection to avoid obsessional motor activity and thought.

Discussion

This patient represents a complex motor and behavioral phenotype that is seen in the PD population. Managing her motor disability required, on our part, a realization of her need to be in control of her appearance and her strong desire to avoid medication. In retrospect, her loss of employment as a hairdresser, and further decline in her ability to manage her own make-up and appearance, may have resulted in her ultimate motivation to begin and abuse antiparkinson therapy. Data from the DOMINION trial suggests that these behavioral traits are more likely to emerge in settings of increasing anxiety, as in the case of this patient. Her DDS and ICD symptoms are almost certainly not fully described. The patient was quite secretive about her medication intake and obsessional thoughts, and both her family and care providers decided to respect these boundaries. It is clear that she had an increased appetite while on levodopa, and this markedly declined when she was taking a dopamine agonist. Her excessive levodopa intake leads to severe motor fluctuations and dyskinesias, cyclical fluctuations in mood, secrecy and paranoia, and impairment of social and occupational activities. It is also clear that she had marked symptoms of panic when wearing off from levodopa and exhibited signs of DAWS when weaning from ropinirole: anxiety, panic attacks, nausea, abdominal bloating, chest pain, and hypotension. While her family hinted at possible behavioral changes, agoraphobia and avoidance of technology may have prevented excessive spending, either locally or through online opportunities. However, it is interesting her weight gain was more an issue while on levodopa, and she lost weight while on dopamine agonists (the opposite is more common). The possibility of hyperlibidinous behavior was never broached with the family.

It should be noted that psychosis is not part of the behavioral spectrum linked to ICD. However, these symptoms certainly emerged with development of delirium associated with a urinary tract infection and in the setting of unsupervised, increasing levodopa dosing (as in DDS). It may be that the delusional behavior was reinforced by her tendency to obsessional thought and her cognitive decline. Auditory hallucinations are less common in PD but may be a symptom of major depression.

Patients with ICD in settings of high conflict choice, or a win-win paradigm, consistently make more frequent errors, and more rapid choices, particularly after deep brain stimulation. This patient, particularly when in an off state, appeared to be increasingly prone to taking more and more dopaminergic replacement therapy, despite pleadings from her family to do otherwise. In the setting of dopamine agonists, an increase in risk-taking is reported. While the measurable outcome or decision is mediated within the basal ganglia, there are additional inputs to the striatum that are important in modulating stimulus value in terms of risk and reward.

Subcortical nuclei composing the basal ganglia, or extrapyramidal pathways, contain parallel circuitry that modulate emotion, decision, and motor control. Conceptually, the indirect (D2/enkephalin-indirect) and the direct (D1/substance P/dynorphin) pathway's input are summated within the striatum and delivered to the subthalamic nucleus. Motor changes, such as dyskinesias, are linked to imbalance between D1 and D2 receptors. Impulsive and compulsive behaviors may result from a mismatch of inhibition within the D2 receptor family, given that the dopamine agonists with greater affinity for the D3 receptor vs. the D2 receptor are more highly associated with ICD and DAWS.

Positron emission tomography (PET) imaging comparing PD patients with and without ICD shows increased dopamine release in the ventral striatum, and in settings of risk anticipation, D2/D3 dopamine agonists increase ventral striatal, orbitofrontal, and anterior cingulate activity. In addition, impairments in executive function and working memory have been linked to changes in the dorsolateral prefrontal cortex. Alteration of input from these brain regions amplifies the differences in direct and indirect pathway input, leading to disturbances in motor activity (dyskinesias), decision-making (impulsivity), and mood and thought content (depression and obsessional psychosis).

Dopamine dysregulation syndrome is a neuropsychiatric disorder characterized by the presence of severe dyskinesias, off-state dysphoria, and cyclical changes in mood associated with addiction to dopaminergic therapy. Self-medication and self-escalation of antiparkinsonian medication are key features. Unlike ICD, DDS is more often associated with levodopa or the short-acting dopamine agonist, apomorphine. Typically, affected patients consume larger than recommended total daily doses of levodopa, far beyond the necessary dosage to treat a motor disability. Attempts to reduce the dose are met with great resistance, making management quite difficult. Similar to patients with methamphetamine addiction, PD patients with DDS demonstrate enhanced levodopa-induced ventral striatal dopamine release, perhaps due to sensitization, compared with levodopa-treated patients with PD who did not have DDS.

While DDS symptoms increase with reduction of dopaminergic therapy, behavioral changes linked to ICD most often respond to reduction or withdrawal of dopaminergic therapy, particularly dopamine agonists. Treatment with selective serotonin reuptake inhibitors, quetiapine, valproic acid, topiramate, donepezil, and clozapine, has been reported to be helpful in case reports, but that is the extent of available evidence for these agents. There are also reports of improvement after deep brain stimulation surgery, in the context of dopaminergic therapy reduction. More recently, improvements have been reported in separate, randomized, controlled settings using cognitive behavioral therapy and naloxone.

Remember, the most important component in managing ICD and related disorders is monitoring to facilitate early diagnosis and treatment. In this case report, the recognition of subtle changes in her behavior was delayed. Determining risk for the development of ICD is an important area of study for the PD population in an attempt to reduce the impact of some of these extremely damaging behaviors.

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Driving in Parkinson's Disease

31

Ergun Y. Uc

Case 1 This 55-year-old man with Parkinson's disease (PD) was working full time and did not complain of any driving issues. His only clinical concern was intermittent resting tremor in the left hand. He was treated with ropinirole 3 mg TID. He performed well on off-road tests except mild executive dysfunction. After 3 years, he was continuing to drive without incident despite some worsening of his tremor and bradykinesia requiring the addition of carbidopa/levodopa to his regimen with good response. He also reported difficulties with nighttime vision, short-term memory complaints, and balance problems and was contemplating retirement within the next 1–2 years.

Case 2 This 76-year-old man had postural instability gait disorder predominantly parkinsonism and showed mild responsiveness to levodopa without any motor fluctuations or dyskinesia. He had restricted his driving to his local small town and in daytime only in accordance with his family's wishes after some near misses at night and in congested traffic. His off-road testing showed severe executive, visuospatial, and memory dysfunction consistent with dementia. His visual contrast sensitivity and useful field of view (measure of visual processing speed and attention) were markedly abnormal. He performed very poorly on the road with many at fault errors, difficulties with navigation, and multitasking. In the simulator, he showed increased swerving and slow reaction to a hazard with resultant crash. We discussed the results with him and his family and recommended driving cessation. He agreed to give up his driver's license.

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Case 3 This 62-year-old, recently retired, man with PD characterized by moderate wearing off and mild peak-dose dyskinesias has been complaining of excessive daytime sleepiness on his regimen of carbidopa/levodopa 25/100, 1 tablet QID, and pramipexole 1.5 mg TID. His off-road testing was consistent with multi-domain mild cognitive impairment and with moderate decrease in visual contrast sensitivity and useful field of view. He committed more safety errors on the road than normal drivers and completely missed a hazard in a foggy environment in the driving simulator with resultant crash. After gradual withdrawal of pramipexole and increase of carbidopa/levodopa, his sleepiness resolved and his driving improved. However, his disease continued to progress with increased mobility and cognitive impairment, and he ceased driving 3 years later after a near miss.

Discussion

Three cases are presented to illustrate how driving can be affected in Parkinson's disease (PD) depending on the demographic and clinical characteristics (Table 31.1). These community-dwelling, active drivers volunteered to participate in our longitudinal cohort study (R01 NS044930) on predicting driver safety in PD. They underwent detailed motor, cognitive, visual testing ("off-road" tests), as well as experimental driving tests, in a road vehicle and in a simulator. They were followed up for several years.

In addition to the characteristic motor dysfunction, PD also impairs cognition, vision, and alertness and is associated with poorer performance on driving simulator experiments and road tests. Drivers with PD fail road tests at higher rates than normal elderly. They have increased difficulties in left turns at intersections, speed and lateral vehicle control, and route finding. Their driving problems worsen with multitasking or under low visibility. One of the greater concerns in drivers with PD is their potential for increased risk of crashes. Indeed, driving simulation studies and retrospective

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Table 31.1 Key characteristics of cases

Age, sex	Disease duration	HY	MMSE	Executive	Visuospatial	Memory	Road	Simulator	Real-life outcome
55, male	4 y	II	30	↓	↓	Normal	Normal	Normal	Still driving
76, male	4 y	III	22	↓↓↓	↓↓↓	↓↓↓	↓↓	↓↓	Immediate cessation
62, male	10 y	II	27	↓↓	↓↓	↓	↓	↓	Cessation in 3 years

HY Hoehn-Yahr stage, *MMSE* Mini-Mental Status Examination

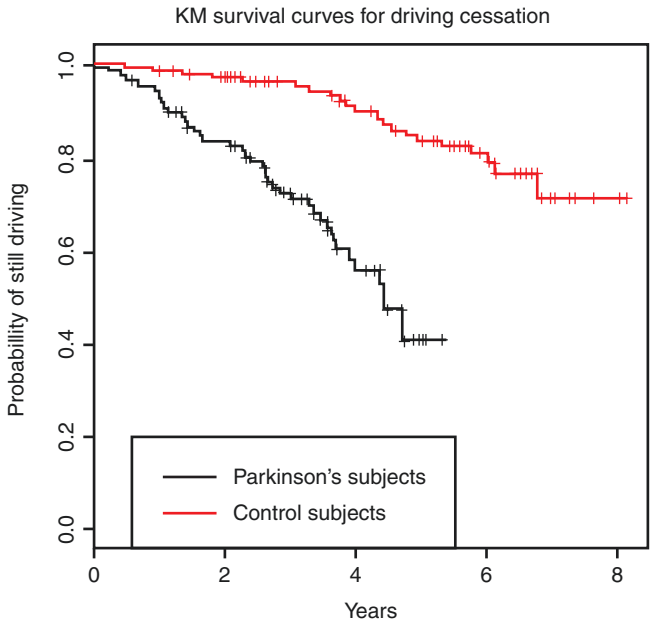

Fig. 31.1 Kaplan-Meier Curves for Driving Cessation (Logrank test $\chi^2 = 37.53$, p-value <0.0001) between subjects with Parkinson's disease and elderly control subjects. (Reprinted from Uc et al. (2011a) with permission from Wolter-Kluwer Health, Inc.)

surveys have demonstrated increased crash rates in drivers with PD. However, increased real-life crash risk in drivers with PD has not been confirmed by community-based, prospective, controlled studies or epidemiological research so far, probably due to attrition of at-risk drivers by voluntary or forced driving cessation. Another potential unfavorable driving outcome in patients with PD is the loss of vehicular mobility (driving cessation) as shown on cross-sectional or retrospective and prospective surveys (Fig. 31.1). The attrition of at-risk drivers as well as self-imposed compensatory strategies may explain lack of observations of increased crash rates in PD.

Michon proposed a hierarchical model of cognitive control of driving at three levels: (a) strategic, (b) tactical/maneuvering, and (c) operational/vehicle control. The decisions to drive during inclement weather or route selection (e.g., freeways vs. urban streets) are examples of strategic behaviors which affect driving performance and safety on a time scale of minutes to days. Adjusting speed and car following distance, choice of lane, or decision to overtake according to road rules and conditions are examples of tactical behaviors and affect driving on a time scale of 5–60 s. Maintaining lane position with ongoing steering adjustments, keeping a safe distance to the car in front from moment to moment, and reacting to hazards represent operational behaviors, which determine driving in the next 0.5–5 s.

At the operational level, driver actions can be analyzed in an information processing model (Fig. 31.2): (1) perception and attention to stimulus (e.g., visual and auditory inputs) and interpretation of the road situation, (2) planning a reaction to the stimulus based on relevant previous experience in similar situations, (3) execution of selected plan (e.g., by applying the accelerator, brake, or steering controls), and (4) monitoring the outcome of the behavior subsequent self-correction. The driver's response to the stimulus (e.g., a hazard such as an illegal intersection incursion by another vehicle) is either safe (able to stop) or unsafe (e.g., crash) as a result of errors at one or more of these stages.

PD pathology involves many regions in the brain, leading to multiple cognitive, visual, and motor impairments that can interfere with driving performance at different levels. For example, decreased decision-making ability/executive dysfunction due to frontostriatal dysfunction can lead to poor strategic and tactical choices such as driving under challenging conditions and making risky maneuvers. Impairments in attention, visual perception, memory, executive functions, motor speed, and self-monitoring can lead to driver errors at operational level with unsafe responses to sudden hazards.

The goal in counseling drivers with PD is prevention of crashes while preserving mobility and independence. Medical diagnosis or a clinician's assessment alone is not accurate enough to determine driving competence, as also seen in case examples. Driving performance in PD may vary from normal to severely abnormal, depending on the age of the patient, duration, motor subtype, and severity of parkinsonism and level of visual and cognitive impairment. While a proportion of drivers with PD use compensatory strategies

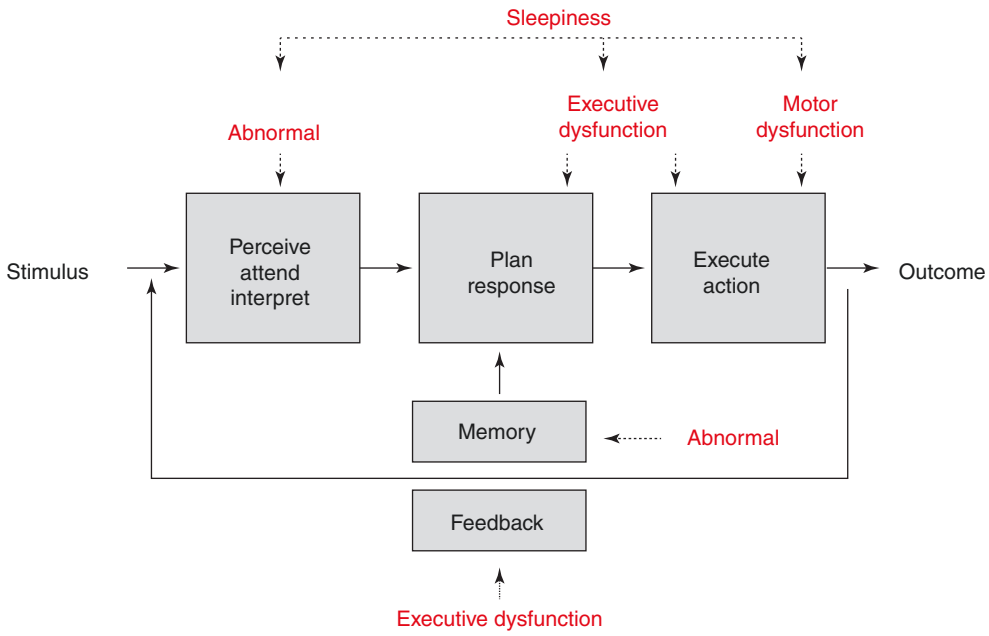

Fig. 31.2 Information processing model for driver error in PD. (Reprinted from Uc and Rizzo (2008))

such as reduction of driving exposure to local regions and avoidance of difficult driving conditions (inclement weather, darkness, rush hour, difficult maneuvers) suggesting some insight into their limitations, both patients and their neurologists have been shown to overestimate the patient's driving ability. The patients' fear of loss of independence due to revocation of their driver's license may also perhaps affect their self-assessments.

There are no evidence-based practice parameters for driving in PD. However, recent National Highway Traffic Safety Administration (NHTSA) and Federal Motor Carrier Safety Administration (FMCSA) guidelines suggest a case-by-case, multidisciplinary evaluation of the patient due to the highly individualized nature of the disease and variable progression. Assessment of visual and cognitive abilities and severity of parkinsonism can inform about the potential risk for undesirable driving outcomes. Additional information can be obtained from recent driving record and insights provided by the patient and family into driving safety concerns or changes in driver habits (e.g., use of compensation strategies to lower risk).

Figure 31.3, developed based on our evidence-based review, may provide a framework to help clinicians determine when drivers with PD are at risk. In general, impairments in visual perception and cognition (especially, executive and visuospatial functions) are the most important determinants of driving ability even if motor impairment is not disabling. However, no cutoffs have been established for different variables and risk factors that would indicate a high-risk driver or a patient with PD who should discontinue driving. In the absence of definitive cutoffs to help clinicians determine fitness to drive, the patient in question should be referred for a multidisciplinary evaluation (e.g., a team consisting of neurologist, neuropsychologist, certified driving rehabilitation specialist-occupational therapists with special training), which includes a comprehensive driving evaluation. If the patient is unwilling or unable to take the evaluation by a certified driving rehabilitation specialist (e.g., no insurance coverage), a referral can be made to the state Department of Motor Vehicles for a road driving test.

Reporting requirements for medically impaired drivers are not uniform across the USA and across the world. The healthcare providers should familiarize themselves with local rules and regulations on reporting of medically impaired drivers. The American Academy of Neurology (AAN) "supports optional reporting of individuals with medical conditions that may impact one's ability to drive safety, especially in cases where public safety has already been compromised, or it is clear that the person no longer has the skills needed to drive safely" and advocates immunity for physicians "both for reporting and not reporting a patient's condition when such action is taken in good faith, when the patient is reasonably informed of his or her driving risks, and when such actions are documented by the physician in good faith."

Disease severity

Mild → Severe

Evaluate for risk factors

	On-road risk factors	Simulator risk factors
Level B evidence	UFOV	None
	Contrast sensitivity	
	ROCT	
	Trails B/Trails B-A	
	UPDRS "off" motor scores	
	Functional reach	
Level C evidence	UPDRS-ADL scores	MMSE
	Trails A	Contrast Sensitivity
	CDR	
	HVLT	
	JOLO	
	Wechsler intelligence test	
	BVRT	
	AVLT	
	Finger tapping	
	Rapid Paced Walk test	
	Timed Get up and Go test	
	Pegboard test	
Other	Age, medications & co-morbid conditions	ADL's (UPDRS & Schwab-England), Trails A/B, UFOV, CFT, JOLO, SDMT, Finger Tapping & reaction time

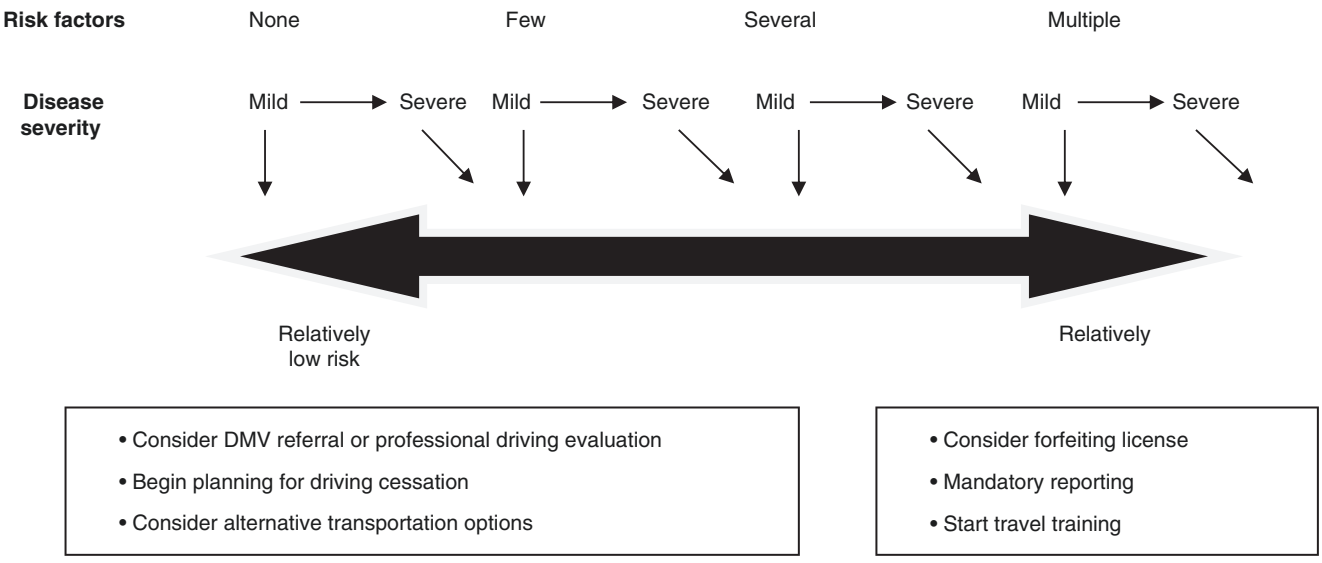

Fig. 31.3 Approach to driving fitness in PD and levels of evidence for various assessment tools. The lower part of the figure shows the interaction of PD motor severity with the presence of visual and cognitive risk factors. For example, a patient with mild motor severity would be at increased risk for unsafe driving if he/she has multiple visual and cognitive risk factors. AVLT Auditory Verbal Learning Test, BVRT Benton Visual Retention Task, CDR Clinical Dementia Rating Scale, ROCFT Rey-Osterrieth Complex Figure Test, HVLT Hopkins Verbal Learning Test, JOLO Judgment of Line Orientation, SDMT Symbol Digit Modalities Test, UFOV Useful Field of View. (Reprinted from Crizzle et al. (2012). With permission from Wolters-Kluwer Health, Inc.)

The literature on driving rehabilitation of elderly or neurologically impaired drivers is limited. Physical retraining and visual perception retraining may improve driving-related skills in older drivers. Speed of processing or reasoning training may delay driving cessation in elderly. There was moderate evidence that educational interventions improve driving awareness and driving behavior but do not reduce crashes in older drivers. Short-term trials using physical conditioning or classroom and road retraining showed improvements in post-training road test performances, but impact on future real-life outcomes has not been reported. An intense simulator training program led to significant improvements within the simulator and was associated with passing an official driving assessment in stroke survivors. However, there was no difference in driving cessation in these stroke patients between the simulator training and control groups at 5 years.

There are no established methods for driver rehabilitation in PD. The challenge is to identify the drivers who would benefit from such intervention, to determine the remediable components of driving impairment, and to design intervention methods that are feasible and useful.

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Part III

Atypical Parkinsonism

Treatment of Progressive Supranuclear Palsy

32

Yuan Xing and Irene Litvan

Case

A 73-year-old man was seen for gait impairment and falls. Three years prior, he began having balance difficulties and falls that progressively increased in frequency, especially in the 6 months prior to evaluation. At the time of initial evaluation, he was falling about three times per month, usually in the setting of descending stairs or turning. Around the same time, his family noticed slurring of speech, and he became progressively increasingly difficult to understand. He was living alone and could still independently perform all activities of daily living. However, he had difficulty with tasks that required fine motor coordination, such as buttoning and typing. In addition, he noted difficulty reading and increased watering of eyes.

On examination, the patient exhibited executive dysfunction on cognitive testing characterized by difficulties with planning and sequencing (Trails), fluency, and retrieval with preserved encoding. He also had impaired attention and inappropriate laughter and crying. Eye movement examination revealed slowing of vertical saccades but not horizontal, attenuated fast phases with vertical optokinetic nystagmus (OKNs), and decreased convergence yet there was no actual vertical ophthalmoplegia at this time. He had axial rigidity in addition to symmetric rigidity and bradykinesia in all extremities, though no tremor. Gait was wide based without freezing or postural instability. The response to the backward pull test was impaired (took several steps and required the assistance of the examiner).

Levodopa was titrated up to 300 mg tid and maintained on this dose for 1 month with no improvement in his symptoms, so it was discontinued. Over the next year, his gait difficulties progressed significantly, and he developed severe freezing when going through doorways and turning. He began using a walker full time, though still had occasional falls when attempting to transfer without a walker. His son moved in to live with him, as he had more difficulty with tasks of daily living, especially stepping in and out of the shower. His speech continued to decline, and he became very difficult to understand, often requiring his son to act as a translator. He underwent speech and physical therapy, which brought mild improvement in his symptoms.

Discussion

Progressive supranuclear palsy (PSP) is the most common atypical Parkinsonian disorder. Patients usually present with severe postural instability and falls, axial Parkinsonism that usually does not respond to dopaminergic therapy, and supranuclear vertical gaze palsy. Although this is the usual presentation of PSP, also known as Richardson's syndrome, atypical presentations are common, and one should have a high index of suspicion for PSP when evaluating patients with Parkinsonism, particularly if there are early falls.

The early falls seen in PSP are likely multifactorial, due to a combination of postural instability, vertical and eventually horizontal gaze palsy, and loss of insight and anticipatory awareness leading to impulsive disinhibited behavior. However, the diagnosis of PSP should be considered in any patient with early falls even if the oculomotor disturbances are not present, as supranuclear vertical gaze palsy often does not present until 2–4 years after motor symptom onset, which was the case in the patient discussed above. In fact, initial presentations with supranuclear vertical gaze palsy are infrequent, seen in less than 10% of patients. PSP should be considered in patients with symmetric, progressive Parkinsonism,

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particularly when it does not respond to dopaminergic therapy or is accompanied by early dysarthria and/or dysphagia. However, PSP can also present as asymmetric Parkinsonism that initially responds well to dopaminergic therapy, resembling PD, and only years later manifests with loss of levodopa responsiveness, postural instability and falls, and eventually supranuclear vertical gaze palsy. Other patients with PSP may present with a corticobasal syndrome with unilateral apraxia, and others present with freezing of gait as a sole feature. In the patient discussed above, axial rigidity, lack of levodopa response, and rapid deterioration in gait ability are strong indicators for the diagnosis of PSP.

In addition to motor findings, patients with PSP may also present with executive dysfunction (e.g., difficulties with abstract thought, multitasking, sequencing, abnormal data retrieval with normal encoding) with or without significant apathy, usually misdiagnosed as depression by family members. At times, patients have emotional lability, with inappropriate laughter or crying that can be disturbing to loved ones and also often misdiagnosed as depression.

Supranuclear palsy, typically manifested as impairment in vertical gaze, is the hallmark finding of PSP. Other oculomotor abnormalities that may be seen are square wave jerks and decreased convergence, and before actual ophthalmoplegia develops, there is a slowing of saccades and impairment of optokinetic nystagmus in the vertical direction with attenuated or absent fast phases with normal horizontal OKN. Many patients experience blurred vision, photophobia, diplopia, or eye discomfort and report difficulty with reading or maintaining eye contact as a result. In addition to eye movement abnormalities, patients may have eyelid retraction, apraxia of eyelid opening or closure, and blepharospasm.

The distinguishing imaging finding in PSP is midbrain atrophy (see Fig. 32.1). In comparison MRI studies of PSP and PD demonstrate both decreased anteroposterior diameter of the midbrain and decreased midsagittal midbrain area in PSP. The rostral midbrain atrophy seen on midsagittal MRI visually resembles the beak of a hummingbird. As such, the "hummingbird sign" can be frequently observed in PSP.

At present, the management of PSP is supportive, and therapy should be targeted toward symptomatic treatment and preventing complications leading to morbidity and shorter survival. However, these treatments can significantly improve the quality of life of those affected with PSP. In addition, there are several therapeutic trials investigating agents that may slow or stop disease progression by addressing the several mechanisms that have been hypothesized to lead to tau aggregation such as inflammation, oxidative injury, and spread of the disease by a prion-like mechanism. Thus, anti-inflammatory agents, antioxidants, and antibodies against tau are being studied.

Lack of response to levodopa can be an important diagnostic tool to distinguish PSP from PD yet some patients may experience benefit. A dose of 300 mg tid for 1 month is

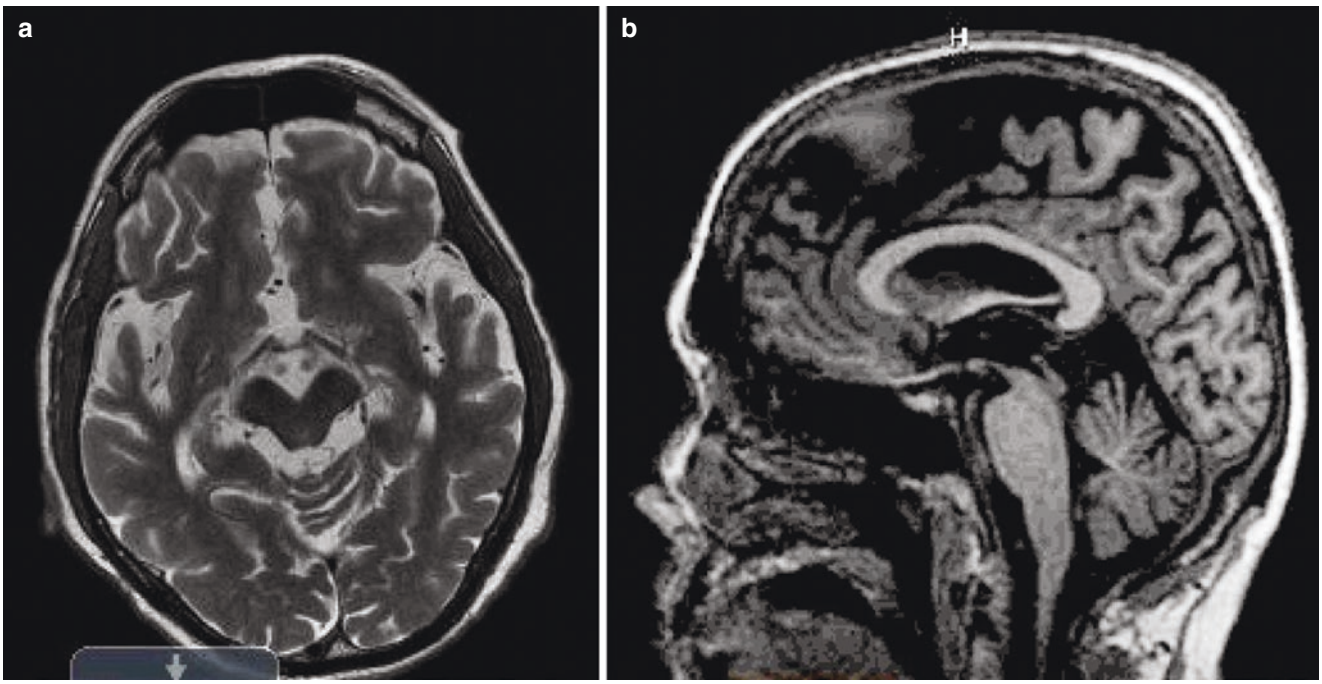

Fig. 32.1 Midsagittal view of the brainstem of a PSP patient showing characteristic midbrain atrophy with preserved pons, resembling the beak of a hummingbird

considered an adequate trial. In the early stages of PSP, there may be mild improvement in bradykinesia and rigidity but this is typically unsustained, and levodopa is usually discontinued as the disease progresses returning only if there is a meaningful deterioration after it is stopped, and the need for continued levodopa therapy should be assessed on an individual basis. Other agents don't have much of a place in the management of the motor symptoms of PSP. However, treatment for the spastic neurogenic bladder in the absence of hypertrophy of the prostate is usually effective and increases patients' and caregivers' quality of life. Physical therapy (PT) with an emphasis on balance should be initiated early, and patients should be encouraged to exercise and remain as active as possible, with proper supervision to reduce the risk of a fall. An assistive walking device should be recommended where there is imbalance or if there has been a fall. We recommend the U-Step walker (ustep.com) as its U-shaped base and reverse-braking mechanism provide stability, improve walking, and may reduce the risk of falling. Some models are equipped with a laser beam as a cue to step over that may be helpful with gait initiation and freezing when ocular movements are still preserved. LSVT (Lee Silverman Voice Treatment) BIG is considered the most beneficial form of physical therapy given its focus on balance. The potential benefit of exercise has not been studied in PSP as it has been in PD, but we encourage patients to maximize activity within safety limitations.

The ocular motility abnormalities seen in PSP can cause significant discomfort and impact quality of life. Conjunctival dryness from decreased blink frequency can be treated with over-the-counter saline eye drops, blepharospasm responds well to BoNT injections, and referral to optometry for prisms can at times be helpful for diplopia.

Cognitive decline and apathy are difficult symptoms to treat in PSP. In a randomized, placebo-controlled study of 21 PSP patients, donepezil provided only modest benefit to cognition while significantly worsening mobility and ADLs. As such, treatment with donepezil is not recommended in PSP. Apathy, impulsivity, and disinhibited personality changes are often very difficult for families to cope with. Families should be educated and counseled about the difference between depression and apathy, and in our experience, support groups and support through CurePSP can be very beneficial for both patients and families.

The mean age of onset of PSP is 63, and the time from symptom onset to death is approximately 5–7 years, with aspiration pneumonia being the leading cause of death. In the earlier years of the disease, modified barium swallow (MBS) and speech therapy (ST) are useful to improve swallow technique and decrease aspiration risk. MBS may identify specific impairments in swallowing and thus guide the use of specific safety tactics, such as chin tuck for retrocollis and optimal food/liquid consistencies. LSVT LOUD ST can improve hypophonia and dysarthria. As the disease progresses, the patient will have more difficulty performing compensatory swallow techniques, and a discussion regarding percutaneous gastrostomy feeding tube may arise. There are no randomized prospective trials assessing the benefit of tube feeding in patients with parkinsonism or dementia, but observational studies and retrospective data in dementia have not been able to demonstrate improved survival with artificial feeding and may lead to increased complications. As with any degenerative disease or end-of-life scenario, patients' advanced directives should be established early, and quality of life issues as well as realistic expectations should be discussed with patients and their families.

We strongly encourage a multidisciplinary team approach in the management of the PSP patient. Given the motor, speech, swallowing, cognitive, urinary, and psychosocial issues encountered in this population, a concerted effort between movement disorder specialists; physical, occupational, and speech therapists; dieticians; neuropsychologists; urologists; social workers; and palliative care specialists is the best approach to provide the most streamlined and coordinated supportive care for PSP patients and their families (Table 32.1).

Table 32.1 PSP treatment algorithm

Motor symptoms/falls	Levodopa trial 300 mg tid × 1 month (usually ineffective) Physical therapy (e.g., LSVT BIG) Occupational therapy Walking aids (U-Step) Home safety evaluation Exercise
Ocular abnormalities	Prisms for diplopia Saline eye drops for decreased eye blink Botulinum toxin for blepharospasm Botulinum toxin for apraxia of eyelid opening
Dysphagia	Modified barium swallow study Speech therapy Percutaneous gastrostomy
Dysarthria	Speech therapy (LSVT LOUD) Speech/communication aids
Dystonia	Botulinum toxin (to be avoided in anterocollis due to the risk of causing dysphagia)
Sialorrhea	Botulinum toxin
Urgent, frequent micturition	Urology consult (urofunctional study) Consider overactive bladder medication
Support	Education Support groups (i.e., CurePSP, community organizations) Counseling Advance directives (POLST) Social work Palliative care/hospice

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Treatment of Multiple System Atrophy

33

Stewart A. Factor

Case

This patient was a 69-year-old right-handed woman who presented for evaluation of her parkinsonism, which was previously diagnosed as Parkinson's disease (PD) 4 years earlier. The initial feature was gait change. A DaTscan was ordered at the time of diagnosis and was abnormal. She was initially placed on carbidopa/levodopa which she says was helpful, and she seemed to do reasonably well for 2 or 3 years before she started having significantly more problems. The biggest issue at the time of the initial visit with us was falling. Her first fall was 4 years earlier resulting in fractured jaw. She started falling regularly 2 years later (2 years post diagnosis) and described the falls as sudden as if she was being pushed. She could fall in any direction. She had three falls in the prior year resulting in injuries including cervical non-displaced fracture, fractured ribs, and knee injury. For the last 4 months, she has been wheelchair bound.

She developed dyskinesia 3 years earlier with worsening in the last few weeks. She experienced wearing off at the time of dyskinesia onset but denied its presence at our initial evaluation. She developed freezing of gait this past year. Fatigue became troublesome as was difficulty chewing and swallowing, and she had significant hypophonia. Her husband indicated she had poor appetite with limited intake, ostensibly eating one meal per day. No sleep apnea or stridor were noted; however she had REM sleep behavior disorder (RBD) with moving and screaming over the last 5 years as described by her husband. She also had developed hallucinations seeing cowboys on the hill about once per week. She expressed depression symptoms and loss of motivation. She currently requires help with all ADLs. She has minimal tremor. She also complains of frequent dizziness and is treated with fludrocortisone, severe constipation (can go a week without a bowel movement) treated with polyethylene glycol and Metamucil, and urinary incontinence since before the PD diagnosis.

Her current relevant medications are carbidopa/levodopa 25/100 1.5 tabs every 2–4 h, carbidopa/levodopa ER 25/100 at night, fludrocortisone 0.1 mg per day, duloxetine 60 mg per day, and clonazepam 0.5 mg 2 tablets at bedtime.

On examination she had severe anxiety. Her BP was 120/60 sitting and 110/50 standing and her heart rate was 92. She had no masked face but had a very low voice volume, hyposmia, and normal extraocular movements. There was no tremor, moderate generalized dyskinesia, moderate to severe rigidity, and bradykinesia. UPDRS part 3 motor score was 41. She had hyperreflexia and no clonus and her toes are downgoing. She needed help standing and could walk only with help. No freezing was seen. There was severe postural instability. Neuropsychological testing was normal.

An MRI scan was ordered and she had hypointensity of the putamen with a hyperintense rim (Fig. 33.1). Her diagnosis was atypical parkinsonism, probable multiple system atrophy.

We arranged psychiatric follow-up for anxiety while switching duloxetine to venlafaxine. We added melatonin for the RBD and decreased the clonazepam because of fatigue. We recommended more vigorous treatment of constipation, prescribed speech and physical therapy, and modified barium swallow study.

Discussion

This patient was diagnosed with atypical parkinsonism for several reasons. (1) She had early gait difficulty and falling; (2) rapid progression to a wheelchair-bound state in 4 years; (3) no tremor; (4) significant autonomic disturbance early in the course including constipation, urinary incontinence, dizziness, and dysphagia; and (5) examination findings of severe

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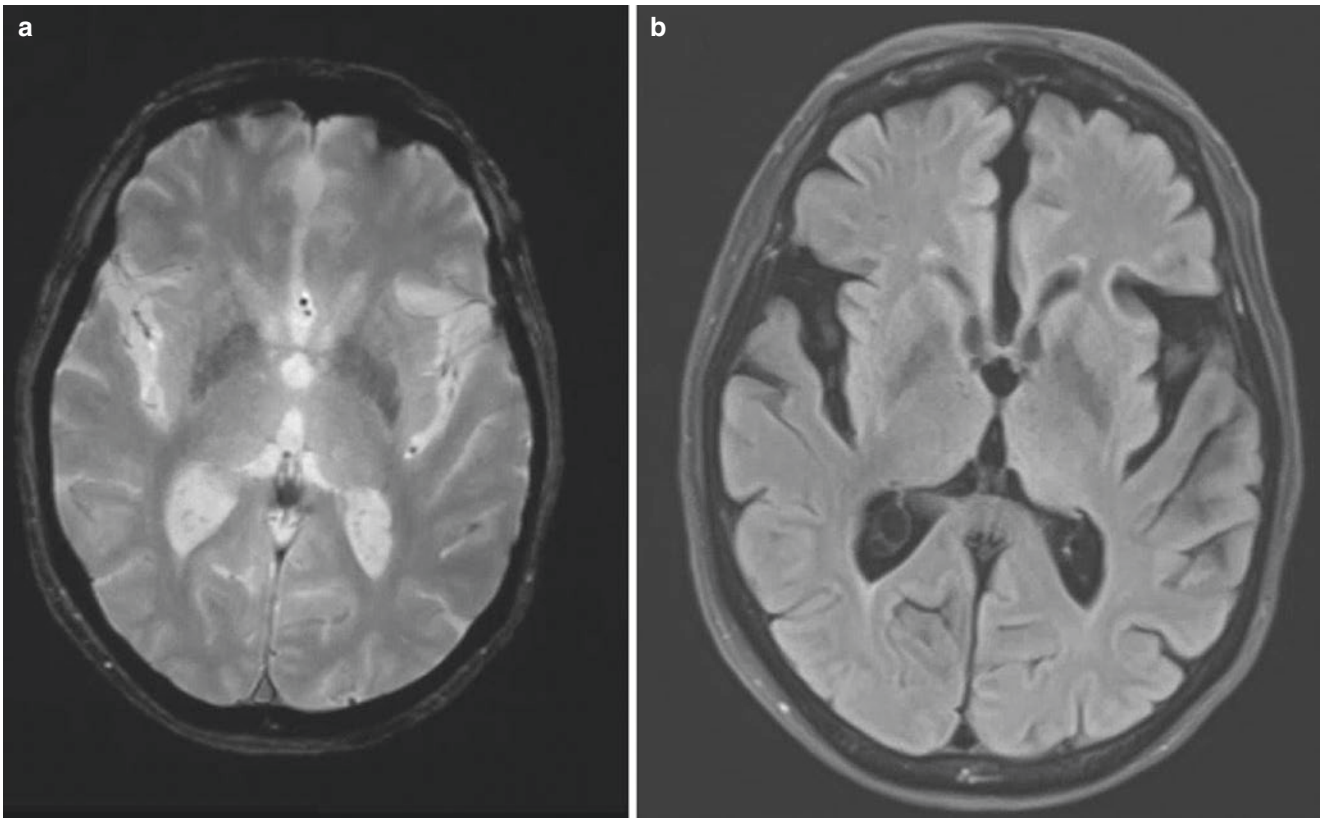

Fig. 33.1 MRI T2 GRE (**a**) and T2-FLAIR (**b**) demonstrate signal changes that include a hypointensity of the posterior putamen and hyperintense lateral putaminal rim

akinesia and rigidity, hyperreflexia, postural instability, (6) and MRI scan result. Her responsiveness to levodopa with development of dyskinesia does not argue against atypical parkinsonism as it is well known that about 30% of patients with several of these syndromes can have this quality in the early stages although it is generally not sustained. The atypical parkinsonian syndromes most frequently seen in the clinic include multiple system atrophy (MSA), progressive supranuclear palsy (PSP), corticobasal syndrome, Lewy body disease, and vascular parkinsonism. Her features best fit probable MSA. It should be noted that MSA and PSP are frequently mistaken for each other.

MSA, a term introduced in 1969, unifies three previously described syndromes, Shy-Drager syndrome (described in 1960), striatonigral degeneration (described in 1960), and olivopontocerebellar atrophy (described in 1900), because of identical pathology. Now MSA is divided into two types, MSA-parkinsonism (MSA-P), where parkinsonian features are the primary signs, and MSA-cerebellar (MSA-C), where cerebellar features, i.e., ataxia, are the primary signs.

MSA is less common than PD with an estimated incidence of approximately 3 per 100,000 in people over 50 years of age and prevalence between 2 and 5 cases per 100,000 population, one tenth that of PD. The mean age of onset is younger than PD, about 54 years of age. Women and men are equally affected and there is no racial predilection. MSA is, for the most part, a sporadic disease. MSA has a poor prognosis as it is a faster-progressing disorder than PD even when patients are responsive to dopaminergic medications. Average length of life is ~7 years.

As one would surmise, the clinical picture of MSA is quite heterogeneous. Core features include akinetic-rigid parkinsonism, autonomic failure including orthostatic hypotension and urogenital dysfunction, cerebellar ataxia, and pyramidal tract signs in varying combinations. Although MSA-P and MSA-C are described, most patients evolve over time to having all the signs and symptoms. Parkinsonism is characterized primarily by akinesia/bradykinesia, rigidity, and postural instability that occurs early (within 3 years as seen in our case). Although it is thought that tremor is uncommon, an irregular jerky postural and action tremor is common (about 2/3 of cases) and actually is telling of the diagnosis. Rest tremor has also been reported but is much less common than in PD. Pyramidal signs include hyperreflexia and extensor plantar responses. Cerebellar features include gait ataxia, limb ataxia, ataxic dysarthria, and cerebellar disturbances of eye movements including gaze-evoked nystagmus, impaired smooth pursuits with saccadic intrusion, and ocular dysmetria.

Autonomic failure is characterized by high rates of urinary dysfunction (>80%), particularly retention and incontinence, and symptomatic orthostatic hypotension (~75%). Nearly all men with MSA develop early erectile dysfunction. Other common early autonomic symptoms include urinary frequency and urgency and incomplete bladder emptying as opposed to PD where there is frequent emptying from detrusor hyperactivity. A post-void bladder ultrasound can be very helpful in diagnosing the problem of urinary retention. This should lead one to suspect MSA over PD if the patient is not prescribed anticholinergics.

There are several other well-known features of MSA that one should look out for. Several spinal abnormalities are commonly seen. Pisa syndrome (subacute axial dystonia with severe lateral flexion of the trunk, head, and neck) and camptocormia (severe anterior flexion of the spine) involve the trunk. Perhaps most characteristic is disproportionate anterocollis or dropped head syndrome which is substantially more common in MSA than PD. The cause of anterocollis and camptocormia in MSA is heterogeneous and controversial. While some authors have suggested they are the result dystonia, there are others who suggest that isolated cervical or thoracic/lumbar myopathy is the cause, at least in certain cases. Others have suggested there is an evolution from dystonia to myopathy, but there is no precedent for that. Electromyography (EMG) usually clarifies the picture, although biopsy may be necessary when the diagnosis is uncertain. Confusing the issue is that it is not entirely clear what a biopsy of normal neck muscle should look like in parkinsonism patients. Other features include orofacial dystonia or dyskinesia, occasionally resembling "risus sardonicus." This may or may not be levodopa induced. Stimulus-sensitive cortical myoclonus is also seen. Dysphagia and speech disorders are also early and common, more so than with PD. The speech abnormalities include hypophonia, and some have an increase in pitch, quivering, and straining element to their voice. Patients with MSA-C have a more typical cerebellar scanning dysarthria.

At least two-thirds of patients have rapid eye movement (REM) sleep behavior disorder. In this disorder dream content becomes violent, and muscle atony in REM sleep is lost. The result is that the patients act out their dreams, which could lead to injury of the patient or bedpartner. This feature of MSA often precedes the motor manifestations, sometimes by decades (as is seen in other synucleinopathies such as PD and Lewy body disease). Another nocturnal problem is laryngeal stridor which may be a risk factor for sudden death. The sound of stridor is high pitched and occurs with inspiration. Patients may also experience sleep apnea and daytime involuntary sighs or gasps. Cognitive function in MSA tends to be relatively well preserved compared with PD and other parkinsonian syndromes. Nevertheless, although cognitive impairment in MSA is uncommon (<20%), it does occur, and its presence does not exclude MSA as a clinical diagnosis. These patients do experience depression and anxiety frequently. Finally, olfactory dysfunction is less frequent and severe than seen in PD. Diagnostic criteria were modified in 2008 (see Gilman et al. (2008)) and are summarized in Table 33.1. This case met criteria for probable MSA.

There are no diagnostic tests for MSA. 123I-FP-CIT SPECT scan or DaTscan (as done in our case) is more readily available currently, but it does not differentiate MSA from PD or other forms of degenerative parkinsonism. All have abnormal putaminal binding. MRI scans provide some

Table 33.1 Clinical diagnostic criteria for MSA: >30 years of age at onset and sporadic disorder plus: (see Gilman et al. (2008))

	Probable	Possible	Supporting features
Primary	Autonomic failure: Urinary incontinence (and erectile dysfunction in males) or orthostatic hypotension (30 mmHg systolic/15 mmHg diastolic drop)	Parkinsonism or cerebellar ataxia	Orofacial dystonia Disproportionate anterocollis Camptocormia Severe dysphonia/dysarthria Inspiratory sighs and snoring Jerky tremor of the hands Cold hands and feet PET and MRI changes
Secondary	Levodopa poorly responsive parkinsonism or cerebellar ataxia	Autonomic dysfunction: Urinary dysfunction – Incomplete bladder emptying, frequency, urgency Orthostatic hypotension to a lesser degree than probable Erectile dysfunction	
Plus		One of the following: Pyramidal tract signs Stridor Dysphagia Rapid progression Poor levodopa response Postural instability in 3 years Combined parkinsonism and ataxia	

diagnostic clues although the changes seen are not universal or specific. For MSA-P T2 MRI signal changes include hypointensity of the posterior putamen and a hyperintense lateral putaminal rim as seen in this case. In MSA-C the "hot cross bun sign" refers to hyperintense T2 signal in the shape of a cross within the pons that arises from degeneration of transverse pontocerebellar fibers.

The definitive diagnosis is through autopsy. Characteristic pathologic findings are glial cytoplasmic inclusions that contain alpha-synuclein, tau, ubiquitin, and other proteins along with neurodegeneration. Pathologic involvement is widespread, and sites include the putamen, caudate nucleus, substantia nigra, locus coeruleus, pontine nuclei (including the pontine micturition area), inferior olivary nucleus, ventral medulla, Purkinje cell layer of the cerebellum, and intermediolateral cell columns (including Onuf's nucleus).

There is no disease-modifying treatment for MSA. All treatments are symptomatic and encompass treatments for parkinsonism, autonomic dysfunction, and sleep and respiratory problems. There are no effective treatments for ataxia. The use of levodopa may be helpful in treating parkinsonian features in about a third of the patients. The response is generally modest and short lived and often requires high doses, perhaps above 1000 mg per day. Some patients develop dyskinesia and motor fluctuations before treatment failure occurs usually within a few years. There is no need to try other dopaminergic drugs including dopamine receptor agonists. If the patients do not respond to levodopa, they will not respond to the other adjunctive agents, and further, autonomic side effects are more common. There is no role for deep brain stimulation in MSA. Physical therapy may be used for fall and contracture prevention and maintenance, at least for a time, of mobility. Therapists will provide guidance for the use of assist devices, and occupational therapists will provide recommendations for maintaining independence in performing ADLs at home. Speech therapists can assess speech and swallowing issues and help determine the need for percutaneous gastric feeding tube. Botulinum toxin injections can be helpful in treating facial or limb dystonia. The use of injections in anterocollis is more controversial. An EMG of neck muscles should be completed first to be sure that the patient does not have myopathy. Also there is a temptation to inject the posterior muscle groups because of pseudohypertrophy, but this will likely make the anterocollis worse.

For respiratory stridor and other respiratory issues, positive pressure ventilation with continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) can be useful. ENT and pulmonary specialists may help with the decision to use this technology or for the need for tracheostomy. It is important to note that tracheostomy may aggravate central sleep apnea which may be life threatening, and tracheostomy though helpful for stridor does not seem to eliminate the risk of sudden death. The treatment of RBD is the same for MSA as for idiopathic and PD-related RBD; take safety measures such as moving objects, padding, and mattresses near the bed and sleeping in separate beds. Medication approaches for RBD include melatonin and clonazepam.

There are several options for the treatment of autonomic dysfunction. Many of the approaches are similar to those in PD which are discussed in chapters "Treatment of Orthostatic Hypotension in Parkinson's Disease", "Treatment of Constipation in Parkinson's Disease", and "Treatment of Urinary and Sexual Dysfunction in Parkinson's Disease". There are some important differences. For example, patients with MSA tend to have urinary obstructive or retentive problems and less irritative or hyperreflexic issues indicating that anticholinergics would not be a choice in MSA and would lead to worsened retention. See Tables 33.2, 33.3, and 33.4 for summaries of the nonmedical and medical treatments for urinary problems, constipation, and orthostatic hypertension. Most of the treatments for these problems have not been studied specifically in MSA, with the possible exception of droxidopa for orthostatic hypotension which was examined in mixed populations. Nevertheless these issues are quite troublesome and require therapy.

Table 33. 2 Treatments of urinary problems in MSA

Nonmedical treatments	Medical treatments
Assess fluid, caffeine, and alcohol intake	Alpha-blockers – α1 – Tamsulosin and silodosin, for obstructive uropathy, will increase orthostasis
Control constipation	Antimuscarinics – Solifenacin, fesoterodine, darifenacin, trospium – For bladder hyperreflexia
Treat ankle edema	Beta-3 agonist – Mirabegron – Helps hypotension
Avoid nocturnal hypertension	
Exercise	
Continence products: Pads, briefs, external collection system	
Scheduled voiding or self-catheterization	

Table 33.3 Treatments of constipation in MSA

Nonmedical treatments	Medical treatment
Adequate fluids	Polyethylene glycol
Fiber supplements	Stool softeners: Colace, Dulcolax
Exercise	Magnesium-based products such as milk of magnesia and citrate of magnesium
	Osmotic laxatives such as lactulose
	Lubiprostone (secretagogue and chloride channel activator)
	Linaclotide (guanylate cyclase-C agonists that increase secretory activity)

Table 33.4 Treatments of orthostatic hypotension in MSA

Nonmedical treatments	Medical treatments
Increase water/salt intake (16 oz. glass of cold water upon awakening) (fluid 2–3 L/day, salt 6–10 gm/day)	Fluid expanders: Fludrocortisone
Conditioning – Lower body	Vasoactive drugs: Midodrine, ephedrine
Avoid standing quickly	Prostaglandin inhibitors: Indomethacin, ibuprofen
Avoid large meals and alcohol	Noradrenergic precursor: Droxidopa
Avoid hot baths or showers	Cholinesterase inhibitor: Pyridostigmine
Avoid straining with defecation	Peripheral D2 receptor blocker: Domperidone
Waist high support hose (difficult to use)	α-2 adrenergic antagonist: Yohimbine
Keep the head of the bed propped up in bed – Head 6–9 inches higher than feet	
Recognize the earliest symptoms: Sit or use an isometric exercise	

Finally, depression and anxiety are common issues in MSA as seen in this case. They should be monitored and treated appropriately. Antidepressants and anxiolytics have not been studied specifically in MSA but should be utilized.

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Treatment of Dementia with Lewy Bodies

34

Holly A. Shill

Case

A 74-year-old right-handed man was self-referred for evaluation of tremor and possible Parkinson's disease. The history is provided by the wife since the patient is having trouble organizing his thoughts. She reports that about 6 months ago, he began noticing a tremor in the L hand when the hand was down at his side or when sitting quietly in the evening. It has become larger in amplitude and more persistent with time but is not really bothering the patient too much. Inquiring further, you learn that the patient is slower with his walking and is less talkative. She thinks he might be depressed as he has withdrawn from some of his previous interests such as getting coffee with his friends and golfing. Querying the patient about mood, he indicates that he feels that his mood is fine and says he is no longer golfing because his buddies like to start too early. You identify this feature as apathy and probe further about cognitive issues. Per the wife, he really began to withdraw about 2 years ago. She has always been the social one, but he seems even less interested in talking when they are out with friends. He used to do all the banking for them and still can do it but needs prompting. His short-term memory seems to be fine. He is still driving, but she is sometimes nervous when with him as he has trouble staying in the lane and has trouble pulling into parking spaces as he cannot judge the size of the cars in relationship to the space. He does not get lost. He can sometimes have trouble expressing his thoughts but does not forget names. She has stopped giving him anything extra to do on his way home from somewhere as he can get overwhelmed easily. He can still do all his activities of daily living such as dressing, bathing, and grooming although the wife relates that he is a little more likely to have to be prompted to do self-care and is slower. His walking is slower but he does not shuffle or fall. Putting the cognitive features together, you decide he is having some executive dysfunction as well as visual spatial issues, but that other domains seem relatively intact. You next inquire about other non-motor features. He has become more irritable when she tries to engage him in discussions or if she asks him to do something for her. He does not sleep well, sometimes getting up at night for an hour or two before coming back to bed. He has "vivid dreams" and talks in his sleep and occasionally will seem to be fighting someone in his sleep as he can shout out and may swing his arms. In retrospect, he has been doing this for several years. The patient is not aware of these dreams. In the evening, he is a little more likely to "space out" which the wife attributes to not sleeping as well. He has no true visual hallucinations. He has no blood pressure issues and denies orthostasis. He has no bowel or bladder complaints other than getting up twice at night to use the bathroom.

Examination shows blunted affect, mild bradykinesia throughout, resting tremor of the left hand, and slow gait speed. You perform a MOCA as it is more sensitive than the MMSE and he scores 23. You discuss your diagnosis of parkinsonism with mild cognitive impairment. You discuss how about 20% of patient with early PD can have MCI, but you are worried that it might be more than just what can be seen with Parkinson's disease and suspect that this might be early dementia with Lewy bodies [DLB]. You discuss the utility of doing dopamine transporter imaging and FDG-PET scanning but decide to hold off as you are not sure it would change management.

Given that he has slowed down, you elect to treat with levodopa. At 1-month follow-up, he has responded to this with the wife noticing that he is moving easier and even seems more talkative. You continue to follow him at 3- to 4-month intervals. After 1.5 years, the wife notes he has voluntarily given up driving. He has started to have low-grade illusions such as mistaking stop signs for people. He is no longer doing the banking. He is even having some mild difficulties dressing. You discuss how you are now fairly certain this is DLB. You begin treating with donepezil 5 mg given

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the increasing cognitive issues. He tolerates this well, and the spouse notes that he seems more engaged in conversations and less irritable. Over the succeeding 2 years, he begins to develop increasing problems with hallucinations, often seeing people standing outside the window at night and animals that sleep at the foot of the bed. These are not that distressing for him. However, he is becoming increasingly concerned that his wife might be cheating on him and often wonders where she has been if she goes out to shop. She can no longer leave him alone. Cutting back levodopa from three times per day to twice daily and increasing donepezil to 10 mg seems to help with the psychosis, but the patient remains with problematic cognitive issues spending most of the day sitting in front of the television and restlessly pacing in the evening. You suggest an adult day health program, and the wife finds this helpful giving her some respite time as well as helping the patient get more exercise and social interaction. Eventually, the wife can no longer manage him at home, and he is placed into a memory facility.

Discussion

The first issue to deal with is the diagnosis of DLB. There are two main ways patients present. In this case, the motor symptoms are what led the patient to the neurologist with the suspicion of Parkinson's disease. The other typical presentation is a primary complaint of "memory loss" with a concern that patient may be developing Alzheimer's disease. The McKeith criteria are often used for the diagnosis of DLB and can be quite sensitive but often lack specificity. The criteria require the presence of dementia as the first sign followed by core features of fluctuating cognition, visual hallucinations, and spontaneous features of parkinsonism. Suggestive features include a REM sleep behavior disorder, neuroleptic sensitivity, and abnormal dopamine nerve terminal imaging by SPECT or PET. In practice, these criteria are often difficult to meet even when the clinical suspicion might be quite high. For instance, a patient presenting with dementia who has a preceding history of PSG-confirmed RBD is quite likely to have DLB pathologically even in the absence of other core clinical features. Also, as in our patient above, the presentation is that of PD with MCI, yet there seemed to be more cognitive impairment than is typical of early PD. Another issue to grapple with is the strict research criteria that the dementia and parkinsonism start within 1 year of each other in order to diagnose DLB. If the motor symptoms start first and cognitive impairment begins greater than 1 year out, it would be called Parkinson's disease dementia by both McKeith criteria and Emre criteria for PDD. However, there is clearly a vast range in how patients present in terms of time course and severity of motor and cognitive symptoms. In my practice, I diagnose DLB using the research criteria strictly but then add comments where appropriate. So, for the patient above, the impression would be "parkinsonism meeting criteria for Parkinson's disease but with early MCI concerning for DLB."

In a memory clinic, the diagnosis becomes even more problematic. Although dementia with Lewy bodies may account for up to 30% of patients presenting with dementia, it is rarely recognized because of either the lack of a classic presentation or failure to look for characteristic features such as an RBD, hallucinations, or mild parkinsonism. There have been attempts to operationalize more clinically useful diagnostic criteria with checklists that be easily scored in the clinic, such as the Lewy Body Composite Score, which captures the salient aspects of the McKeith criteria in a more clinically relevant manner. The final issue diagnostically is the pathology of DLB. The vast majority (if not all) of patients with DLB will also have sufficiently high Braak staging for AD to meet criteria for this dementia as well. Coming the other way, there are many AD patients who have Lewy bodies that are insufficient to meet pathological criteria for DLB. These could be called ADLB. For both groups, the impact of other additive pathologies on the cognitive profile of the patient is still not clear.

Next, we will discuss the individual core symptoms of DLB. The cognitive profile of DLB should be distinguishable from AD. Although short-term memory and language difficulties are often most problematic in AD, the pattern in DLB is different. Attention problems that might seem like a memory problem to the patient can often be teased out by inquiring or testing for free recall and comparing it to cued recall with DLB patient often performing better with cueing. Executive dysfunction often starts with apathy and a reduction in verbal fluency. The actual content of the language is normal without word substitutions or forgetting names. Apathy should be distinguished from depression. Visual spatial impairment often starts subtly, for instance, with mild changes in driving. With disease progression, problems such as not being able to eat due to inability to "find" food on the plate can be seen.

The cognitive fluctuations are an interesting phenomena with the pathophysiology poorly understood. Family members will notice that the patient is often drowsy or sleeps during the day and has periods of staring into space and episodes of disorganized speech. This can prompt a concern for seizure or TIA, but it is surprisingly rare to find either of these problems as a cause.

Hallucinations in DLB often begin with low-grade illusions of a sense of presence or something moving and with time may become well-formed, seeing people or animals. When cognitive impairment is not severe, patients can often give detailed descriptions of the hallucinations. Caregivers are often surprised at the complexity of the hallucinations. Other types of hallucinations can occur but visuals are the

most common. Delusions can also be seen in DLB with paranoia of infidelity being quite common.

Mood changes also occur in DLB so inquiring about both depression and anxiety is important. "Sun downing" can be seen with DLB as with AD. Wandering behaviors seem to be less common, perhaps reflecting more apraxia than in AD; the patients might not be able to operate doors and locks in order to get out. True aggression is less common in DLB, perhaps reflecting greater impairment of mobility than seen in AD; if aggression occurs in DLB, it usually does so in the setting of delusions or hallucinations.

Autonomic dysfunction is seen in DLB as well as PD. Patients may have orthostatic hypotension, syncope, and urinary urgency.

Treatment of DLB can be quite complex as one attempts to address the cognitive, motor, and non-motor aspects of the disease as well as the significant caregiver issues. Despite the high frequency of DLB, there have been relatively few treatment studies specifically for DLB. Therefore, best practices come from extrapolating what is known in the treatment of PD, PDD, and AD.

Cholinesterase inhibitors such as donepezil and rivastigmine can be used to treat cognition. Surprisingly, DLB may seem to have a more robust response than AD. Family members will often report that the patient is more talkative and can express thoughts more easily. Hallucinations may also respond to these agents. Tolerability is generally good for this class at lower dosing but may be less well tolerated at the higher dosing used in AD. If the patient has resting tremor, this can worsen, and gastrointestinal upset might be more common than with AD.

Memantine can be tried with about 1/3 of patients responding. Behavioral issues in particular might improve with this agent. With both of these classes of medication, there is little evidence that they slow progression or delay placement into a nursing home setting so I typically use them for symptomatic improvement only and stop them if no clinically evident response after 1–2 months of treatment.

Psychosis in DLB can be quite challenging to manage. Drugs such as levodopa and other dopaminergic agents used for mobility can make psychosis worse so may need to be reduced or stopped. Drugs that are being used to treat comorbid conditions such as bladder dysfunction can contribute to psychosis, and these may need to be stopped or changed. Most antipsychotics can make parkinsonism worse, often severely, so should be avoided. Quetiapine can be used for acute agitation and as needed but likely has little long-term benefits. Pimavanserin is approved for use in PD psychosis and should be safe in DLB, but it is still relatively new. Clozapine has been shown to be safe and effective for PD psychosis and likely is efficacious in DLB psychosis but requires frequent blood monitoring for agranulocytosis. As above, cholinesterase inhibitors can be helpful. In my experience, benzodiazepines for agitation often cause paradoxical agitation, somnolence, and prolonged confusion so should be used with caution. Lastly, one should not forget the benefit of non-pharmacological approaches such as removing or covering mirrors in the home, closing curtains at night, keeping extra light on at night, avoiding disturbing television, and improving social outlet as through adult day health programs. Educating caregivers is also important. Mild non-threatening hallucinations may not need to be addressed. Reassurance and redirection of the patient rather than confrontation can be quite beneficial.

Parkinsonism should be treated if significantly impairing activities of daily living. A slow, shuffling gait in particular should prompt consideration for treatment as this can predict fall risk. Executive dysfunction in DLB can increase fall risk as patients are often not mindful of their own walking ability and fall risk and will "forget" they are supposed to walk with assistance of a walker or caregiver. Levodopa is the drug of choice given the higher frequency of hallucinations and confusion with drugs such as dopamine agonists and anticholinergics.

Orthostasis can and should be treated if symptomatic. Non-pharmacological approaches can be tried first followed by drugs such as fludrocortisone, midodrine, and droxidopa. The former includes drinking plenty of water, liberal use of salt, head of the bed at 20 degrees, avoiding large meals and arising quickly, and especially eliminating drugs known to lower blood pressure.

Sleep issues can be challenging. Melatonin can be used for RBD, while clonazepam is the drug of choice for RBD in PD, but with DLB, increased sedation and confusion might limit its use. If clonazepam is used, the orally dispersible tablet comes in 0.125 mg which might be tolerated better. For insomnia and restlessness, I typically use mildly sedating antidepressants such as trazodone or mirtazapine.

Caregiver strain should be discussed. Because of the fluctuations in behavior, patients might be on their best behavior when you see them in the clinic only to completely change personalities when they are home with their spouse. Placement can be challenging as memory units often require that patients be mobile and those with frequent falls due to parkinsonism or orthostasis might not do well unless continuously supervised, often nearly impossible in a larger care facility. Smaller group homes with more one-on-one attention might be a better fit for some of these patients. Resources in the community can be found through the various PD and dementia organizations. Home health agencies for home safety assessments and social work support can be helpful. Caregiver respite opportunities can be utilized including supervisory and nursing help within the home and adult day health programs outside the home.

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Treatment of Corticobasal Syndrome

35

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Case

A 69-year-old right-handed man presented with 3 years of progressive motor and cognitive difficulties. He first noticed that he would miss balls when swinging his golf club. This progressed to problems using his hands to button his shirt, put his tie on, tie his shoelaces, and put his belt on. His dressing deficits related to problems orienting his clothes correctly, such as figuring out the front versus back of a T-shirt or problems putting his socks on, such that the heel would end up on the dorsum of his foot. His wife observed a subtle tremor in his left hand, mostly when trying to reach for things. He remarked that his left hand seemed to give him more problems than his right. Although it was hard for him to articulate, he did not feel hand weakness or stiffness, more than it did not follow his commands. He had no difficulties using his right hand or either leg. At work, it took longer to complete routine tasks. He became more easily distractible and had difficulties organizing papers on his desk, typing text on his computer, and writing checks. His deficits in visuospatial processing were evident at work. For example, he had trouble orienting a business card in such a way that he could read it. When driving, he reported problems judging distances between cars and developed new difficulties with parallel parking. These symptoms caused increasing frustration and anxiety, and he had a few emotional outbursts of tearfulness. Sometimes he would cry out of the blue and without an apparent reason or over minor problems.

He reported pruritus on his back for about 2 years. He also had polyuria that he attributed to prostate problems. He had increased appetite and a new preference for eating fruit that led to a 10 lb weight gain in the prior year. He reported moderate insomnia and daytime somnolence, but no snoring or dream enactment. He denied memory or language problems. He had no double vision, balance problems, falls, or dysphagia. He had no recent changes in personality, apathy, socially inappropriate behavior, or hallucinations. He was still working as a financial counselor and continued driving despite his reported difficulties. He was able to manage his finances, and other than needing help with dressing, he was independent with activities of daily living. His medical history was significant for hyperlipidemia, diabetes, and benign prostatic hypertrophy. His medications included metformin, lisinopril, atorvastatin, and aspirin. He had no family history of dementia or movement disorders. He had a healthy lifestyle and reported drinking a glass of wine once a week with no history of tobacco or drug use.

The neurologic exam revealed normal eye movements. He had difficulties demonstrating the use of a knife to cut a loaf of bread and flipping pancakes with a spatula with his left hand (ideomotor apraxia). He also had problems imitating hand figures, completing the Luria (fist-hand-palm sequencing) test, and doing sequential finger tapping, mostly on the left. The left upper extremity revealed cogwheel rigidity, worse with activation maneuvers, mild weakness (4+/5) of finger abduction on the left and subtle dyskinesias, and continuous dystonic posturing of his thumb in opposition. There was subtle dysmetria on finger-to-nose on the left and left-greater-than-right reduced speed of finger tapping. His foot tapping was clumsy bilaterally, more on the left, especially with heel tapping or toe tapping only. His lower extremities showed mild paratonia bilaterally. He was unable to detect numbers or letters traced on his palms, and he had decreased vibration and temperature sensation on the left foot. On gait assessment, he had left-greater-than-right decreased arm swing and some difficulties with tandem walk. There was no bradykinesia, or changes in his facial expression or speech. His Mini-Mental State Exam score was 27/30, losing points on delayed recall, name of county, and pentagons.

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Formal neuropsychological testing was significant for prominent visuospatial dysfunction, with difficulties copying figures and performing calculations. His visual memory and executive function were only mildly affected at expense of visual-related tasks. A brain MRI revealed right-worse-than-left perisylvian, dorsolateral, and medial frontal sulci enlargement. The anterior and mesial temporal lobes also showed sulci enlargement, but there was a relative preservation of hippocampal volumes. FLAIR images revealed a few discrete foci of frontal subcortical white matter hyperintensities, some of them juxtacortical. A brain positron-emission tomography (PET) scan with ^{11}C-labelled Pittsburgh Compound-B (^{11}C-PiB) to visualize beta amyloid showed no cortical tracer retention. Investigational brain flortaucipir PET to detect tau showed abnormal basal ganglia and right sensorimotor cortex retention (Fig. 35.1).

The concomitant presence of lateralized apraxia, cortical sensory loss, extrapyramidal signs, and mild cognitive impairment, visuospatial subtype, in the setting of lateralized frontotemporal brain atrophy and molecular neuroimaging findings was concerning for corticobasal syndrome (CBS) likely due to corticobasal degeneration (CBD), a condition in the frontotemporal lobar degeneration (FTLD) spectrum. Because his extrapyramidal symptoms were non-disabling, a levodopa trial was deferred, with plans to initiate a trial if his motor symptoms worsened. He was started on citalopram 20 mg daily before bed, with significant improvement of his anxiety, crying spells, and insomnia. He engaged in a structured program of moderate-to-intense aerobic exercise. He underwent physical, occupational, and speech therapy evaluations and started a yoga program with subjective improvement of movement, balance, and coordination. He started using voice recognition software which supported some functions at work, including interaction with clients. He was referred to an independent driving evaluation. He and his family received counseling regarding the neurodegenerative and progressive nature of his disease. He was referred to a research center for enrollment in an observational cohort and consideration for clinical trials.

Discussion

Corticobasal syndrome is a clinical syndrome encompassing asymmetric parkinsonism that is not responsive to levodopa, and appears in the setting of cortical sensorimotor, behavioral,

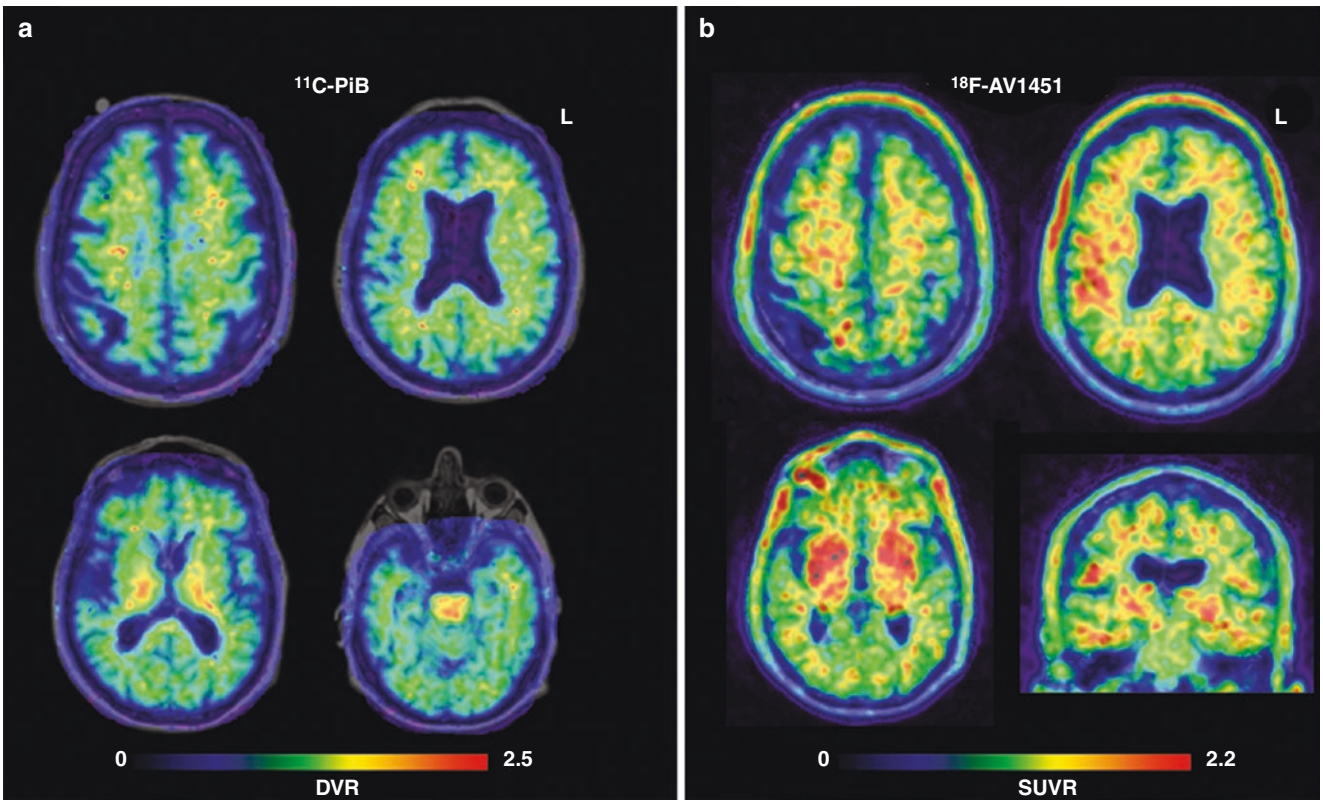

Fig. 35.1 Brain amyloid and tau PET results. Images show negative ^{11}C-labelled Pittsburgh Compound-B (^{11}C-PiB) retention supporting no significant amyloid accumulation (**a**) and positive flortaucipir (^{18}F-AV1451) retention, supporting the presence of focal and asymmetric abnormal tau accumulation, especially in basal ganglia and right perirolandic cortical regions (**b**). DVR distribution volume ratios, SUVR standardized uptake value ratios. (Images are courtesy of Richard Tsai and Gil Rabinovici)

or cognitive deficits, usually within 1-2 years of symptom onset. It should be considered after non-neurodegenerative causes have been ruled out (see Lee et al. 2011). Initial symptoms of CBS can be quite varied, ranging from isolated appendicular fine motor incoordination to complex combinations of motor, cognitive, and behavioral changes. Cardinal features of CBS include symmetric or asymmetric extrapyramidal signs; perceptual motor dysfunction, especially sensorimotor deficits suggesting perirolandic involvement; and cognitive impairment. The extrapyramidal deficits may or may not be lateralized and may initially be responsive to levodopa, although the response is usually not as dramatic or long lasting as seen in Parkinson disease (PD).

Cortical sensorimotor deficits frequently appear in one limb and slowly progress to affect the ipsilateral or contralateral limbs or may involve visual neglect. Cortical motor deficits include limb-kinetic or ideomotor apraxia or myoclonic jerks. Dystonic posturing that is initially intermittent but may later become persistent and sometimes disabling, painful, and deforming is a frequent source of disability. Subtle dystonia that may be exacerbated with stress maneuvers such as toe or heel gait is sometimes present. A characteristic sensorimotor deficit seen in CBS is the alien limb phenomenon. Its most subtle form is an occasional drifting out of position or levitation when held in front of the body, or a sense that the limb may not be part of one's body. Such deficits are thought to localize more to the parietal lobe. A more grasping or semi-purposeful mirror movement type of alien limb is more frequently localized to medial frontal lobe regions (supplementary motor area). Common cortical sensory deficits include tactile agnosia, agraphesthesia, or impairment of two-point discrimination. Some patients have sensory phenomena such as localized paresthesias, pain, or pruritus. The cognitive impairment may precede, be concomitant with, or follow the appearance of motor symptoms. Upon presentation, cognitive impairment is usually mild, sometimes yielding scores in the normal range with bedside screening batteries such as the Mini-Mental State Exam or the Montreal Cognitive Assessment. Cognitive impairment is usually progressive, and it may involve any domain including language, visuospatial processing, or executive function, although it is more commonly multidomain. Short-term memory impairments are sometimes present. Behavioral abnormalities may range from none to sleep and mood changes or more dramatic behavioral abnormalities as seen in behavioral variant frontotemporal dementia.

CBS (corticobasal *syndrome)* refers to a clinical syndrome with a number of potential underlying causes, whereas CBD (corticobasal *degeneration*) refers to a particular pathological diagnosis in the FTLD spectrum that sometimes, but not always, presents as CBS. Thus, CBS and CBD are not equivalent terms. CBS may be the presentation of a number of neurodegenerative diseases including entities in the FTLD spectrum such as CBD (24–35%), progressive supranuclear palsy (PSP) (12–28%), and FTLD-TDP type A (10–12%) (Lee et al. 2011). CBS may also be the presentation of Alzheimer's disease (AD) (22–24%) or cases with mixed or rare pathology (5–13%) such as FTLD/AD; Pick's disease; FTLD associated with *MAPT*, *GRN*, *C9ORF72*, *or TBK1 mutations*; monogenic forms of parkinsonism; Lewy body disease; or prion disease. Depending on the underlying pathology, it is not uncommon that CBS overlaps with some phenotypic characteristics of particular pathological entities such as PSP (falls, ocular motor abnormalities, and insomnia), FTLD-TDP (personality changes and socially inappropriate behavior), CBD (nonfluent aphasia or apraxia of speech), and AD (episodic amnesia or biparietal deficits).

Our initial CBS workup includes formal neuropsychological testing for delineation of involved cognitive domains, MRI to assess for the presence of perirolandic atrophy (Fig. 35.2), and search for evidence of the AD pathophysiological process through amyloid brain PET or quantification of Aβ42, tau, and p-tau levels in CSF. Novel quantitative structural neuroimaging techniques, including voxel-wise morphometry and diffusion tensor imaging, are sensitive to structural changes in CBS over intervals as short as 6 months. These imaging modalities will likely be used more in the near future, especially as biomarkers relevant for clinical trials. For example, CBS patients exhibit baseline and longitudinal atrophy in bilateral cortical and basal ganglia regions including precentral gyrus, postcentral gyrus, supplementary motor cortex, putamen, and frontoparietal white matter (Dutt et al. 2016) (Fig. 35.3). Brain FDG-PET has been useful when MRI, amyloid PET, or CSF studies are not available. FDG-PET may be helpful to predict the underlying pathology in CBS based on the pattern of hypometabolism. Although it is not a strict rule, bilateral posterior (i.e., parietal, precuneus, posterior cingulate) hypometabolism is in general associated with the presence of positive amyloid PET, whereas CBS cases associated with negative amyloid PET or pathologically confirmed FTLD have a higher rate of asymmetric hypometabolism in frontotemporal areas (anterior cingulate, insula, anterior temporal lobes, dorsolateral prefrontal, and orbitofrontal) (see Sha et al. 2015). DAT scans add little information regarding the differential diagnosis of CBS, and we consider them less clinically useful. Finally, tau-based molecular neuroimaging with ligands such as flortaucipir, also known as ^{18}F-AV1451, is a promising tool for the in vivo imaging of tau deposits in CBS. For example, it has been shown that tau-PET in pathologically confirmed CBD reveals increased signal in putamen, pallidum, thalamus, precentral cortex, rolandic operculum, supplemental motor area, and left Broca's area, with an excellent correlation with underlying, quantitatively measured tau in pathological specimens (see Josephs et al. 2016). It is likely that tau imaging will be used as part of the diagnostic approach of CBS and screening process of CBS clinical trials (Fig. 35.4).

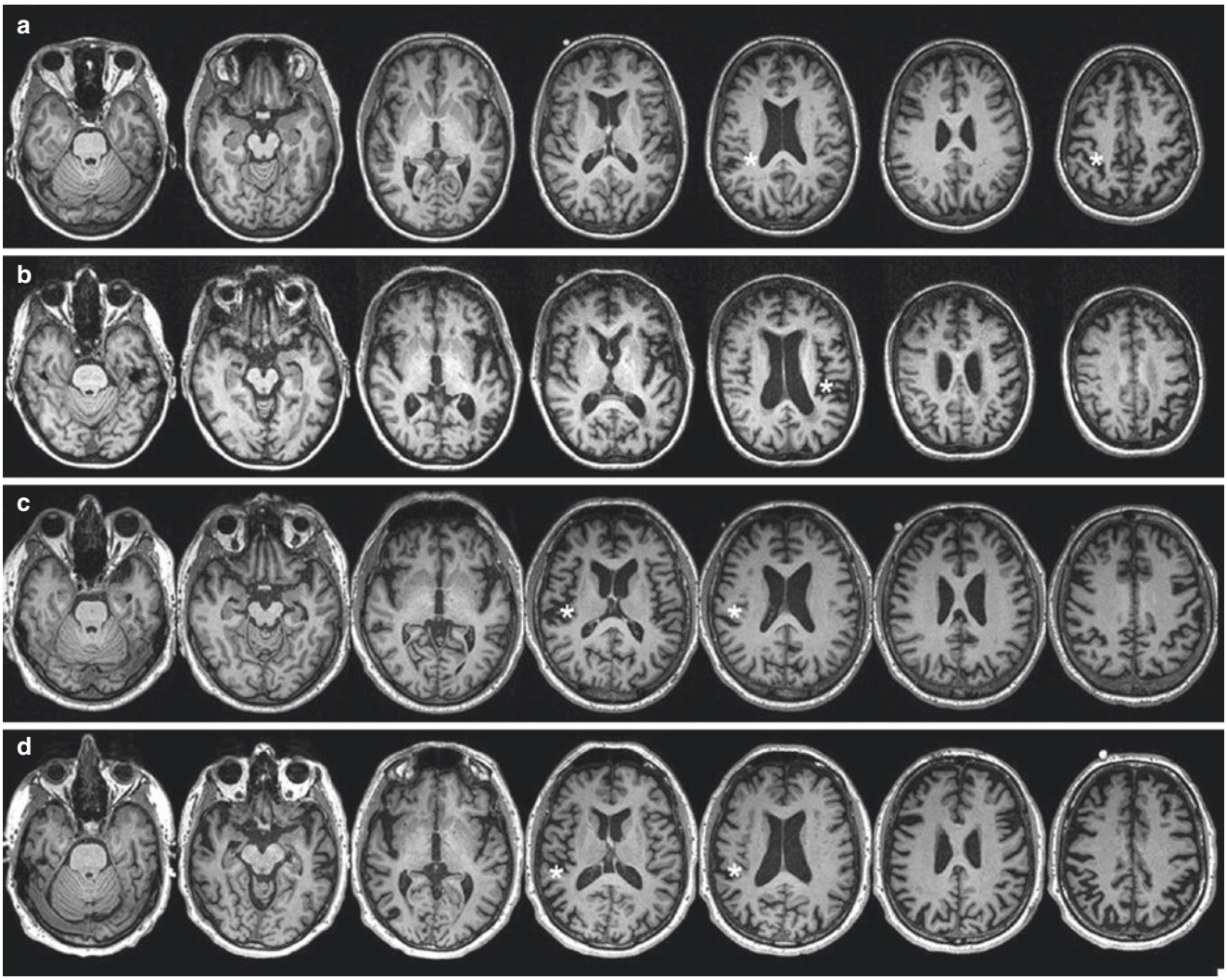

Fig. 35.2 Structural features of corticobasal syndrome. Axial T1-weighted MR images show cases of corticobasal syndrome (CBS) due to corticobasal degeneration (CBD) (**a**), progressive supranuclear palsy (PSP) (**b**), frontotemporal lobar degeneration associated with TAR DNA-binding protein type A (FTLD-TDP A) (**c**), and Alzheimer's disease (**d**). Note that particular patterns of atrophy are indistinguishable between cases by visual inspection, but volume loss around the primary sensorimotor cortex (asterisk) is a common feature

At this time there are no disease-modifying or specific treatments for CBS, but novel disease-modifying therapies are currently under development. Because a large proportion of cases of CBS are associated with an underlying tauopathy, development of anti-tau therapies, also relevant to PSP and AD, is expected to be important for CBS. These include anti-tau monoclonal antibodies, microtubule stabilizers, acetylation inhibitors, and aggregation inhibitors (Fig. 35.4). Despite the lack of approved treatments, a number of pharmacological, physical, and behavioral interventions can be implemented to provide symptom relief and improve quality of life. These are used based on small series observations, anecdotal reports, and expert experience. Our management approach to CBS focuses on motor, sensory, functional, and cognitive/behavioral deficits.

Motor deficits A trial of L-DOPA should be considered for CBS patients who have disabling parkinsonian signs (typically bradykinesia or rigidity). About 30% of CBS patients have a positive response to L-DOPA, although rarely to the degree seen with PD and it is often short-lived; doses of 600–900 mg per day are a reasonable target. Some patients have minor to modest motor responses that may translate into meaningful functional changes, such as being able to use one finger to type or hold a straw. Zolpidem, an imidazopyridine with selective agonist action on the benzodiazepine-1 receptor, may have a role in the management of extrapyramidal motor symptoms in CBS suspected to be associated. Zolpidem has been reported to transiently ameliorate motor and bulbar deficits in patients with PSP. Dystonia may respond to long-acting benzodiazepines such as diazepam or

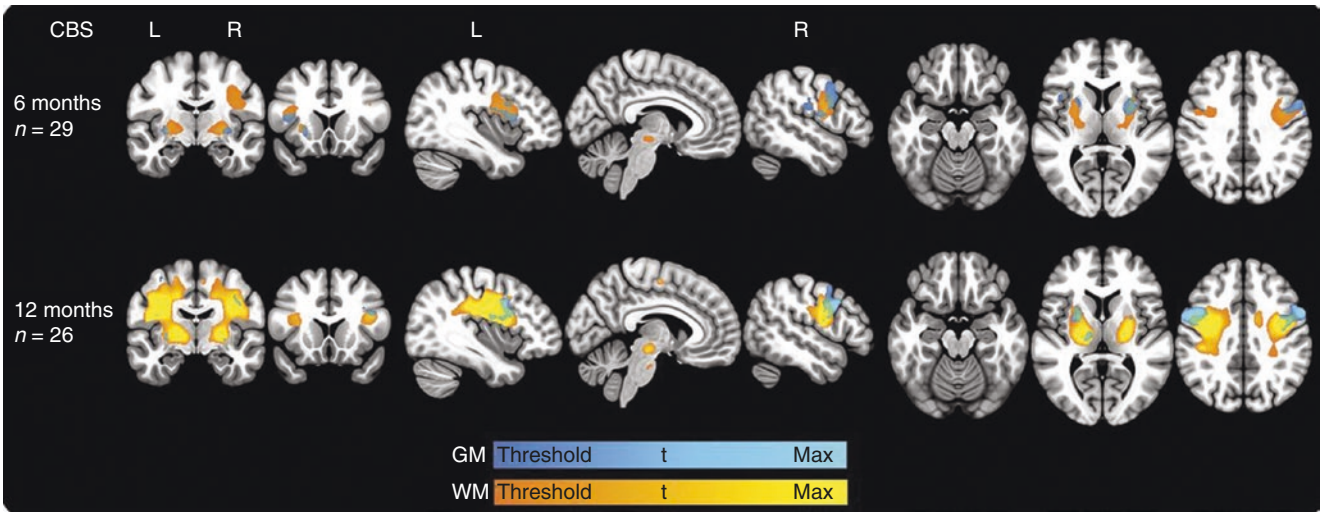

Fig. 35.3 Longitudinal gray and white matter voxel-based morphometry analysis in corticobasal syndrome. The colored areas show gray matter (blue) and white matter (orange) brain regions with significant volume loss at 6- and 12-month intervals in patients with corticobasal syndrome, compared to controls, after correction for age, sex, and total intracranial volume. The most prominent regional volume loss at 6 months occurs at the precentral gyrus and putamen. The most prominent regional volume loss at 12 months occurs in the precentral gyrus, opercular part of the inferior frontal gyrus, putamen, pallidum, and medial frontal gyrus. White matter atrophy occurs in adjacent regions. (Reproduced from Dutt et al. (2016) with permission from Wolters Kluwer Health, Inc.)

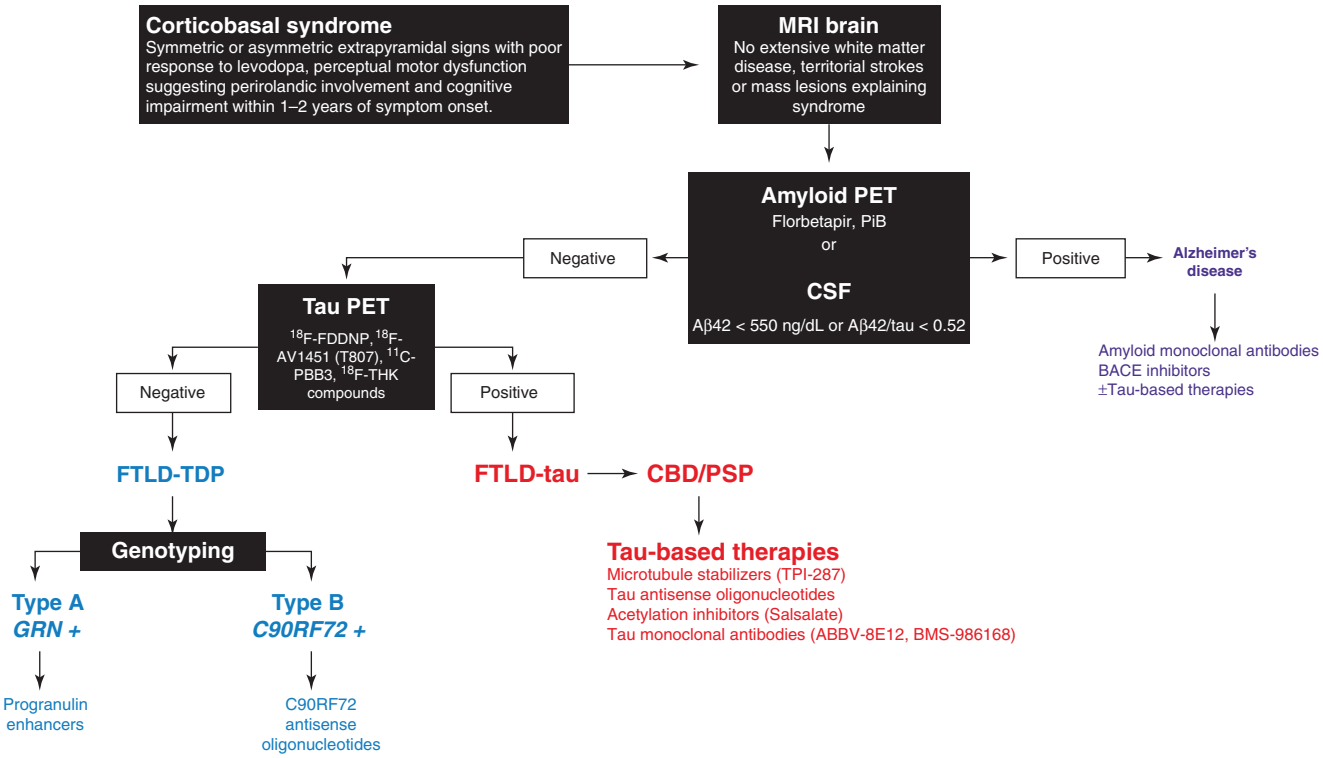

Fig. 35.4 Diagnostic approach to corticobasal syndrome relevant to clinical trials of experimental disease-modifying therapies. In the setting of typical clinical features, brain MRI should be the first step to investigate for the presence of vascular, inflammatory, or neoplastic conditions that can mimic the neurodegenerative CBS phenotype. Brain amyloid PET or cerebrospinal fluid (CSF) studies can help evaluate for the presence of Alzheimer's disease. Although CSF biomarkers and amyloid PET data in CBS derive mostly from clinically diagnosed, but not pathologically confirmed, cases, positive results may support Alzheimer's disease as a leading pathology in CBS cases. Negative CSF studies or amyloid PET could be followed by brain tau PET, which may determine the presence and neuroanatomical pattern of tau deposition. With the emergence of novel tau tracers, it is expected that in the near future, tau PET will be able to confirm or rule out the presence of a tauopathy and expedite referral to trials of tau-based therapies. CBS patients with negative amyloid and tau PET could be potential candidates for future therapies against FTLD-TDP

clonazepam, although they should be used with caution, due to their risk of cognitive side effects. Myoclonus may respond to levetiracetam (up to 3000 mg/day) or benzodiazepines (clonazepam up to 5 mg/day) (see Marsili et al. 2016). We discourage the use of amantadine and muscle relaxants such as baclofen, carisoprodol, or tizanidine due to their lack of efficacy and negative cognitive side effect profile, especially in cases of CBS suspected to be due to AD. We also discourage the use of direct dopamine agonists due to the risk of hallucinations and compulsive behavior, which could be a baseline trait in FTLD phenotypes. In cases of focal dystonia or blepharospasm, chemodenervation with botulinum toxin may be a reasonable intervention to prevent deformity and pain. Eyelid opening apraxia may also respond to injection of botulinum toxin into the pretarsal area of the orbicularis or lid crutches that can be fit to eyeglass frames. Some groups have attempted a multidisciplinary approach including repetitive transcranial magnetic stimulation with some success, and this intervention, which is experimental, can be considered if available, especially when paired with physical therapy. Limb deformities from dystonia can also be addressed with the use of wrist, finger, or foot orthotics under the supervision of an occupational therapist, and consultation with plastic surgery should be considered in severe cases.

Sensory deficits Unpleasant sensory symptoms such as dysesthesias or central pain may respond to agents for neuropathic pain such as gabapentin, pregabalin, or duloxetine. Although gabapentin may be associated with cognitive side effects, in our experience, it is tolerated by CBS patients, especially in low doses and in cases not suspected to be due to AD. An ophthalmological evaluation should be performed to rule out reversible refractive errors that may exacerbate visuospatial processing deficits. Patients should be screened for problems of bladder control, and medical control of urinary retention or incontinence may be attempted under urological consultation. Agents for bladder control should be used with caution, as they may cause cognitive side effects. Antispasmodic agents such as trospium and tolterodine are preferred over oxybutynin or darifenacin since they are more selective for peripheral cholinergic receptors.

Functional deficits Patients should be referred for physical, occupational, and speech therapy evaluations. Tailored interventions should be implemented to address gait and balance problems, dysphagia, communication difficulties, and sensorimotor control problems. A number of functional adaptations may be attempted depending on the deficits and needs. For example, training in the use of clamps may substitute the use of forks, which could provide some independence during eating. Patients with communication problems due to perceptual motor dysfunction may benefit from recorders or voice recognition software. Environmental adaptations may include clothes or utensil reorganization to facilitate selection, and installation of handles and raised seats to facilitate transfer. Patients who continue driving should be referred for an independent driving evaluation or be reported according to local regulations. Range of motion exercises should be encouraged, and orthotics for areas affected by persistent dystonia should be considered to prevent painful deformities. Patients should engage in a structured program of aerobic exercise as tolerated, based on recommendations of the American Heart Association (i.e., 30–45 min of moderate-to-intense aerobic exercise most days of the week). Consultation with a palliative care specialist should be considered for additional patient and family support regarding symptom management. This may be especially useful when placement of a percutaneous endoscopic gastrostomy tube to support feeding to treat severe dysphagia is a consideration. Hospice care is an important intervention for CBS patients in advanced stages, especially when life expectancy is less than 6 months due to complications from immobility or other forms of severe motor or cognitive disability.

Cognitive/behavioral deficits Symptoms of depression or anxiety in CBS usually benefit from antidepressant treatment. Selective serotonin reuptake inhibitors (SSRIs) are preferred due to their safe cognitive side effect profile. We discourage the use of tricyclic antidepressants due to anticholinergic effects. We prefer to use SSRIs with minimal anticholinergic and antihistaminic activity such as citalopram and escitalopram or the selective norepinephrine reuptake inhibitor venlafaxine and avoid agents such as fluoxetine, paroxetine, or sertraline, which have some anticholinergic activity. Venlafaxine is a reasonable alternative, especially when an activating effect against apathy is needed. SSRIs may also improve compulsions and impulsivity present in some CBS cases. Insomnia is usually addressed by counseling on sleep hygiene and using hypnotic agents with minimal cognitive side effects such as melatonin or trazodone. In general, we avoid hypnotic/sedatives with direct GABA-ergic agonist activity such as lorazepam or eszopiclone due to increased incidence of daytime drowsiness and postural instability. The use of dextromethorphan/quinidine may be considered if pseudobulbar affect is present and disruptive. The use of cholinesterase inhibitors should be considered if CBS is suspected to be caused by underling AD, especially if cognitive symptoms include memory or attention deficits. We discourage the use of antipsychotics for the management of behavioral symptoms in CBS; however they can be used when there is significant aggressive behavior unresponsive to behavioral measures. Management of cognitive dysfunction requires reliable caregiver support for maintenance of function. The stress associated with some cognitive deficits may be mitigated by specific interventions such as aerobic exercise for executive dysfunction, structured routine and reminders for memory dysfunction, speech therapy in nonfluent language dysfunction, and environment simplification in visuospatial dysfunction.

Finally, patients and their families should be provided with specialized resources for information, education, and support. Resources relevant to CBS include CurePSP (www.psp.org), Corticobasal Degeneration Solutions (www.cbdsolutions.se), the Association for Frontotemporal Degeneration (www.theaftd.org), and the Alzheimer's Association (www.alz.org). If available, patients should be counseled on research participation in academic centers, including observational cohorts and clinical trials. Research participation contributes to patient well-being through preservation of identity, value, autonomy, and hope. Concomitantly, progress in diagnostic and therapeutic development for CBS is only possible with the participation of patients and their families. Research options relevant to CBS include the 4 Repeat Tauopathy Neuroimaging Initiative (4RTNI, www.memory.ucsf.edu/research/studies/4rtni) and the NIH-funded North American research network Advancing Research and Treatment for Frontotemporal Lobar Degeneration (ARTFL, www.rarediseasesnetwork.org/cms/artfl), which includes multiple recruiting sites in the United States and Canada.

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Is There Vascular Parkinsonism?

36

Alberto J. Espay

Case

This 60-year-old woman had a 6-year history of progressive gait impairment and mild hand tremor. She initially noticed balance impairment, slow walking with foot dragging, and a tendency to fall forward. Mild hand tremor became obvious when holding objects. Within 4 years, she required a wheelchair for ambulation. She endorsed short-term memory loss, which accelerated in the year prior to her evaluation. She had medical history of hypertension and sleep apnea. There was no family history of movement disorders. Two of her sister's children had intellectual disability. She did not have children due to infertility.

On exam, she exhibited symmetric reduction of amplitude in alternating movements with mild tremor, but no rigidity. She was unable to walk unaided and had a wide base and difficulty turning with freezing. Her MoCA score was 12/30 based on errors in orientation, visuospatial/executive tasks, attention, phonemic fluency, and delayed recall (she was unable to recall any words but recognized 3/5 when multiple choices were given). Her brain MRI demonstrated mild atrophy with moderate leukoencephalopathy (Fig. 36.1a). Given the gait impairment and the findings on brain MRI, my initial tentative diagnosis was vascular parkinsonism.

Upon further review, however, other elements of diagnostic value were overlooked. The patient had a family history of intellectual disability and personal history of infertility. She was found to be a carrier of 82 and 132 CGG expansions in the *FMR1* gene, which falls in the premutation range, forcing a diagnostic revision from vascular parkinsonism to fragile X-associated tremor-ataxia syndrome.

Discussion

Vascular parkinsonism is a diagnosis that can be made simply by fulfilling three relatively non-specific criteria, proposed by Ziljmans and colleagues in 2004: (1) parkinsonian features, (2) evidence of cerebrovascular disease by imaging, and (3) a relationship between the two. The latter criterion is said to be supported if the clinical course is staggering or stepwise. While these criteria are easy to apply, the confirmation of a vasculopathic disorder is not as straightforward as it may seem. The definitions of parkinsonism and cerebrovascular disease are problematic on clinical and imaging grounds.

Let's tackle first *parkinsonism*. This clinical category is substantiated in the context of slowness of movement. However, slowness does not represent parkinsonism in many disorders, including apraxia in moderate to severe Alzheimer's disease, executive dysfunction in frontotemporal dementias, psychomotor retardation in severe depression, and spasticity with pyramidal weakness in motor neuron disease or due to a stroke. Slowness of movement without sequence effect, which is defined as the progressive reduction in amplitude and speed with repetitive movements, does not qualify as *bradykinesia*, the core feature of parkinsonism. As a result, many of the disorders we have collectively qualified within the umbrella of parkinsonism are, in fact, pseudoparkinsonian. The vascular syndromes leading to pseudoparkinsonian states include akinetic mutism from bilateral anterior cerebral artery strokes, which affect the anterior cingulate gyri, and apathetic depression due to left frontal and bilateral striatum lacunar strokes, impairing the frontal-striatal network.

Moving on to the link with *cerebrovascular disease*. The main problem rests on the assumed strong correlation between high signal intensity on T2-weighted and FLAIR brain MRI sequences (or hypodensity on CT) and small vessel ischemic brain disease. Such correlation has been based on early cadaveric imaging studies with minimal subsequent

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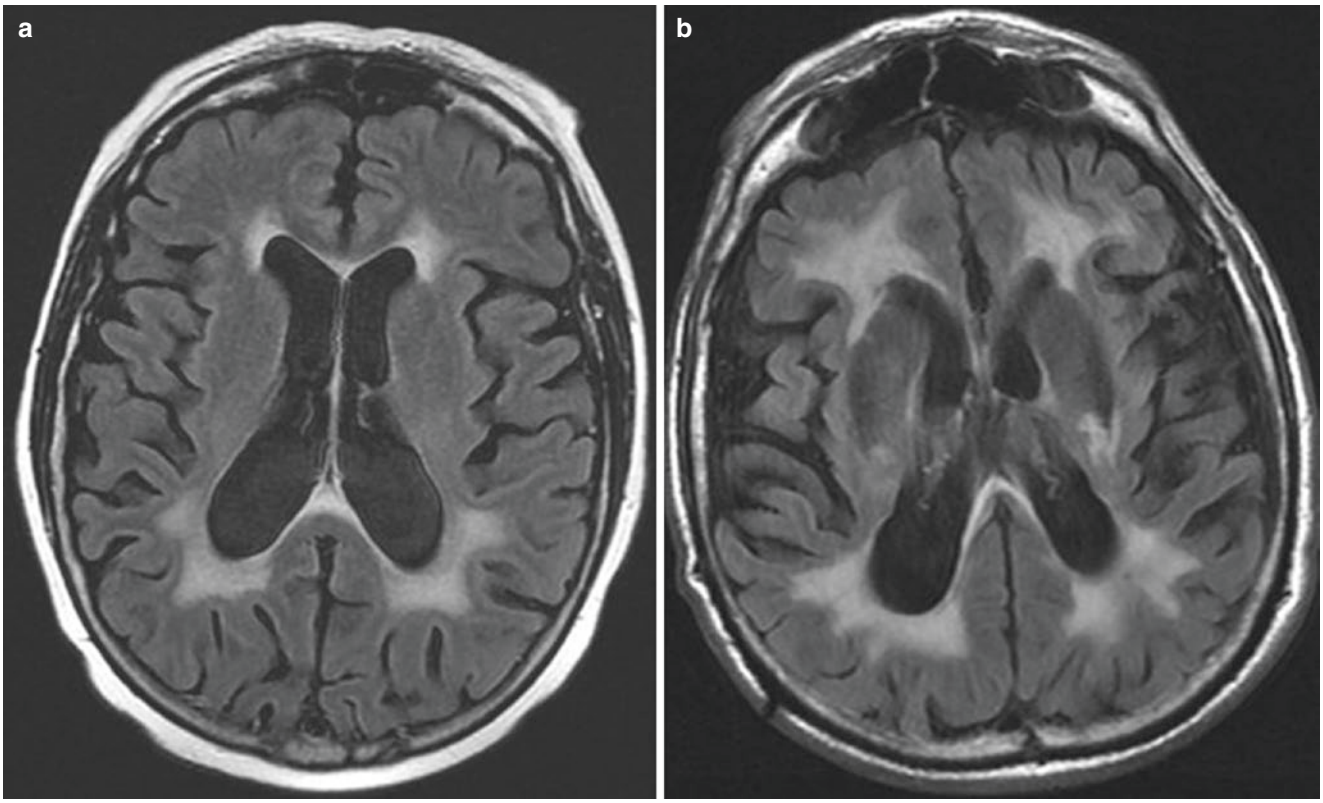

Fig. 36.1 FLAIR axial brain MRI in this patient (**a**) and one of a more advanced case with similar diagnosis (**b**). Note the confluent white matter hyperintensities in the periventricular and corpus callosum splenium. The range of white matter involvement can be extensive in Fragile X tremor ataxia syndrome. (Part B courtesy of Dr. Mathieu Anheim, Hôpital de Hautepierre, Hôpitaux Universitaires de Strasbourg, Strasbourg, France)

imaging-pathologic confirmations. In fact, nonvascular disorders, which may be as or more common in those with progressive gait impairment, are often dismissed when considering white matter hyperintensities on imaging (Table 36.1). Overlooking these diagnoses misguides the therapeutic approach toward secondary stroke prophylaxis (antiplatelet therapy, cholesterol-lowering agents, aggressive blood pressure control), which will be expected to yield no benefits.

Nevertheless, our field has continued to support the vascular link by referencing seminal papers, such as Thompson and Marsden's description of 12 patients with CT-diagnosed Binswanger's disease, including 5 with "lower-half parkinsonism" for whom there was no pathologic confirmation. My skepticism about vascular parkinsonism started in 2006. That year, I evaluated an 80-year-old man I thought had "classic" vascular parkinsonism (stepwise impairment in gait with history of hypertension, hypercholesterolemia, and a 60 pack/year-history of accumulated smoking, in the context of mild brain atrophy, hydrocephalus, and periventricular and deep white matter signal abnormalities on brain MRI). Against my prediction, he responded dramatically to continuous lumbar drainage. Acknowledging the possible "coexistence" of normal pressure hydrocephalus, he underwent ventriculoperitoneal shunting but died of complications from peritonitis in the postoperative period. The neuropathologic evaluation of his brain showed absolutely *no* vascular pathology, confirmed by two additional independent assessments. The case I once considered classic for vascular parkinsonism had not even a trace of microangiopathy.

Given the low correlation between cerebrovascular disease and parkinsonism (Table 36.2), there are no defined therapeutic guidelines for this syndrome. Screening for and treatment of hypertension, hypercholesterolemia, and other metabolic risk factors (e.g., obesity, diabetes mellitus, hyperhomocysteinemia), critical for secondary prophylaxis of cerebrovascular disease, have never been shown to be beneficial for patients with "vascular parkinsonism." Similarly, levodopa tends to yield negligible benefits. Robust responses have only been reported in cases associated with true macro-

Table 36.1 Selected disorders leading to increased white matter signal on brain MRI that do NOT represent cerebrovascular disease

Category	Disorder
Neurodegenerative	Fragile X tremor ataxia syndrome Multiple system atrophy
Demyelinating	Multiple sclerosis Progressive multifocal leukoencephalopathy Acute disseminated encephalomyelitis
Dysmyelinating	X-linked adrenoleukodystrophy Metachromatic leukodystrophy α-Galactosidase deficiency (Fabry disease)
Toxic/metabolic	Osmotic demyelination syndrome Marchiafava-Bignami disease Cyclosporine toxicity Phenytoin toxicity Heroin abuse Toluene abuse Methotrexate toxicity
Neoplastic	Primary CNS lymphoma Glioblastoma multiforme Astrocytoma
Infectious	Viral infections HIV encephalopathy Whipple's disease
Other etiologies	Hypoxic-ischemic encephalopathy Transependymal exudate in hydrocephalus Post-ventricular shunting Radiotherapy Chemotherapy

Table 36.2 Vascular disorders and parkinsonism: evidence to the contrary

Vascular predisposition	Impact on parkinsonism	References
"Silent infarcts" in basal ganglia: 40.2%	None: these were consecutive normal adults ($N = 219$)	Uehara et al. (1999)
"Silent infarcts" in basal ganglia: 46%	None: these were neurologically normal adults ($N = 121$)	Lee et al. (2000)
622 consecutive strokes: 27 striatal infarcts (4.3%)	Parkinsonism: only 1	Peralta et al. (2004)
Post-stroke movement disorders ($N = 56$)	Parkinsonism: only 6/56 (only 2 were leg predominant)	Alarcon et al. (2004)
CADASIL[a] cohort ($N = 45$)	Parkinsonism: only 5 (11%)[a]	Ragno et al. Stroke 2013;44:1147–1149
Consecutive brain autopsies of patients with infarcts ($N = 220$)	Parkinsonism: only 5 of 220 No correlation between location/size and lateralization/ severity of parkinsonism	de Reuck et al. (1980)
Systematic review of 25 VaP vs. PD articles	No correlation between location/size and lateralization/ severity of parkinsonism	Kalra et al. (2010)

VaP vascular parkinsonism, *PD* Parkinson's disease
[a]CADASIL: Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy is the most common hereditary small vessel brain disorder

scopic infarcts in the substantia nigra, which are the rare examples of true vascular parkinsonism. Nevertheless, levodopa is worth trying on anyone with a parkinsonian or even pseudoparkinsonian phenotype. Ultimately, therapeutic progress will rest on fostering the notion that the diagnosis of "vascular parkinsonism" should prompt the search of potential genetic, toxic, or dysmyelinating leukoencephalopathic disorders – with parallel research efforts allocated to the development of biomarkers for vasculopathic versus dysmyelinating versus neurodegenerative etiologies.

In conclusion, the following caveats need to be kept in mind when entertaining a diagnosis of vascular parkinsonism based on a picture suggestive of lower body-predominant "parkinsonism" and increased white matter signal on brain MRI such as the one illustrated by the case in this chapter: (1) most true vascular disorders do not cause parkinsonism and many "lower body parkinsonism" phenotypes are in fact pseudoparkinsonian (often of cognitive origin, yielding the so-called highest-level gait disorder), (2) a history of stepwise decline in a patient with vascular risk factors does not necessarily imply vascular disease, and (3) hyperintense periventricular lesions on brain MRI do not suffice to document underlying vascular disease. In the context of the next patient with impaired ambulation and hyperintense parenchymal signal on MRI, let us pause before embracing any sense of security when the radiology report "strongly suggests small vessel ischemic disease."

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Part IV

Tremor

Treatment of Essential Tremor: Medical Therapy

37

Stephen G. Reich

Case

A 71-year-old woman was seen for tremor of the hands that was first noticed 20 years earlier. The tremor had not been much of a problem until a few years prior to presentation when it started interfering with many activities including writing, holding a newspaper or magazine, using eating utensils, and drinking from a cup. She noticed an occasional tremor of the head, and others commented about her voice, but neither was very bothersome to her. Her mother, maternal grandmother, and maternal aunt all had essential tremor (ET). The patient did not drink alcohol. She denied being embarrassed by the tremor. On examination, there was a subtle, horizontal tremor of the head and a slightly tremulous voice. No rest tremor of the upper limbs was seen, but a symmetric tremor was present with maintenance of posture and especially in the "make wings" position with the hands in front of the nose with arms extended at the same level. The tremor was also present with finger-to-nose testing, but there was no actual dysmetria. There were no signs of parkinsonism or dystonia, and the remainder of the neurological examination was normal. A handwriting sample was typical for essential tremor ("Today is a nice day in Baltimore") as was a spiral drawn with each hand (Fig. 37.1).

Since the tremor interfered with several routine activities, treatment was indicated. She was started on propranolol 20 mg twice per day which was escalated slowly to 60 mg twice per day. She noticed that it became easier to drink from a glass and use utensils, but handwriting was still a problem. As her pulse was 53, I was reluctant to increase propranolol further so primidone was added starting with 25 mg at night and slowly escalated to 50 mg twice per day. She noticed additional improvement but was fatigued. I encouraged her

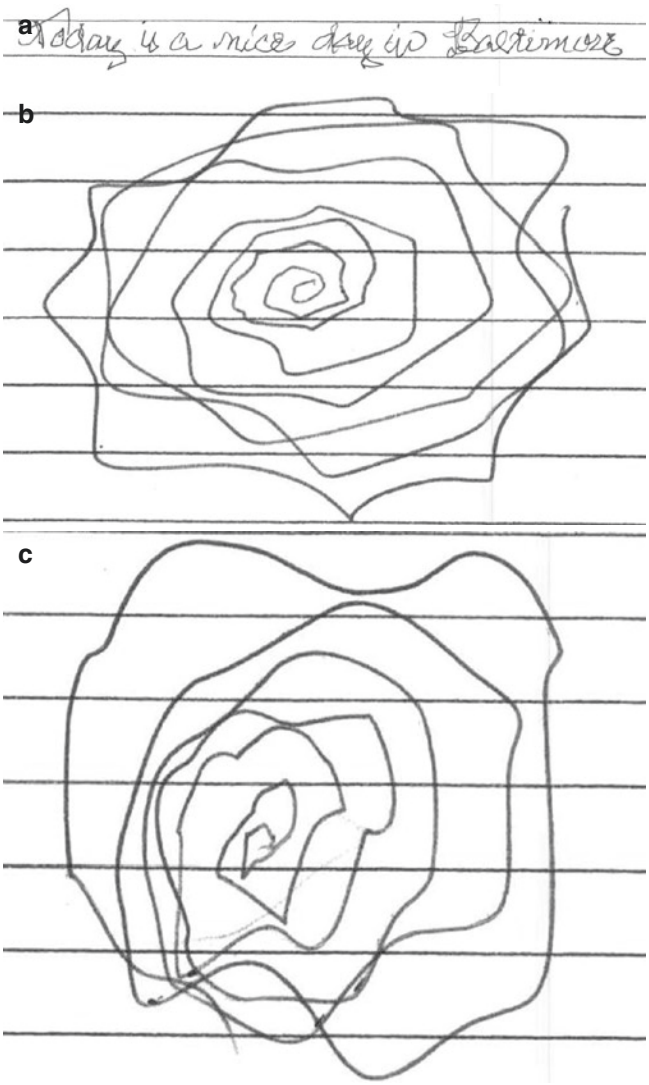

Fig. 37.1 Handwriting sample demonstrates tremor. It is also apparent when drawing a spiral with the right hand (left image) and the left

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to give it more time, and several weeks later, the fatigue subsided. From there, the dose was escalated gradually to 100 mg twice per day, which she remains on. Her handwriting improved, and she was able to thread a needle. The tremor is now considered to be under "acceptable" control.

Discussion

Essential tremor is the most common movement disorder, and in most cases the diagnosis is straightforward, based on the history and physical examination. In adults, the main differential diagnosis is whether a patient has ET or Parkinson's disease (PD). Other considerations include drug-induced tremor (i.e., valproic acid, lithium, cyclosporine, antidepressants), necessitating a careful medication history, hyperthyroidism (rare to present as just tremor without other clinical clues), Wilson's disease in young patients, and dystonic tremor. The suggested references provide a more comprehensive list of tremor disorders, some of the subtleties and pitfalls in the diagnosis of ET, as well as evolving evidence that ET is now appreciated to be more than simply a "monosymptomatic" disorder manifested by tremor alone.

A very helpful clue for distinguishing ET from PD is the duration of symptoms (Table 37.1). ET is usually present for at least several years and sometimes decades (ET may begin in childhood) before a patient seeks medical attention, whereas patients with PD, who have tremor, generally seek attention in less than 1 year. ET typically begins in both hands (it may only be noticed in the dominant hand but on exam is bilateral), whereas PD begins unilaterally. ET often (60–70%) improves transiently with alcohol which usually has no effect on PD tremor. There is a positive family history in ~60% of ET patients, and, as in the case above, it has an autosomal dominant pattern of inheritance, whereas PD is usually sporadic with 5–15% of patients having an affected first-degree relative. On examination, ET is a postural and kinetic tremor best observed with the hands outstretched or held in front of the nose, and with finger to nose, but there is no actual dysmetria. Most patients have both a postural and kinetic tremor, but either type may dominate. ET is typically absent when the hands are at rest but may be apparent if the patient is not fully relaxed, giving the impression of a rest tremor. However, with long-duration ET, there may be an actual resting component, sometimes resembling a parkinsonian tremor. In contrast, tremor in PD is maximal at rest and typically suppresses with posture and movement but, after a brief time, may "reemerge" while maintaining posture. In early PD, the tremor and other signs are unilateral or markedly asymmetrical, whereas ET is almost always bilateral but may be asymmetrical. The tremor of PD is often present when the patient walks, but this is not seen in ET. The parkinsonian tremor has a characteristic "pill-rolling" morphology in the fingers or pronation-supination of the forearm, whereas ET is predominantly flexion and extension at the wrist. It is worth pointing out that for many of these typical features, there are occasional exceptions.

Table 37.1 Distinguishing PD from ET

Feature	PD	ET
Usual duration of symptoms prior to medical contact	6–12 months	Usually several years or more
Family history	Generally negative (5–15% with an affected first-degree relative)	Often positive (>60%), autosomal dominant
Response to small amount of alcohol	Little or none	Often improves
Position of maximal activation	Rest	Maintenance of posture or with movement
Frequency	3–6 Hz	6–12 Hz
Morphology	Pill-rolling	Flexion-extension
Onset	Unilateral	Bilateral
Body part(s) affected	Upper limb, lower limb, chin, lips or tongue	Upper limb, head, voice,
Handwriting	Micrographic, atremulous	Normal size, tremulous
Associated signs (bradykinesia, hypomimia, etc.)	Present	Absent
Hand tremor while walking	Present	Absent

Associated signs are also helpful for distinguishing ET from PD. Coexistent tremor of the head or voice suggests ET rather than PD, which, in addition to the upper limb, may also involve the ipsilateral lower extremity, chin, lips, or jaw, which are uncharacteristic locations for ET. The diagnosis of PD depends on signs in addition to tremor including bradykinesia and rigidity which are not present in ET. Of particular note is the presence of normal arm swing in ET. In most circumstances, a handwriting sample alone is enough to distinguish ET from PD. As the case demonstrates, handwriting in ET is of normal size or larger, but tremulous, whereas in PD, handwriting is small but without evidence of tremor when the dominant hand is affected. Likewise, the spiral in PD is atremulous and small.

Admittedly, there are cases where the distinction between ET and PD is not clear and the two may coexist. Some patients with PD give a history to suggest preexisting ET long before the appearance of a new, typical resting PD tremor. And, some patients with longstanding ET may eventually develop parkinsonian signs or frank PD. Although DaTScan is approved to distinguish ET from PD, in most cases, it is not necessary, and if the diagnosis is not clear, then my recommendation is referral to a movement disorder specialist before embarking on a DaTScan.

The first step in treating ET is educating and reassuring the patient. Most are worried that they have PD and are relieved to learn that this is not the case and often the clinical visit is for that purpose alone. If the tremor is not interfering with normal daily functioning in a meaningful way, then no treatment is needed. It is important to ask patients about embarrassment since it can by itself be a significant source of "disability" limiting socializing or causing emotional distress, which in turn can worsen tremor, and is an indication for treatment even if the tremor is not otherwise physically problematic. When treatment is required, the two first-line drugs are propranolol (including long-acting propranolol) and primidone, which are equally effective for upper limb ET and are the only drugs given a level A evidence recommendation by the AAN (see references). Patients should be counseled that no medication will eliminate tremor and that the goal is to reduce it to a more tolerable level and improve functioning. To judge the effectiveness of treatment, it is best to follow a few tasks that are most problematic for the patient such as writing, pouring, applying makeup, drinking, or using utensils.

Propranolol is a good choice for the patient with hypertension as it can serve double duty, possibly substituting for another antihypertensive. If the patient is already on propranolol, then the dose can be increased. If on another beta-blocker, then I usually recommend switching to propranolol if possible since it has the greatest supporting evidence, although other beta-blockers can be used for ET including atenolol, metoprolol, nadolol, or sotalol, but not pindolol. Potential contraindications to propranolol include brittle diabetes, asthma, cardiac arrhythmia, and others, and if there is any question, its use should be cleared with the patient's primary care physician or cardiologist. For young patients with ET, I usually start with long-acting propranolol 60 mg, and this can be escalated slowly to a maximal dosage of 320 mg, but most patients, particularly the elderly, will not tolerate such a high dose. For older patients, I start with 10 or 20 mg twice per day and escalate gradually based on effectiveness and tolerance. Potential side effects include bradycardia, hypotension, fatigue, exercise intolerance, erectile dysfunction, memory loss, and somnolence. If there is inadequate improvement on the maximally tolerated dose, then I next add the other first line drug, primidone, as they can be synergistic. If there is no improvement, then I slowly taper off propranolol before adding primidone to avoid polypharmacy. Not uncommonly, a patient will appreciate during the taper that propranolol was helping more than appreciated, and if so, it can be continued.

The anticonvulsant primidone can be used alone or combined with propranolol or another beta-blocker. It can rarely cause the poorly understood "first dose effect" in which the first dose, despite being very low, causes varying combinations of dizziness, sleepiness, imbalance, nausea, and fatigue. Although frightening to the patient, these symptoms usually resolve in 24 h, and from there, primidone can usually be resumed and well tolerated. If counseled about this potential side effect, and encouraged to start taking it on a night where they are uncommitted the next day, this can be managed. Furthermore, having had this reaction is not a contraindication to retrying primidone on another occasion. Sometimes I will have a patient take the first dose in the clinic and remain there for most of the day. Primidone is started at 25 mg (one-half of a 50 mg tablet) at night and escalated gradually to an initial maintenance dose of 50 mg twice per day; an occasional patient will notice significant improvement on 25 mg twice per day and can remain on that dose. Some advocate taking primidone just at night. Although the dosage can be increased to as much as 1000 mg per day, if there is no significant benefit at 300–400 mg, then further escalation is often not helpful. As above, propranolol can be added if there is some but inadequate improvement with primidone. Side effects include somnolence, imbalance, fatigue, and depression, and they may improve with sustained use. Since the second-line agents for ET are not as helpful, everything should be done to get patients to optimize propranolol and/or primidone before calling it quits, and this is especially the case for moderate or moderately severe ET.

The AAN practice parameter has given the following drugs a level B recommendation for ET: gabapentin (1200–1800 mg/day), topiramate (up to 400 mg per day), atenolol (50–150 mg/day), and (sotalol 75–200 mg/day). Although alprazolam (0.5–3 mg/day) was also given a level B recommendation, it came with a caution about its potential for abuse. I only use alprazolam for patients who require treatment on an occasional as-needed basis, largely to treat embarrassment. Another similar option is the judicious, intermittent use of alcohol. For patients who cannot tolerate any of these agents, the following level C recommendations can be considered: clonazepam (0.5–6 mg/day), nadolol (120–240 mg/day), and nimodipine (120 mg). The following are considered level U meaning that there is insufficient evidence to support or refute use: clozapine (up to 75 mg/day), noting the potential for leukopenia and the need for monitoring, pregabalin, and zonisamide.

Botulinum toxin for limb ET was given a level C recommendation by the AAN. I have largely abandoned its use for this indication having found that the dose necessary to adequately suppress tremor is also enough to cause problematic weakness. In contrast, I usually go straight to botulinum toxin for tremor of the head or voice (both given level C recommendations) when patients find them problematic as they usually do not respond adequately to oral agents. Yet, it is worth noting that many patients with ET of the head or voice are either unaware of it or not bothered by it, and when troubled, it is more often because of embarrassment which can be difficult to treat even when there is less tremor.

If the maximally tolerated dose of propranolol combined with primidone is not helpful for disabling ET of the limb, then I encourage patients to consider deep brain stimulation (DBS) as second-line drugs are not likely to provide adequate relief of tremor. Focused ultrasound is an emerging investigational therapy which has the advantage of being noninvasive, and both of these options are discussed in chapter "Treatment of Palatal Tremor".

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Treatment of Essential Tremor: Surgical Therapy

38

Ritesh A. Ramdhani

Case

A 67-year-old man presented with a 40-year history of essential tremor (ET) which started in his head and spread to his hands shortly afterward. He was not bothered by his head tremor, but over the past 8 years, his hand tremors progressed with modest benefit from primidone 150 mg daily and propranolol LA 120 mg daily. His dominant right hand was more affected, and his handwriting had become illegible. He used a straw to drink from a cup and had difficulty eating with utensils. He made frequent errors when dressing and shaving. His tremor markedly improved after drinking a mug of beer.

On examination, there was a regular "no-no" head tremor with absence of directionality. There was a mild vocal tremor on sustained /AA/ and /EE/ that was primarily a result of transference of the head tremor, as stabilization of the patient's head by the examiner dramatically reduced the vocal tremor. There was no tremor in his upper limbs at rest; there was a 6-Hz postural tremor as well as a severe kinetic tremor in both hands, of greater amplitude on the right. He did not have tremor in his legs or torso. His gait was normal, and when pouring, he spilled approximately 25% of water with either hand. There was a severe writing tremor to the extent that his handwriting and signature were illegible.

Discussion

Essential tremor is characterized as a rhythmic, oscillatory movement with a frequency of 6–12 Hz, which most often affects the hands but can also involve several other body regions such as the head, voice, trunk, and lower extremities. For tremor of the upper limb, the kinetic component is usually worse than maintaining posture. Progression of ET produces task-specific disabilities including eating, writing, dressing, and speaking, among others. In addition, for many, the tremor is source of embarrassment, and this itself can further affect quality of life.

When tremor causes functional impairment, pharmacologic treatment is usually warranted. Propranolol and primidone are considered first-line treatments, while numerous other second-line agents carry low-grade recommendations and serve as adjunctive therapy to the first-line agents. Furthermore, intolerable side effects and medical contraindications can limit use of these treatments. Approximately, 30–50% of all patients with ET fail to experience a significant response to pharmacologic treatments. In such cases, where quality of life has significantly declined despite taking tremor medication(s), a surgical option should be considered.

Deep brain stimulation (DBS) of the ventral intermediate nucleus (VIM) of the thalamus offers a very effective means of treating patients with severe ET that is refractory to medication. Historically, stereotaxic high-frequency coagulative lesions were directed at the ventral intermediate VIM nucleus, where tremor cells were mapped. Imaging and physiologic mapping demonstrate that the VIM is the receiving centering for cerebellar projections, with a homunculus representation within the nucleus—the kinesthetic leg cells are positioned laterally, juxtaposed to the internal capsule while the arm cells are directly medial and facial cells are most medial, bordering the third ventricle.

Due to the high morbidity, especially with bilateral procedures, implanting electrodes into the VIM supplanted lesioning surgery in the 1980s. The FDA approved thalamic DBS for treatment of ET in 1997. However, unilateral ablative surgery remains a viable option for patients who do not qualify for DBS or cannot obtain it. There are various surgical techniques for implanting DBS. Variables such as CT or MRI stereotactic guidance, intraoperative microelectrode or semielectrode recording, surgical planning, and angle of lead trajectory are usually at the discretion and preference of the neurosurgeon.

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Therefore, it is recommended that patients undergo a comprehensive clinical assessment with neuropsychological testing at a movement disorders or DBS center when being considered for DBS. This would also enable a review of surgical benefit and risk, programming approaches and timeline, and long-term outcomes with the prospective DBS candidate—ensuring reasonable expectations are established.

Long-term outcome studies show that tremor improvement is on the order of 50–90% and is sustained for at least for 5–7 years. Unilateral stimulation has been reported to significantly improve quality of life; however bilateral stimulation is not only efficacious in managing severe upper limb tremor but also improves head (60–90%) and voice tremor (40–80%). Optimal programming parameters consist of amplitudes between 2 V and 4 V, pulse widths 90–120 μs, and frequency ranges of 160–185 Hz. Ventral contacts tend to produce the greatest benefit. Patients usually can reach their best clinical results within 1 month of programming, with immediate benefits realized during the first programming session. Furthermore, patients are able to turn off the stimulators during the night to save on battery life.

Stimulation-associated side effects include paresthesia related to spread of current into the ventralis caudalis nucleus (VC), motor contractions of the face or arm due to spread into the internal capsule, or dysarthria and gait abnormality, which occur at a higher incidence among patients undergoing bilateral DBS. Depending on the stimulation threshold, these symptoms can be amenable to adjustments, such as switching the polarity configuration to bipolar or interleaved settings. However, dysarthria and ataxia can persist despite efforts to modify the parameters in patients with bilateral stimulators.

Although the tremor reduction with thalamic DBS is robust, a considerable subset of patients, as high as 40–70% in some studies, can experience some waning of benefit with time. This may represent just natural progression of the condition or tolerance to stimulation, accounting for the need to gradually increase stimulation parameters in some patients.. The worsening of action tremor and/or spread of the tremor to other body regions offers support for the former explanation. A malpositioned lead has also been posited as a reason for loss of stimulation benefit. Modest deviations of the electrode within the VIM may be enough to play a role and can be suspected when adverse stimulation effects are produced at lower thresholds than would be expected. Electrophysiological data accounting for location of tremor cells within the VIM has shown that changes in electrode polarity such as activating an elliptical field through a bipolar configuration may be necessary to achieve optimal tremor control in such circumstances.

The waning of benefit and the potential for developing dysarthria and ataxia with bilateral thalamic stimulation has led some to investigate other potential implantable neural substrates. Stimulation of the caudal zona incerta (cZI), which lies ventral to the thalamic nuclei and medioposterior to the subthalamic nucleus (STN), has been implicated in the genesis of tremor. Studies have revealed that stimulation of this target is as efficacious as the VIM for tremor control with a suggestion of greater reduction of action tremor. In addition, there is a lower prevalence of side effects (i.e., dysarthria, ataxia) from bilateral stimulation reported for the cZI. STN stimulation for ET remains investigational, but limited studies have demonstrated robust tremor reduction as well.

Focused ultrasound (FUS) is a noninvasive way of lesioning the VIM, which has gained attention recently. Though published data demonstrate marked improvement in tremor, there have been no head-to-head studies with DBS or long-term outcome analyses. FUS has not been shown to reduce midline tremor (i.e., head or voice), and since there is no adjustability, patients with suboptimal results have limited options aside from further lesioning.

This patient underwent placement of a left ventral intermediate (VIM) nucleus DBS utilizing intraoperative frame-based stereotaxis and microelectrode recording. He experienced marked tremor reduction of his right hand with stimulation of 4 V, PW 90, and frequency 185 through the ventral contacts within 1 month of implantation. His handwriting became legible, and there was improvement in other fine movements. Due to this response, he opted to have his left hand tremor treated 1 year later. A right caudal zona incerta DBS was implanted. Complete disappearance of all aspects of the tremor was achieved during the initial programming. This response has been sustained with no adverse effects observed from bilateral stimulation for the last 1 year. Subsequently, primidone was titrated down to 50 mg daily, and propranolol was tapered off after the second stimulator implantation.

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Treatment of Orthostatic Tremor

39

Pinky Agarwal

Case

A 65-year-old woman presented with an 8-year history of feeling unsteady while standing. At onset, she would feel unsteady after standing for 1–2 min, but over time, the unsteady sensation started happening almost immediately upon standing and became more intense and frequent. She described it as an uneasy feeling in her legs which worsened on standing and improved with walking, sitting, or lying down. Thus, whenever there was prolonged standing, she felt a sense of imbalance and had to either sit or support herself by leaning against the wall or holding on to furniture. In addition, she sometimes noticed a slight tremor in her hands while leaning forward to hold onto furniture. She did not experience tremor in her head or other part of the body. She denied numbness, pain, or tingling in the extremities. She did not have slowness, stiffness, or balance problems once she started walking. She did not notice any improvement with alcohol or worsening with caffeine. She denied a restless sensation in legs, and there was no abnormal twisting or posturing of the leg. There was no history of trauma to legs, no abnormal discoloration of skin, and no complaint of pain in the legs. There was no family history of tremor or movement disorders. She was not on any medications and denied exposure to antipsychotic medication.

On examination, she did not have features of orthostatic hypotension. She was alert and oriented to time, place, and person. No abnormalities were noted on the cranial nerve examination. Strength, sensation, and reflex testing were normal. In the upper limbs, there was no rest, action, or intention tremor. She had a bilateral postural tremor of the upper limbs when standing and leaning on the table but not when sitting or lying down. There was no rigidity or bradykinesia. When examined seated in a chair, there were no abnormal movements in the legs and in particular no tremor or heel–shin ataxia. Fine *ripples* were noted in the quadriceps almost immediately after standing and increased over a period of 1–2 min to the extent that she had to sit down. When the diaphragm of the stethoscope was placed behind the knee, a thumping sound, like a helicopter rotor, was heard when the patient stood up and disappeared on sitting down. She was able to walk normally including tandem walking.

Surface EMG electrodes were placed on the right and left vastus lateralis, tibialis anterior, and gastrocnemius muscles, and the patient was observed in supine, sitting, and standing position. Recordings from vastus and tibialis anterior while standing showed rhythmic activity of 16 Hz, with an alternating pattern of agonist and antagonist muscles. Concentric needle EMG of the quadriceps muscles showed discharges of muscular activity at the frequency of 16 Hz while standing which disappeared when the patient was supine or sitting with the feet dangling. The tremor had a high frequency and high coherence between homologous muscles of the two legs (e.g., the left and right quadriceps).

The patient was informed that her diagnosis was orthostatic tremor, and medication options were discussed. She was hesitant to start a benzodiazepine and asked for something milder. She was started on gabapentin, which was slowly increased to 900 mg/day which had modest benefit; however the sensation of unsteadiness on standing was still problematic, so she requested a trial of clonazepam and was put on 0.5 mg at bedtime and gradually increased to 2 mg at bedtime, whereupon some improvement was noticed during daytime activities. Increasing the dose further and adding propranolol did not have any additional effect. Adding clonazepam during the daytime caused unacceptable sedation. During a 6-month follow-up, the patient still had mild tremor of legs on standing, but it was not disabling.

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Discussion

Orthostatic tremor is manifested by a rapid tremor of the lower extremities while standing. Yet, patients often do not appreciate that they have a tremor and instead usually present with a feeling of unsteadiness while standing but typically have no symptoms while sitting or walking. This characteristic history of difficulty standing but not walking should lead to the suspicion of OT. The tremor is of such a high frequency tremor (13–18 Hz) that it may not be readily apparent on examination, unless one is specifically looking for it. Sometimes patients complain of subjective unsteadiness without any visible tremor which improves with lightly touching a table, wall, or the examiner's hand. On examination, one usually sees or palpates a mild "rippling" rather than a clinically observable tremor in the lower extremity muscles, mainly the quadriceps and gastrocnemius, in the standing position. When the diaphragm of a stethoscope is placed behind the knee, a characteristic whirring sound called the "helicopter sign" may be heard as it sounds like the rotor on a helicopter. In addition to lower extremity tremor while standing, there may also be tremor of the trunk or upper limbs.

The diagnosis of OT can be confirmed by EMG recordings from the quadriceps or other lower extremity muscles demonstrating a tremor frequency 13–18 Hz. The muscles of the legs, trunk, and even arms can show this tremor which is typically absent while the patient is sitting or lying.

MRI of the brain and spinal cord is not required in OT patients unless other neurologic signs are present and OT-plus is suspected (see below)**.**

In contrast to other pathological tremors, orthostatic tremor demonstrates coherence (i.e., tremor is synchronous in homologous muscles) of both legs suggesting involvement of a primary central tremor generator. Electrophysiological findings can distinguish orthostatic tremor from essential tremor (ET). Orthostatic tremor has high frequency of 13–18 Hz, whereas ET has a much lower frequency of 4–10 Hz. In addition, unlike ET, OT rarely improves with alcohol. Although ET may involve the lower extremities, it is not exclusively present on standing and often seen when the patient is seated.

There are two forms of OT, primary and secondary. Primary (or isolated) OT is diagnosed when there are no additional neurologic signs, and when other signs are present, then OT is referred to as secondary or OT-plus. Secondary OT can be seen in the setting of other diseases such as Parkinson's disease, dementia with Lewy bodies, progressive supranuclear palsy, parkinsonism due to vascular causes, and drug-induced parkinsonism. Some patients, who start off with isolated OT, may go on to develop additional signs including parkinsonism and ataxia. As Table 39.1 illustrates, there are a variety of other conditions that may cause difficulty standing, with tremor or related movement disorders, but most of these have characteristic features or associated signs to distinguish them from primary or secondary OT.

The pathophysiology of OT is not known. There is evidence suggesting that it results from a central oscillator in the brainstem, spinal cord, basal ganglia, or cerebellothalamic loops. As mentioned above, since some patients with isolated OT go on to develop additional neurological signs (parkinsonism or ataxia) or simply worsening of OT itself, it is possible that OT is a neurodegenerative disorder referable to the basal ganglia or cerebellum.

A variety of drugs have been used to treat orthostatic tremor. However, due to its low incidence, only a few clinical trials have been conducted, using gabapentin as a first-line or add-on therapy. Gabapentin has been shown to improve tremor, postural instability, and overall quality of life when used as add-on therapy in patients with OT. Symptomatic benefit occurred between 300 and 2400 mg/day and was well tolerated.

The most commonly recommended first-line drug for OT is clonazepam. This is typically introduced at 0.5 mg at bedtime and, if tolerated, gradually titrated upward to 2 mg three times a day. Second-line therapies include gabapentin, levodopa, primidone, phenobarbital, levetiracetam, sodium valproate, and pramipexole which can be used as monotherapy or in combination with clonazepam. Patients should be counseled that medication rarely cures OT and that the goal is to reduce it to a level that allows them to stand for a longer period of time and feel less unsteady when doing so. The treatment response can be modest and inconsistent. Physical aids like portable stools may offer some symptomatic relief. Patients often prefer to sit rather than stand for a long time while in queue.

Bilateral Vim thalamic DBS implantation has been performed in a few refractory cases of orthostatic tremor with improvement in standing time. In case of obese patients, weight reduction may be helpful.

Table 39.1 Differential diagnosis for unsteadiness and tremulousness on standing

Disease conditions	Clinical features	Aggravating and relieving factors
Orthostatic myoclonus (OM)	Orthostatic myoclonus causes unsteadiness on standing which disappears on walking or sitting On auscultation with a stethoscope, myoclonic bursts, when occurring semi-rhythmically in multiple muscles, sound like "pop corns heating" EMG demonstrates nonrhythmic (in contrast to OT which is rhythmic), synchronous, short-duration bursts (50–100 ms) recorded from the lower limb muscles while standing	May worsen with eye closure Worsens with pro-myoclonic drug such as tricyclic antidepressants
Akathisia	Patients complain of inner feeling of restlessness and anxiety They are unable to sit still Patients constantly move their feet and pace around Symptoms persist while walking Not rhythmical	History of antidopaminergic medication
Cerebellar ataxia	Accompanied by dyssynergia and dysarthria Intention tremor with a tremor frequency ~ 3hz may be present Nystagmus may be observed. Patients may have trouble standing with feet together and eyes open	
Parkinson's tremor	In addition to orthostatic tremor, there are additional signs Upper limb rest tremor of 4–6 Hz (asymmetric, pill rolling), jaw, tongue, or lower extremity tremor at rest Bradykinesia is present Postural instability is common	Alcohol does not cause improvement, and caffeine does not worsen Emotional stress worsens tremor amplitude Tremor improves when the hands are in motion
Essential tremor	Familial history often present It may appear in childhood or adulthood Insidious onset with varying progression Occurs with hands held outstretched and during finger to nose, with a frequency 4–8 Hz No past pointing is noted	Exacerbation with caffeine and stress Alcohol improves tremor In some patients, the tremor is most severe with movement
Dystonic tremor	Tremor in a body part affected by dystonia. Leg dystonia may be accompanied by tremor and also twisting of the foot Focal tremors with a variable frequency (usually less than 7 Hz) Mainly postural/kinetic tremor May occur during complete rest and it is very activity specific	In many patients with dystonic tremor, sensory trick or *geste antagoniste* may lead to a reduction of the tremor amplitude
Enhanced physiological tremor	Physiologic tremor occurs when attempting to maintain posture. The frequency in the hands may be 8–12 Hz, but frequency may be as slow as 6.5 Hz in other body parts. Physiologic tremor is not symptomatic except when the patient tries to accomplish tasks that require fine motor activity.	Certain circumstances like emotional stress, exercise, and drugs (amphetamines, certain anticonvulsants, and antidepressants) enhance physiologic tremor
Psychogenic tremor	Tremor may be a manifestation of a psychogenic disorder at any age Patients may present with combination of rest, postural, and action tremors Abrupt onset with variable course Absence of other neurological signs Tremor may occur in multiple varying body parts Tremor varies in pattern and frequency	Stress exacerbates psychogenic tremor Distraction may reduce tremor Entrainment

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Treatment of Essential Tremor: Deep Brain Stimulation

40

Mahlon R. DeLong

Case

A 73-year-old professor with a 45-year history of essential tremor (ET) was referred for evaluation for deep brain stimulation (DBS). Mild intermittent postural and action tremor of both hands was first noted when the patient was 27 years old. His father had a similar tremor. The patient also had a history of bipolar disorder which was treated successfully with duloxetine and aripiprazole. Over the years, his tremor gradually progressed and became more noticeable, embarrassing, and disruptive. He found that alcohol attenuated his tremor and used it for this purpose at times. He had been evaluated in our clinic 13 years earlier and was considered to be a candidate for DBS but initially decided against it. Over the past several years, his tremor significantly increased in both arms, with some additional involvement of the head and voice. He had also noticed intermittent right leg tremor. The arm and head tremor interfered significantly with eating and drinking, requiring the use of a straw, and he complained of significant difficulty with dressing, grooming, and other activities of daily living (ADLs). He had become extremely embarrassed by his tremor and avoided public events and eating out. He had tried, unsuccessfully, multiple drugs, including therapeutic doses of primidone, propranolol, gabapentin, and topiramate. He used clorazepate as needed when socializing. At one point, he became addicted to alprazolam, which he used similarly. He denied dysphagia but felt his balance was not quite right, although he had not fallen.

On examination, he exhibited mild voice tremor and moderate no-no head tremor with pronounced bilateral postural and action tremor of both arms, which was largely distal, and was not accompanied by dysmetria. He had no abnormal posturing or rest tremor of the upper limbs. He had difficulty with drawing, pouring, and drinking. His posture was mildly stooped, but his gait was normal with normal arm swing and no tremor while walking. He had no problems turning and had a normal pull test. He had a tremor rating score of 69 (see Table 40.1, "pre-stim" column). The patient was felt to have a clear case of classic ET and to be an excellent candidate for DBS of the ventral intermediate nucleus of the thalamus (VIM).

The patient underwent formal screening, and it was recommended that he undergo staged bilateral DBS targeting the VIM. The first surgery was performed on the left side, in order to benefit his dominant right hand. The second surgery (placing a DBS lead on the right side) followed 3 months later. Leads were placed and tested with the patient awake, using microelectrode recording, mapping and macro-stimulation techniques. He had an excellent response to both procedures with control of tremor of the extremities, head, and voice, as shown in Table 40.1 (compare the preimplantation tremor rating scale ["pre-stim"] values with those after the first [L-VIM] and second procedure [R-VIM]). The patient's tremor was controlled with monopolar stimulation at 130 Hz with a pulse width of 90 microsec and under 2 volts on each side. Interestingly, his voice tremor improved after the first surgery. He remarked after his second surgery that he felt he had gotten his life back and was exceedingly pleased with the outcome. At 2 years' post-op, his benefit has been fully sustained with only minor adjustments in initial programming parameters.

Discussion

Referral Patients referred to our movement disorder center for DBS undergo formal screening by a multidisciplinary group, including visits to a movement disorder neurologist, psychiatrist, neuropsychologist, and a neurosurgeon who is trained in functional stereotaxic surgery. The initial contact with our group is with a movement disorder neurologist, who does the screening necessary for determining that the diag-

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Table 40.1 Tremor rating scale scores completed at baseline and at the programming session 1 month after the second side was done. Tremor rating scale has 21 items, some with multiple scores for resting, postural, and action tremor, rated 0–4 (0 = none, 1 = slight, 2 = moderate, 3 = marked, 4 = severe)

Tremor rating scale	Pre-stim	L VIM	R VIM
Face tremor: rest	0	0	0
Tongue tremor: rest	0	0	0
Tongue tremor: posture	1	0	0
Voice tremor: action	1	0	0
Head tremor: rest	0	0	0
Head tremor: posture	1	1	0
RUE: rest	0	0	0
RUE: posture	2	0	0
RUE: action	2	1	0
LUE: rest	0	0	0
LUE: posture	3	3	1
LUE: action	3	3	1
Trunk: rest	0	0	0
Trunk: posture	0	0	0
RLE: rest	0	0	0
RLE: posture	1	0	1
RLE: action	1	0	0
LLE: rest	0	0	0
LLE: posture	0	0	0
LLE: action	1	1	0
Handwriting	4	1	1
Drawing A: right	3	1	0
Drawing A: left	4	4	0
Drawing B: right	4	1	0
Drawing B: left	4	4	0
Drawing C: right	3	1	0
Drawing C: left	3	3	0
Pouring: right	4	1	0
Pouring: left	4	4	1
Speaking	1	0	0
Feeding w/o liquids	3	1	0
Bringing liquids to mouth	4	1	0
Hygiene	3	1	0
Dressing	3	1	0
Writing	3	1	0
Working	3	1	0
Total	69	35	5

nosis is correct, assuring that the patient has had adequate trials of medication, is aware of the benefits and potential complications of surgery, and has appropriate expectations before proceeding with formal screening. This consists of cognitive testing, psychiatric evaluation, motion analysis, head MRI, and a clinic visit with the neurosurgeon.

Although ET is, numerically, the most common movement disorder, people with ET do not represent the majority of patients seen in movement disorder centers or referred for DBS. This may be true for a variety of reasons, but predominantly, I believe, because patients and often other affected family members who have lived with tremor for many years view it as something they share and endure without seeking formal care, unless it significantly impairs ADL and becomes a cause of significant embarrassment or out of concern that it might be Parkinson's disease. Other factors are the lack of awareness of DBS as a highly effective treatment for tremor among both physicians and patients and a fear of what is often lumped into the broad category of "brain surgery," even though it is a relatively minor and lower risk procedure.

Classic ET ET is viewed as postural and/or kinetic tremor of the hands with, not infrequently, additional tremor of the head, neck, and voice. ET may appear at almost any age, even in childhood. Although most often embarrassing and disruptive, many patients are in their 60s or 70s when finally referred for DBS.

As discussed in Chap. 37, the main concern is to distinguish ET from Parkinson's disease and drug-induced, dystonic, and enhanced physiologic tremor. It is now clear that the classic concept of ET is increasingly questioned in view of the fact that it is often a polygenic disorder and may be compounded by a variety of associated signs and symptoms including impaired gait and balance, mild dystonic posturing, as well as hearing loss, depression, and anxiety and even cognitive impairment. Although not the chief concern of the patient, these should be weighed in the assessment for DBS. Patients with just tremor may be referred to as "isolated" tremor, whereas patients with other motor or nonmotor features may be viewed as cases of "combined" tremor. ET is now increasingly viewed as a syndrome rather than a single disease that may manifest simply as tremor or in combination with other neurologic and psychiatric problems.

Patient Assessment The most important issues regarding DBS for tremor are the correct diagnosis and whether the patient has had an adequate trial of anti-tremor medications. It is also important to assess whether the impact is primarily psychological in the sense of embarrassment or depression and anxiety with social isolation or more directly physical impacting ADLs and QOL. It is important to emphasize in speaking with patients that the decision is really theirs and that the role of the physician and multispecialty team is to be sure that the diagnosis is correct, that the tremor is medication-refractory, and that the odds of improvement are substantial when weighed against the risks. Consideration must be given to socioeconomic issues, as well, in terms of the impact on job performance and retirement. The potential of DBS to keep patients employed and functioning socially is a major advantage of DBS. Patients who are very much in the public eye obviously may want surgery at an earlier time than retired or non-working individuals.

Pharmacologic Treatment It has been reported that as many as half of patients with ET are intolerant or fail to respond to medical treatment. We have found that patients referred for surgery, in some cases, have not had clearly documented or adequate trials of anti-tremor agents. Although propranolol and primidone have most often been tried unsuccessfully, it, not uncommonly, appears that they were not given in adequate doses or in combination. It is frequently necessary to try them once again before proceeding to formal screening for surgery. The value of second-line drugs, such as gabapentin, topiramate, and atenolol, is limited in most patients with significant tremor but can be tried. Alprazolam and other such agents should be used only for limited times and specific situations. When to conclude that tremor is treatment resistant is not always agreed upon, but failure of the aforementioned drugs is adequate to move forward with surgery if there are, otherwise, no considerations. Clozapine can be considered in patients who do not want or are not candidates for DBS for medical or neuropsychiatric reasons.

VIM Thalamotomy and DBS for ET Almost all functional surgical interventions for the treatment of essential tremor target the VIM. Essential tremor has been treated with surgical ablation (thalamotomy) since the 1950s and with DBS since the 1990s. Tremor was the first condition given FDA clearance for DBS, targeting VIM. Since the 1990s, DBS has replaced thalamotomy because it is adjustable, reversible, and less invasive.

Many patients require bilateral surgery because of severe bilateral hand or arm tremor combined with significant head, voice, or truncal tremor or because they suffer from significant medication side effects. However, bilateral thalamotomy is best avoided, because it associated with increased complications, specifically speech impairment and dysphagia. In contrast, VIM DBS can be performed safely bilaterally. Most often, bilateral DBS is carried out in a staged fashion, since some patients with bilateral tremor, after receiving unilateral DBS with restoration of function in the dominant hand, decide against a second procedure. Staging also reduces any negative impact of the procedures, given the several months' interval between the two surgeries. Less than optimal benefit or unmanageable stimulation-related side effects, such as numbness or tingling, are most often due to suboptimal placement of the electrode, necessitating repositioning of the lead.

The ventral subthalamic white matter (zona incerta) is a potential alternative target for DBS. DBS in this area has been explored and utilized with some success because of the difficulty with controlling proximal tremor and problems with loss of benefit with VIM DBS.

Patient Selection Patient selection involves consideration of multiple physical, medical, and psychosocial issues. The indication for DBS is clearest when tremor interferes with feeding, drinking, or writing, or causes excessive embarrassment, which significantly impact the patient's quality of life. ET is generally managed successfully with DBS even in the elderly, but patients under the age of 75 are considered optimal candidates. There is no absolute evidence against surgery in patients over 80, and we have done this with good benefit in "biologically young" individuals. It is important to recognize that the goal of DBS treatment is to almost completely eliminate tremor. In fact, even an 80% reduction of large amplitude tremor may not be adequate to restore eating, writing, and grooming. Contraindications to DBS include general medical disorders which significantly reduce life expectancy or increase the risks of surgery. Patients with lowered resistance to infection or skin conditions that make the implantation of the required hardware difficult are not suitable candidates. Significant psychiatric disorders, alcoholism, and drug abuse are also strong contraindications. Major depression and/or anxiety must be treated and controlled before surgery. Finally, cognitive impairment is an important consideration, particularly in the elderly. Preexisting dysphagia, dysarthria and disturbances of gait or balance should raise caution since these can be exacerbated by surgery.

Managing Expectations It is important to explore and potentially correct a patient's inappropriate expectations of DBS. It is also important to make it clear that while DBS is a form of brain surgery, it is not major brain surgery and involves implantation of leads through a small burr hole in the skull, done as a routine procedure. It is sometimes difficult to reason with patients who may have a good benefit from medications but just want to have DBS so they could come off of medications because of the inconvenience. Such patients must weigh the potential risk of DBS versus the expected benefits.

Patients must understand that the risk of a significant neurologic deficit resulting from hemorrhage is 1–2% and the risk of infection, requiring antibiotics or potentially removal of the hardware and electrodes, is 5% or more in the 5 years following surgery. Seizures are also possible, but fortunately rare. The risk of equipment malfunction is exceedingly low. Patients must also be clear about the need and serious commitment for long-term programming and follow up with the treatment team.

Patients should also be informed that more than half of all patients treated with DBS may have a recurrence of tremor or the development of proximal tremor within several years of surgery or even earlier. Whether this is due to disease progression or a decay of benefit due to developing treatment

tolerance is not clear, but disease progression seems most likely. Recurrent tremor may be manageable with programming changes (involving selection of contacts, mono- vs. bipolar stimulation, pulse amplitude, frequency, and duration) in most cases, but may require repositioning of the DBS lead in others. Patients should also be made aware that while distal hand tremor is generally well controlled by VIM DBS, benefit for proximal tremor is variable. Although some patients notice benefit for head and voice tremor after unilateral DBS, as was true for the case mentioned above, generally this requires bilateral surgery. On the negative side, bilateral surgery has a higher incidence of worsening of gait, dysarthria, and cognitive function. Stimulation-induced speech disturbances, paresthesias, ataxia, and gait disturbances are the most challenging complications of programming, especially in bilateral cases.

Future of DBS and Role of Ablation? The technological advances in the pipeline for DBS will provide improved lead placement and significant improvements in electrode design and "current steering," which can decrease side effects and improve the response to stimulation, with more efficient and effective stimulation. Other advances include the use of multiple independent stimulation current sources, as well as closed loop control of stimulation and parameter optimization algorithms. It is hoped that these advances will lead to better treatment outcomes and facilitate programming.

Radiofrequency ablation, which is the earlier standard technique for thalamotomy, remains a good treatment option for those patients who are not good candidates for DBS or who do not want to be treated with an implanted device. As an alternative to radiofrequency ablation, a new noninvasive technique of lesioning using focused MRI-guided ultrasound has now received FDA approval. There have been no head-to-head comparisons of the effectiveness, side effect profile, and long-term effectiveness between ultrasonic thalamotomy and DBS. Furthermore, it has not been studied whether ultrasonic thalamotomy can be used bilaterally. Many of the disadvantages of the earlier use of radiofrequency ablation likely also apply to this newer technique, including suboptimal or excessive lesioning, with transient or permanent deficits, respectively. However, it is possible that the pendulum may swing again away from DBS, and toward ablation, at least for individuals excluded from DBS because of preexisting conditions or advanced age.

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Treatment of Palatal Tremor

41

Anthony E. Lang

Case 1

This 60-year-old right-handed woman was well apart from a history of treated hypothyroidism and hypertension. In April 2012, she presented to hospital with a left third nerve palsy. Investigations revealed a brainstem cavernoma which was initially treated conservatively. In March 2013, she presented with progressive neurological symptoms resulting from a further hemorrhage in the brainstem. She underwent resection of the cavernoma and postoperatively had diplopia secondary to a partial third nerve palsy, dysarthria, dysphagia, right-sided weakness, and ataxia. In October 2013, she developed prominent "shaking" of her right leg which interfered with standing and compromised ongoing rehabilitation therapy. On examination by me in January 2014, she had dysconjugate gaze with 30% restriction of elevation and 10% restriction of adduction of the left eye, and the left pupil was larger and slower to react than the right. There were no spontaneous movements of the eyes. She had a prominent scanning dysarthria, a questionable spastic catch and brisk reflexes but full power in the right limbs, dysmetria, and dysdiadochokinesia in all limbs, worse on the left side. She was wheelchair-bound and could not ambulate without considerable assistance. There was a 3–4 Hz rhythmical movement of the eyelids on light closure and a similar frequency, possibly synchronous, tremor of the soft palate. Since the onset of her symptoms, she had been unaware of involvement of the lids and palate and denied ear clicking. A similar frequency, somewhat irregular, tremulous movement (myorhythmia) was present in the right leg. At times, with complete relaxation, this movement would briefly subside. At other times, either during volitional movement or following activation, the amplitude of the leg tremor increased markedly. Standing and weight-bearing accentuated the leg tremor, further impairing her ability to stand without support. MRI in March 2013 showed a hemorrhagic lesion extending from the inferior left thalamus to the mid-pons with some extension to the right side of the brainstem (Fig. 41.1). At that time, no abnormalities were seen below the pons. Repeat MRI in September 2013 on FLAIR sequences showed a mixed hyper- and hypointensity lesion largely involving the medial right midbrain tegmentum. The inferior olives were now enlarged and hyperintense, the left more than the right (Fig. 41.2).

Treatment with trihexyphenidyl, gradually increasing to 2.5 mg TID, provided benefit that the patient and her husband rated at 75%, reducing the frequency of occurrence and severity of the leg tremor and allowing her greater independence in ambulation using bars in the home (e.g., no longer needing assistance from her husband to get from her bed to the bathroom at night). Examination showed improvement in the right leg tremor but no change in the palatal tremor. The addition of amantadine 100 mg TID provided mild further benefit without side effects. The response obtained from this medical therapy allowed her to return to an active physiotherapy program with overall further improvement in function.

Case 2

This 33-year-old previously healthy woman developed the sudden onset of a rhythmic but impersistent clicking noise in her right ear on her way home from the hospital having just delivered her first child. Within 1 month, the clicking became continuous. This interfered with her sleep and was associated with marked anxiety and depression. She was seen at another institution and given a diagnosis of "essential palatal tremor." MRI showed scattered areas of high signal intensities on T2 throughout the subcortical white matter with a frontal lobe predominance but normal brainstem including

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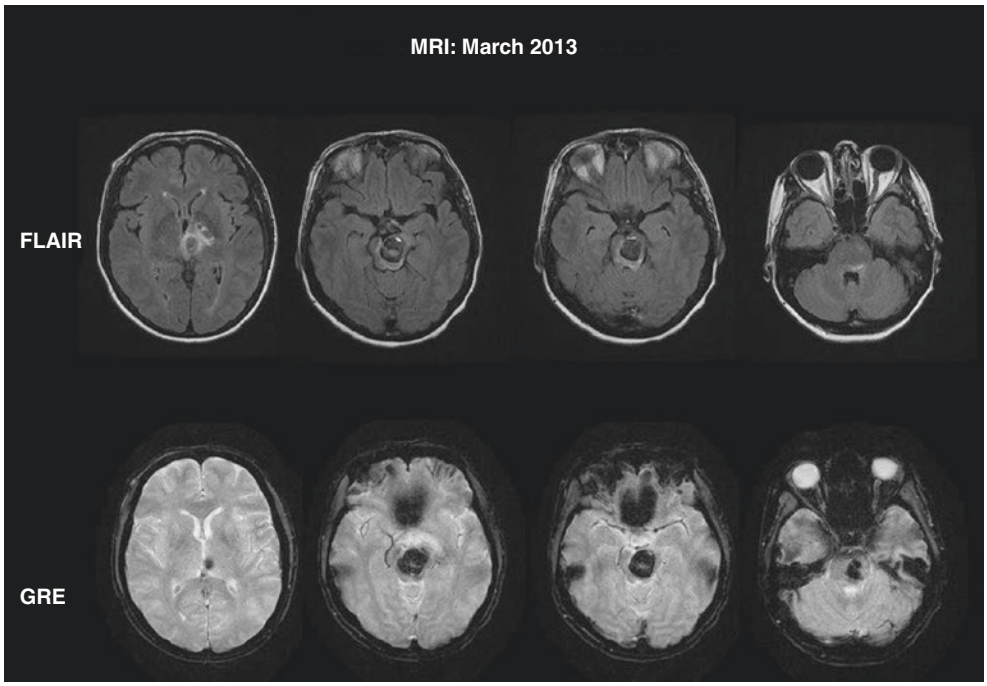

Fig. 41.1 FLAIR and GRE MRI scans in Case 1 from March 2013. Hemorrhage in cavernoma extending from the left thalamus to the mid pons

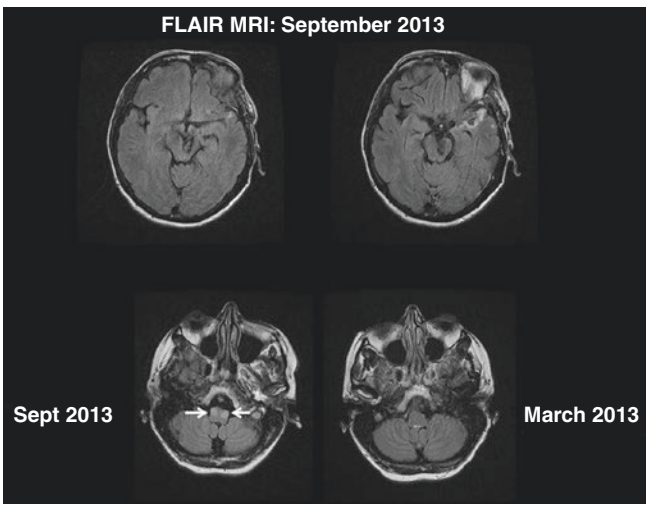

Fig. 41.2 FLAIR MRI scans in Case 1 from September 2013 showing partial resolution of the hemorrhage and the development of enlargement and hyperintensity in the inferior olives not present on the scan obtained 6 months earlier

volume and signal intensity of the inferior olives. She was given multiple drug trials including clonazepam and levetiracetam without benefit and received botulinum toxin injections to the soft palate every 3 months for 2 years with no benefit but occasional hoarseness of voice and nasal regurgitation of fluids.

She was seen by me 7 years after the onset of symptoms. She was anxious and tearful complaining about the persistent clicking as well tightness in the throat, lower face, and perinasal region. Clicking was audible when sitting close to her. The neurologic examination was normal apart from the soft palate which demonstrated a quite variable, at times rhythmical (2–3 Hz), movement which subsided completely on breath holding and with distraction maneuvers and at other times could be entrained to repetitive movements performed to command with the fingers. Assessment by a neuropsychiatrist diagnosed a major depressive disorder. Clonazepam was gradually discontinued and replaced by clomipramine. On follow-up, she noted that she did not hear the click when busy or occupied with something such as cooking and working around the house. However, it continued to bother her on attempting to sleep and sometimes awoke her from sleep, although since starting clomipramine she found her sleep had improved considerably and she was able to sleep 4 h without interruption.

Case 3

This patient was reported previously (see Kern & Lang in suggested readings). He was a 19-year-old man who had noticed bilateral ear clicking since age 7 which impacted his ability to concentrate. In early childhood he had middle ear atelectasis causing bilateral hearing impairment for which he underwent removal of a right ear cholesteatoma and placement of bilateral tympanostomy tubes. When he was seen by me, his neurologic examination was normal apart from mild left ear hearing impairment and a semi-rhythmic (≈2 Hz) palatal tremor associated with audible clicks. The frequency was quite variable and could be entrained or completely subsided with distraction.

We postulated that the palatial tremor was a learned behavior that developed in childhood because of his otolaryngological problems to help open the Eustachian tubes. We

demonstrated to him the effects of entrainment and distraction and taught him that he could do this purposefully. We asked him to practice controlling the movements, and within 1 week of routinely doing this at home using a mirror, he was able to obtain complete voluntary control including stopping the movements entirely for prolonged periods. At a 1-year follow-up visit, he showed maintenance of excellent control, only demonstrating the palatal movements when asked to reproduce them to command at various frequencies.

Discussion

Palatal tremor (PT), usually referred to as palatal myoclonus in the older literature, is subdivided into two general categories: "essential" PT (EPT) and secondary (or symptomatic) PT (SPT). SPT is typically caused by lesions involving the dentato-olivary pathway (Table 41.1) resulting in trans-synaptic hypertrophic degeneration of the inferior olivary nucleus evident on MRI (Case 1). As Case 1 demonstrates, in patients with acute causative brainstem lesions, the olivary changes typically develop after a variable latency following the initial insult. SPT involves the levator veli palatini muscle (the posterior soft palate) innervated by cranial nerves IX and X. The palatal movements of SPT show little change in frequency on examination, are generally not accompanied by ear clicks, and persist in sleep. SPT typically begins later in life (usually after age 40). Given the nature and location of the lesions / diseases causing SPT, these patients have a number of other neurological abnormalities including synchronous movements of other cranial muscles, especially the eyes, causing pendular nystagmus, as well as ataxia and other brainstem signs. Depending on the location of the lesion, patients occasionally have rhythmical movements of the limbs (as in Case 1), often referred to as myorhythmia (see Baizabal-Carvallo JF et al. and Ure RJ et al. in suggested readings). In contrast to the other neurological abnormalities, most patients are unaware of the palatal movements. They may complain of oscillopsia due to the abnormal eye movements.

In contrast to SPT, EPT begins at a much younger age (adolescence to early adult life) and presents with ear clicks that often can be heard by others. The ear clicks are typically the only symptom, but these can be associated with profound distress. The clicks typically originate from the sudden opening of the Eustachian tube through contraction of the tensor veli palatini (the anterior soft palate), innervated by cranial nerve V. The movement frequency is often noted to be variable and subsides in sleep. Apart from the palatal movements and ear clicks, and occasional similar movements seen in the tongue and anterior neck, these patients lack other neurological abnormalities, and neuroimaging is normal. We proposed an alternative designation of "isolated palatal tremor" (IPT) (see Zadikoff C et al. in suggested readings) to emphasize the isolated nature of the movements, without other neuro-

Table 41.1 Classification and subtypes of palatal tremor

Major category	Etiology	Subdivision/etiology	Comments
Isolated palatal tremor			
	Voluntary/special skill		Patient recognizes that they can cause the movement and clicks and can control the movements including changing the speed
	Functional	Learned behavior	Case 3
		Psychogenic	Case 2
	Tics		Usually occurs in setting of a known tic disorder. Patient will typically recognize the urge similar to their other tics
	Essential palatal tremor	No distraction, entrainment	Unclear whether such an entity exists
Symptomatic palatal tremor			
	Vascular disease		
	Trauma		
	Tumor		
	Multiple sclerosis		
	Degenerations	Hereditary – e.g., Alexander's disease, SCA20, POLG mutations, GM2 gangliosidosis	
		Sporadic – e.g., "idiopathic" progressive ataxia with palatal tremor (PAPT), progressive supranuclear palsy, associated with dystonia	
	Encephalitis	For example, Whipple's (palatal involvement is uncommon in Whipp le's in contrast to ocular, facial and masticatory movements)	
	Others	Cavernoma, AVM, H. zoster, neurosarcoidosis, steroid responsive (Hashimoto's) encephalopathy, brain abscess	Case 1

logical findings or imaging abnormalities, and to highlight that this is not a "primary" movement disorder similar to essential tremor or idiopathic dystonia. We suggested a number of possible underlying mechanisms including a psychogenic movement disorder (as in Case 2) and tics. A subsequent retrospective review of ten patients with IPT found that 70% had clinical features supportive of a diagnosis of a psychogenic movement disorder (i.e., distractibility, entrainability), two had tics, and one was diagnosed with EPT (see Stamelou M et al. in suggested readings). In proposing the category of IPT, we also emphasized the etiology of a voluntary or learned special skill (perhaps comparable to ear wiggling and voluntary nystagmus) causing isolated palatal tremor as sometimes seen in scuba divers and wind instrument players, probably developed to open the Eustachian tubes to normalize the pressure in the middle ears. In our report of Case 3, we argued that although the clinical features of distractibility and entrainability might be used to support a psychogenic etiology, the lack of underlying psychological factors, the development in the setting of clear otolaryngological pathology, and the voluntary control that the patient established by simple education and practice all favored the classification of a "functional movement disorder" secondary to a learned behavior. This may apply to many other patients with IPT given the common history of onset in the setting of past upper respiratory tract infections.

Management

The management of PT will obviously depend on the etiology and the complaints of the patient. As indicated, most patients with symptomatic PT are not aware of the palatal movements, and extra-palatal movements are generally not a major source of disability in contrast to their other accompanying neurological deficits. Case 1 represents an uncommon situation where palatal tremor was combined with myorhythmia in the right leg which responded to modest doses of trihexyphenidyl with a possible further improvement on amantadine. As with Holmes tremor, patients can also be given trials of levodopa, clonazepam, and other agents; however, there is little evidence to support the preferential selection of specific treatments in this disorder (see Chap. 45). Similarly, in patients complaining of oscillopsia, a variety of treatments can be used, but there is very little strong supportive evidence available on the treatment of nystagmus and none specifically related to the problem associated with SPT. Trials of an anticholinergic, gabapentin, memantine, 4-aminopyridine, clonazepam, or baclofen could be considered in patients bothered by this symptom (see Thurtell MJ in suggested readings).

The approach to management of isolated/essential PT is entirely different. Here, patients often complain bitterly of the consequences of the palatal tremor – i.e., the ear clicks. However, the fact that this disorder is probably functional or psychogenic in the majority of patients has only been recognized recently. As we have argued in our original publication of Case 3, these two terms (functional and psychogenic) are not necessarily interchangeable (they have been separated in Table 41.1), and this distinction will be important in the therapeutic approach. Our experience with Case 3 suggests that when patients can appreciate the potential for voluntarily altering the tremor, the patient education, teaching them to bring the tremor under complete voluntary control, is the optimal first-line therapy. I have no further experience with this approach so am unable to comment on its success or failure rates. In patients with the possibility of a psychogenic cause, evaluation and possible care by a psychiatrist is important, and this was clearly helpful in Case 2. It is also possible that these patients could be trained to control the PT as in Case 3 but recognition and management of the accompanying psychopathology will also be important.

A variety of treatments have been claimed beneficial in patients with "EPT"; however none of these treatments have been studied in a placebo-controlled fashion, and these reports largely preceded the recognition of the predominant psychogenic/functional cause raising the strong possibility that placebo responses accounted for the benefit reported. The commonest treatment reported in recent years is the injection of botulinum toxin into the tensor veli palatini muscle. Single cases and small case series have claimed benefit to both the palatal movements and the accompanying ear clicks. As emphasized by Slengerik-Hansen and Ovesen in a recent systematic review of the literature involving 51 patients (see suggested readings), the studies available "form an extremely low evidence level with several sources of bias." Once again, a critical problem with these studies is the failure to recognize the functional/psychogenic etiology (not mentioned by Slengerik-Hansen and Ovesen) and the lack of placebo-controlled trials. In general, these injections have been relatively well-tolerated although complications have included self-limited dysphagia, trans-nasal regurgitation, changes in speech (e.g., hyper-nasality), and aural fullness, and rarely temporary nasogastric feeding has been required due to the severity of the dysphagia. Improvement has been reported in the majority of patients described, and remarkably, in the majority of these, the problem "resolved" completely, and in many, this effect lasted for the entire follow-up of months to 1–2 years, further raising the concern about a possible placebo response (although Slengerik-Hansen and Ovesen proposed several other poorly substantiated mechanisms). At this time, there is no consensus of opinion on how to best manage these patients. In those resistant to either simple education and retraining or management of underlying, possibly contributory, psychiatric problems who remain extremely distracted and disabled by the ear clicks, a cautious trial of botulinum toxin could be considered. In view of the reported

success of using very low doses of botulinum toxin combined with strong suggestion in patients with functional/psychogenic dystonia (see Edwards MJ et al. in suggested readings), this approach should also be considered in patients receiving botulinum toxin for IPT. However, in contrast to the care received by Case 2, this treatment should be discontinued if the first one or two injections fail to provide clear benefit.

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Treatment of Cerebellar Tremor

42

Susan L. Perlman

Case

A 38-year-old right-handed man was seen in consultation for an 8-year history of progressive imbalance (requiring a walker for the past year) and a 6-year history of increasing tremor. During the year prior to this assessment, the tremor was causing significant difficulty with writing, using a keyboard, using knives, and driving, forcing him to seek disability from his job as an architect. There was a strong family history of ataxia including the patient's father, paternal uncle, and paternal grandmother—the father and uncle with onset in their 30s as seen in the patient and the grandmother with onset in her 40s. The patient's uncle underwent genetic evaluation and was found to be positive for a CAG expansion in the gene for spinocerebellar ataxia type 2 (38 repeats, full mutation ≥36). The patient had not been tested.

Pertinent positives on his exam included blood pressure 108/60, pulse rate 72, slowed saccadic eye movements, decreased upgaze, moderately slurred speech, muscle fasciculations and intermittent cramps, decreased primary sensory modalities in the feet, depressed deep tendon reflexes with downgoing toes, moderate dysmetria with slowed rapid alternating movements in the limbs, wide-based gait requiring at least one-hand support, and a moderate amplitude rotatory action tremor in the trunk and arms. His signature is shown in Fig. 42.1.

Since the tremor interfered with several routine activities, treatment was indicated and attempted. Use of wrist weights and adaptive eating utensils was discussed. He was initiated on propranolol 20 mg three times per day, which was escalated slowly to 60 mg three times per day, with mild reduction in tremor, making drinking and eating easier. However handwriting was still a problem. Blood pressure was stable at 109/67, with mild pulse reduction to 66. Primidone was added starting with 50 mg at night and slowly increased to 50 mg three times per day. He noticed additional improvement in tremor but felt that his balance was worse. Primidone was tapered off, and clonazepam started, beginning with 0.25 mg at night, and slowly increased to 0.5 mg at night and 0.25 mg twice daily. The patient noted tiredness and no improvement in tremor with the combination of propranolol and clonazepam, so clonazepam was tapered off. Amantadine was then added to the propranolol regimen, at 100 mg morning and noon. Mild constipation was the only reported side effect. He returned for follow-up 1 year after beginning the treatment regimen, now on propranolol 60 mg three times per day and amantadine 100 mg twice per day. The tremor demonstrated reduced amplitude and frequency in his dominant hand and improved speech. Handwriting is still difficult. For his current signature, see Fig. 42.2.

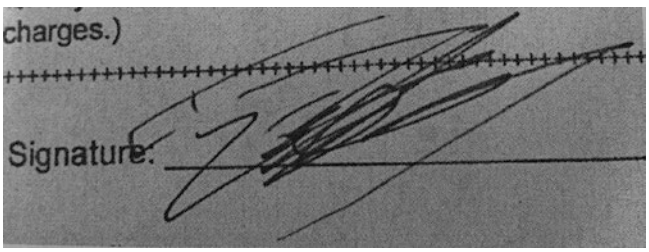

Fig. 42.1 Signature prior to treatment

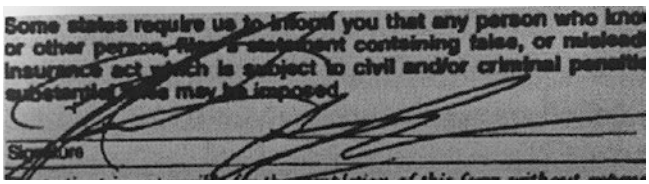

Fig. 42.2 Signature on propranolol and amantadine

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Discussion

The three key components of a successful management plan for cerebellar tremor are:

1. Identify and control triggers or causes of variability (e.g., fatigue, anxiety). The better the patient understands the tremor, the better the patient can control it.
2. Utilize physical and occupational therapy techniques for postural control and assistive strategies (exercise, bracing, weighted/adaptive devices).
3. Identify pharmacological agents, including the use of botulinum toxin, which could modify the tremor. Noninvasive and invasive stimulation or ablative techniques (TMS, tDCS, DBS, thalamotomy) have been tried in cases where nothing else has helped a disabling cerebellar tremor.

There are many acquired and hereditary causes of cerebellar dysfunction which can lead to tremor. Of the dominantly inherited spinocerebellar disorders, SCA 2, 8, and 12 have tremor as a key symptom. In the recessive ataxias, the ones with central cerebellar involvement are more likely to have tremor than the spinocerebellar forms (Friedreich's ataxia). Cerebellar stroke or tumor, multiple sclerosis, and alcoholic cerebellar disease are other more common causes of cerebellar tremor.

Cerebellar dysfunction can cause several different types of tremor (See Table 42.1), which may respond to different types of treatment.

A search of the literature for "ataxia" and "treatment" will yield many publications and case reports, including some controlled and many open studies of a number of pharmacological agents. 4-aminopyridine, riluzole, varenicline, buspirone, amantadine, and TRF (thyrotropin releasing factor) are just a few. Any agent that improves "ataxia" or is disease-modifying for a particular ataxia could have a beneficial effect on any associated cerebellar tremor. Other agents include those used in essential tremor, including propranolol and primidone, as demonstrated in the case (see Table 42.1). Unfortunately there are currently no FDA-approved drugs for cerebellar ataxia, and all agents used to manage cerebellar tremor are "off-label." There is limited evidence for treatment of cerebellar tremor.

Practical recommendation include:

1. Try one candidate drug at a time.
2. Allow at least a week between tapering off/stopping one drug and moving to the next.
3. Give each drug a few days for early side effects to wear off, before assessing benefits.
4. Continue a promising drug (or titrate the dose) for up to 8 weeks before a final assessment is made.
5. Establish a set of standard measures and patient reported measures to determine if a drug is truly working (allow for "good" and "bad" days). For example, the patient finds it easier to write, eat with utensils, drink from a cup, etc.
6. If more than one type of cerebellar tremor is present, optimal tremor control may require use of more than one agent.
7. Be aware that agents that benefit tremor may worsen imbalance and incoordination.

Practice Guidelines are under development by the AAN (American Academy of Neurology).

Table 42.1 Types of cerebellar-mediated tremor

Feature	Essential type	Action or intention	Rubral	Orthostatic
Pathophysiologic origin (still poorly understood)	Loop through cerebellum	Cerebellar hemisphere/deep nuclei	Cerebellar outflow/red nucleus—dentato-rubral Cf. Holmes tremor	Functional connectivity between lateral cerebellum and supplementary motor area is abnormally increased
Response to small amount of alcohol	Often improves	Little or none, may worsen	Little or none, may worsen	Little or none, may worsen
Position of maximal activation	Maintenance of posture	At the end of purposeful movement	At rest and with posture and movement	Standing
Frequency	4–12 Hz	2–4 Hz	2–4 Hz	13–18 Hz
Morphology	Flexion-extension in line of movement	Side to side in line of movement If severe/high amplitude, may appear myoclonic	Rotatory	Associated with a strong feeling of instability, fear of falling, fatigue, pain
Body part(s) affected	Upper limb, head, voice	Limbs, trunk	Upper limbs, trunk	Legs, trunk
Commonly tried medications	B-blockers, primidone, gabapentin, topiramate	Same medications as used for essential type tremor, other anticonvulsants (carbamazepine, clonazepam, levetiracetam)	Carbidopa-levodopa, clonazepam, often in combination with medications used for essential type tremor	Clonazepam, levetiracetam

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Treatment of Holmes Tremor

43

Tigran Kesayan and Theresa A. Zesiewicz

Case

A 71-year-old right-handed man presented for evaluation of an irregular tremor in his right arm that occurred at rest, while maintaining posture and with action. It began several months following a brainstem stroke. The patient's medical history included hypertension, diabetes, dyslipidemia, and a 40-pack year smoking history. Two months ago, he awoke with a right hemiparesis gait ataxia, vertigo, and speech difficulty. He had discontinued his aspirin and statin medication several weeks prior to this event. During hospitalization, he was found to be hypertensive. His neurological examination demonstrated moderate dysarthria, horizontal nystagmus on rightward gaze, 3/5 weakness in his right upper and lower extremities, and right arm dysmetria. An electrocardiogram (EKG) was significant for left ventricular hypertrophy. Magnetic resonance imaging (MRI) showed restricted diffusion on DWI sequence in the left pons, consistent with acute ischemia; chronic subcortical and thalamic ischemic lesions were also present. The patient received medical management with aspirin and a statin and was eventually transferred to a rehabilitation service, where his neurological symptoms improved.

The patient reported that he developed a rest, postural, and action tremor in his right arm 2 months following the brainstem stroke. The tremor was present in his right arm during relaxation, but worsened when he reached for objects or performed tasks with his right hand. The tremor interfered with his activities of daily living, but disappeared during sleep. He had no prior history of tremor, nor any family history of tremor or Parkinson's disease. He denied any new neurological symptoms, nor had he changed any of his medications since the stroke. The tremor did not improve with alcohol ingestion. His right arm was unaffected by pain or spasm.

The neurological exam was significant for mild right hemiparesis, right arm dysmetria, gait ataxia, and an irregular proximal and distal tremor of moderate amplitude in his right arm of 3–4 Hz at rest, posture, and during purposeful movements. There were no signs of Parkinson's disease or dystonia, and only his right arm was affected. A repeat MRI of the brain without contrast showed resolution of the pontine restriction seen on DWI sequence in the original MRI. A diagnosis on HT was made, and the patient was treated with carbidopa/levodopa 25/100 three times daily with moderate improvement in tremor.

Discussion

Gordon Holmes first described the tremor that eventually bore his name (HT) in 1904. HT has been called rubral tremor, mesencephalic tremor, and midbrain tremor; however, lesions in these areas do not always produce HT, and HT has been associated with lesions in other areas of the brainstem, as well as the thalamus or cerebellum. HT is a rest, posture, and action tremor characterized by slow frequency (<4.5–5 Hz) and varying amplitude that worsens with target pursuit. There is usually a delay between the brain insult and tremor onset, often ranging from weeks to several months. Comorbid findings often include hemiparesis, ataxia, dysarthria, and cranial nerve abnormalities.

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The most common causes of HT are ischemic or hemorrhagic stroke, but other etiologies include progressive multifocal leukoencephalopathy (PML), multiple sclerosis, herpes simplex type 1, toxoplasmosis, neuroparacoccidiomycosis, hyperglycemia, cerebral vascular formation, head trauma, or tumors. MRI of the brain usually shows abnormalities in the thalamus, midbrain region, and cerebellum. However, the exact pathophysiology of Holmes tremor is unclear. Possible explanations include damage to nigrostriatal dopaminergic circuits and cerebellar circuitry including the cerebellothalamic and cerebello-olivary circuits including the dentato-rubro-olivary pathway, also known as the Guillain-Mollaret triangle.

Treatment of HT is often challenging. The tremor is typically debilitating and may significantly affect activities of daily living. Several noncontrolled studies have found levodopa to improve HT in about 50% of patients in doses ranging from 300 to 1000 mg/day. Other case series have reported varying degrees of benefit with beta-blockers, zonisamide, levetiracetam and topiramate, pramipexole, lamotrigine, clonazepam, clozapine, flunarizine, carbamazepine, trihexyphenidyl, baclofen, gabapentin, valproic acid, piracetam, and piribedil. Botulinum toxin injection may be considered in pharmacologically refractory cases, as well as deep brain stimulation (DBS) of the ventral intermedius nucleus (VIM) of the thalamus or the globus pallidus internus (GPi).

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Part V

Dystonia

Classification of the Dystonias

44

H. A. Jinnah

Case 1

A 58-year-old woman complained of involuntary turning of the head to the right that began 3 years ago and worsened over a period of 12 months. By the time of her visit, her head was turned nearly constantly to the right. Sometimes she noticed jerky movements of the head if she tried to turn it leftward, and she developed chronic soreness in the right posterior neck region. There were no accompanying neurological or medical problems, no exposure to dopamine receptor blocking drugs, and no relevant family history.

The neurological examination at rest revealed severe right torticollis (head turned right), moderate left laterocollis (head tilted left), and minor retrocollis (head tilted back). There was a jerky tremor-like movement when she tried to turn it to the left. There was visible hypertrophy of the left sternomastoid and tenderness in the posterior left upper neck region in the region of the splenius capitis and semispinalis capitis. There were no other significant exam findings.

According to the new classification system, this patient would be described as having *isolated, focal cervical dystonia*, with onset in late adulthood that initially progressed but is now static. She has "isolated" dystonia because she has no other relevant neurological or medical problems. Her problem is focal because only one body region is involved. The problem started in adulthood and does not appear to be progressive. Cervical dystonia is the most common of all of the adult-onset focal dystonias, and she had a relatively common pattern of abnormal head movements. Many patients with cervical dystonia also have a coarse tremor-like movement of the head, particularly when they attempt to move away from the dystonic position. Many also have neck pain due to chronic muscle pulling. Cervical dystonia is usually idiopathic, so an extensive laboratory workup is not necessary. It is usually readily treatable with botulinum toxin.

Case 2

A 14-year-old boy complained of stiffness and cramping of his left leg when walking. The problem started about 9 months ago and appeared to be progressing. He had no other complaints, but his parents raised concern regarding poor school performance and sloppy writing.

The neurological exam revealed hypomimia with a fixed smile, mild dysarthria, and a reduced blink rate. There were frequent movements of the head and upper trunk that appeared to be stereotypical readjustments of his posture. There was a subtle postural tremor of both hands, with slightly slowed fine finger movements. When writing with the dominant right hand, he gripped the pen very tightly with excessive flexion of the wrist. His script was large and irregular. Resting arm tone was normal. His standing posture revealed mild scoliosis, and his gait revealed abnormal stereotypical posturing of the left leg when walking. His foot turned inward with plantar flexion, and he had a steppage gait with excessive elevation of the thigh. Walking backward was better than walking forward.

According to the new classification system, this patient would be described as having combined, generalized dystonia, with onset in adolescence that appears to be progressive. He has "combined" dystonia because of the coexisting Parkinson-like features of hypomimia, reduced blink rate, and slowed movements. His problem is generalized because the trunk is involved (scoliosis) along with two limbs and possibly the neck as well. The adolescent onset and apparent worsening with time raise concern for a biological process that is progressing.

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Further workup included a serum chemistry profile that revealed only a minor increase in liver enzymes, and a low ceruloplasmin. Ophthalmological assessment with slit-lamp exam revealed Kayser-Fleischer rings, and genetic testing revealed heterozygous mutations in the *ATP7B* gene. A diagnosis of Wilson disease was made, and the patient started medications to reduce body copper stores.

Discussion

In 1911, Oppenheim coined the term "dystonia" to describe a disorder in which individuals appeared to be hypotonic at rest and hypertonic with any voluntary action. Since that time, many different clinical features have been described. As a result, the definition of dystonia has evolved, and an international consensus panel settled on the following definition in 2013:

Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive movements, postures, or both. Dystonic movements are typically patterned, twisting, and may be tremulous. Dystonia is often initiated or worsened by voluntary action and associated with overflow muscle activation.

The consensus panel also provided a framework for classifying the many different types of dystonia (Table 44.1). They are subgrouped according to two main axes: clinical features and etiology. Important features for the clinical axis include the age at onset, the body region affected, and temporal features such as mode of onset or progression and whether or not there are any related neurological or medical problems. Important features for the etiological axis include whether there is evidence that the disorder was inherited or acquired or evidence of nervous system pathology. A recent review described more than 100 different disorders in which dystonia may occur.

The clinical and etiological axes are independent but work together. More specifically, careful delineation of the clinical features can lead to a more focused differential diagnosis. One of the most useful means for appreciating the value of the new classification system is to apply it to some typical cases.

The 2013 classification system for the dystonias was designed to improve its utility in both the clinical and research settings. The four clinical domains used for classification, including body area affected, age at onset, temporal aspects, and associated features, were selected to aid in grouping patients for more targeted diagnostic testing or treatment decisions (Table 44.1). The three etiological domains were introduced to organize the many subtypes according to currently known biological causes to aid scientific discovery of shared pathways (Table 44.1).

Table 44.1 Classification of the dystonias

Axis	Dimension for classification	Subgroups
Axis I: Clinical features	Age at onset	Infancy (birth to 2 years)
		Childhood (3–12 years)
		Adolescence (13–20 years)
		Early adulthood (21–40 years)
		Late adulthood (40 years and older)
	Body distribution	Focal (one isolated body region)
		Segmental (2 or more contiguous regions)
		Multifocal (2 or more non-contiguous regions)
		Hemidystonia (half the body)
		Generalized (trunk plus 2 other sites)
	Temporal pattern	Disease course (static vs progressive)
		Short-term variation (e.g., persistent, action-specific, diurnal, paroxysmal)
	Associated features	Isolated (with or without tremor)
		Combined (with other neurological or systemic features)
Axis II: Etiology	Nervous system pathology	Degenerative
		Structural (e.g., focal static lesions)
		No degenerative or structural pathology
	Heritability	Inherited (e.g., sex-linked or autosomal, dominant or recessive, mitochondrial)
		Acquired (e.g., brain injury, drugs/toxins, vascular, neoplastic)
	Idiopathic	Sporadic
		Familial

The classification by body region affected has clear and direct value for guiding diagnostic testing and treatment recommendations. For example, for adults with focal or segmental dystonia, extensive diagnostic testing is not generally recommended, because a cause is only rarely discovered. On the other hand, adults with generalized dystonia or hemidystonia warrant more investigation, because a genetic or structural cause is more likely. When considering treatment options, patients with focal or segmental dystonia are likely to benefit from botulinum toxin injections, while those with more widespread involvement may require oral medications or surgery.

The classification by age at onset similarly has clear value for guiding diagnostic testing and counseling regarding prognosis. Dystonias that begin in infancy are most often due to discoverable inherited metabolic diseases, often with a grave prognosis. Dystonias that begin later in childhood are also likely to have a discoverable cause, such as one of the isolated dystonias or an early-onset neurodegenerative con-

dition. Dystonias that begin later in adults are least likely to have a discoverable cause and are unlikely to progress and if so usually just to contiguous regions.

The classification by temporal features is important for identifying common syndromic patterns and for providing clues regarding underlying causes. For example, the most common adult-onset focal dystonias may progress during the first few months or years, with a risk of spread that depends on the first site affected. Approximately half of patients with blepharospasm spread to have abnormal movements of the lower face or neck within 5 years, but only 20% of patients with cervical dystonia will spread during this period. After this period, further spread is sufficiently slow that the disorder may seem static. In contrast, acute-onset dystonia is unusual and raises concern for neuroleptic exposure, specific genetic disorders such as rapid-onset dystonia-parkinsonism, or a conversion disorder. On the other hand, a slowly progressive disorder should raise concern for an underlying metabolic or degenerative process. There also are other temporal patterns that point to specific diagnoses, such as diurnal variations suggestive of dopa-responsive dystonia, or intermittent episodes suggestive of one of the paroxysmal dyskinesias.

Finally, classification as *isolated* (previously primary) versus *combined* (previously dystonia plus or heredodegenerative dystonia) was introduced to emphasize the importance of syndromic patterns in recognizing certain disorders. More than 100 such disorders are now recognized, so diagnostic testing for all of them is not feasible. By delineating the clinical features which coexist with dystonia, the list of likely diagnostic possibilities can be reduced. For example, dystonia combined with abnormal ocular motility reduces the number of likely possibilities to disorders such as dystonia with ocular motor apraxia, Niemann-Pick type C, the mitochondrial disorders, and a few others. On the other hand, dystonia combined with Parkinson-like features leads to a different differential diagnosis.

The second main axis for classification addresses potential etiologies. Our understanding of the many biological causes for dystonia has grown rapidly in the past few years, and the many causes can be grouped in a variety of different ways. One of the most well-recognized groupings include those where there is evidence for overt pathology, such as a focal lesion, signs of degeneration, or abnormal brain MRI suggestive of metabolic or inflammatory processes. The other clinically relevant grouping is genetic, so information regarding pattern of inheritance becomes important.

Although the clinical and etiological axes are distinct, they were not envisioned to function independently. Instead, the goal of precisely delineating the clinical phenomenology (clinical axis) is to build a comprehensive picture of a syndromic pattern (Fig. 44.1), which is then used to prioritize specific disorders for diagnostic testing.

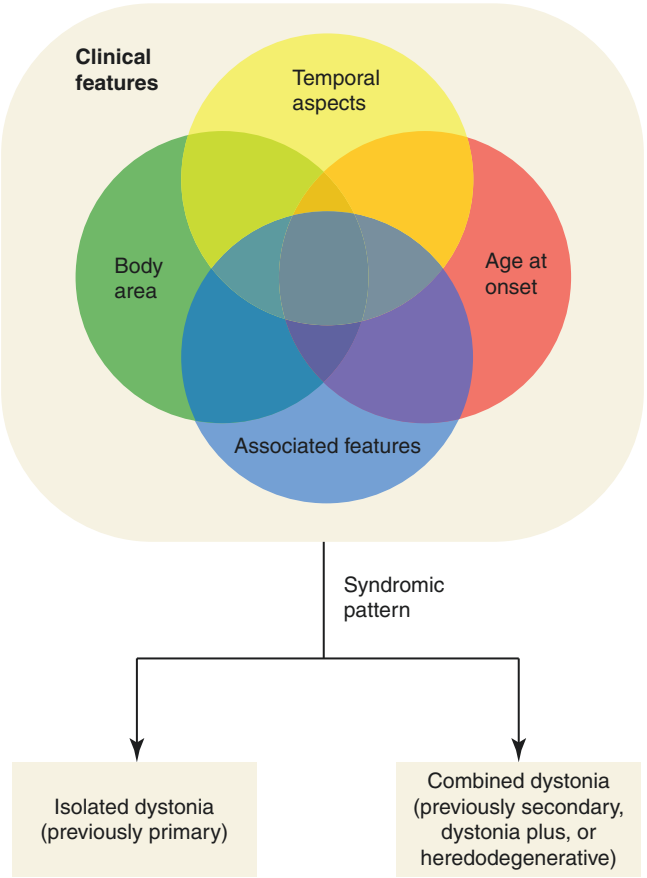

Fig. 44.1 Clinical classification of dystonia. The classification system for dystonia emphasizes four main clinical aspects, with overlapping value for recognizing syndromic patterns that aid diagnostic recognition or testing

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Treatment of Blepharospasm

45

Eric S. Molho

Case

A 59-year-old man presented in 2001 with 6 years of eyelid spasms. The symptoms began in the left eye as a feeling of "vibration" in the lid, and within a year, both eyes were involved equally. Over time the symptoms worsened and were more like a "spasm" of the lids and at times sustained enough to cause sudden and unpredictable impairment of vision. Reading, driving, and even watching television had become difficult in the last year. Friends and family had also noticed some twitching around the nose and upper face. Exacerbating factors included stress, fatigue, and bright morning light. He denied any sense of urge or relief associated with blinking, and there was no history of childhood "tics." He denied being able to suppress the spasms voluntarily, but he did sometimes attempt to open his lids by touching the upper lid with his finger. He denied any other involuntary movements or neurological impairments. There was no family history of similar symptoms and no history of neuroleptic medication exposure, head trauma, birth injury, or other vision or ocular conditions. He was healthy otherwise and still working full time as an electrical engineer. He had two previous MRI scans of the brain which were normal, but no diagnosis had been proposed.

On examination, there were bilateral, synchronous, arrhythmic, visible spasms of the orbicularis oculi muscles. With more severe spasms, there was furrowing of the brow, and at times there was irregular mild spasm adjacent to the nares, in the upper cheeks, as well as subtle pursing and twisting movements of the mouth. The movements were not suppressible. Between spasms there was no delay in eyelid opening. There was no facial muscle weakness, no sensory disturbance, and no signs of parkinsonism, and the remainder of the neurological examination was normal.

A diagnosis of blepharospasm was made, and no additional diagnostic testing was recommended. The spasms were severe enough to interfere with vision, cause disability, and represent a significant danger to the patient, especially related to driving. Treatment was justified, and botulinum toxin type A injections were offered as the treatment of choice. His initial treatment dose with onabotulinumtoxinA was 2.5 units in each lower lid, 2.5 units in each lateral canthus, and 1.25 units on each side of each upper lid. This was well tolerated, but only resulted in about 40% improvement. With subsequent treatments the dose was increased to 5 units in the lower lids and lateral canthi, the upper lid dose to 3.75 units in the medial upper lid, and 2.5 units in the lateral upper lid, and 2.5 unit injections were added for the nasalis, corrugator, and frontalis muscles. His dose has been stable over the last 13 years (between 45 and 48.75 units total), and the benefit typically is 90% over a period of 10 weeks then gradually wearing off thereafter. He has received treatment every 3 months for the last 15 years without decrement in the response, and the only side effects have been rare, transient bruising, and rare subtle transient ptosis. He has never required adjunctive therapy with oral medications, and he continues to drive and work full time as an engineer.

Discussion

Blepharospasm is an adult-onset form of focal dystonia characterized by involuntary spasms of the orbicularis oculi muscles that are fairly symmetrical, synchronous, irregular, and arrhythmic. Orbicularis oculi spasms may occur in isolation, but it is common to have some involvement of other facial muscles in the upper or lower face, and less commonly blepharospasm can be part of a segmental or generalized dystonia. Limb dystonia (writer's cramp) and hand tremors (dystonic tremor) are not uncommon in patients with blepharospasm. Meige syndrome is the term used to describe segmental craniocervical dystonia with additional features being some combination of oromandibular,

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cervical, and laryngeal dystonia occurring with blepharospasm. The incidence of blepharospasm is quoted as 5 per 100,000 and is probably underestimated; it typically begins in the sixth decade of life, a bit later than other adult-onset focal dystonias. Women are more affected than men. In addition to the obvious impact on vision, patients often experience photophobia, eye irritation, social anxiety, and embarrassment. Disability is common due to interference with driving, reading, and other similar activities often resulting in job loss, loss of independence, and social isolation.

The diagnosis of blepharospasm, like other forms of dystonia, is made on clinical grounds. Unfortunately, the diagnosis is often delayed, or patients are misdiagnosed as having dry eyes, allergies, or anxiety. Table 45.1 summarizes the clinical features that are useful in distinguishing blepharospasm from other similar appearing conditions that cause facial spasm or lid dysfunction. One way to distinguish blepharospasm from similar appearing disorders is to look at the distribution of symptoms. Primary forms of dystonia are often action induced and tied to particular motor activities. For example, upper limb dystonia may be isolated to the activity of handwriting (writer's cramp), or leg dystonia may only be seen with walking. In primary blepharospasm, the distribution is that of the motor activity of blinking and is bilateral. Hemifacial spasm, on the other hand, is a peripheral nerve disorder, and the distribution of muscular spasm is that of the muscles of facial expression innervated by the seventh cranial nerve. Idiopathic or "isolated" blepharospasm should also present as a pure motor disorder without sensory, cognitive, or long tract signs. "Trick" maneuvers are commonly employed by patients with blepharospasm such as touching the lid with a finger, whistling, or opening the mouth, as they transiently suppress the spasms. The use of sunglasses to avoid bright lights is also common in these patients. Eye blinking tics are common in Tourette syndrome and chronic tic motor disorders, which, unlike blepharospasm, usually begin in childhood and can be easily separated from dystonic eyelid spasms by the presence of supressibility, a history of tics occurring in other body regions, and associated psycho-emotional phenomena such as the urge to produce the movements and a feeling or relief upon performing the movement and comorbid obsessive-compulsive traits.

Adult patients presenting with typical blepharospasm and an otherwise normal examination do not require an extensive workup for secondary causes, and as the case above demonstrates, usually no testing is necessary. However, any person experiencing dystonia prior to middle age should be screened for Wilson's disease with a serum ceruloplasmin. Blepharospasm has been rarely attributed to basal ganglia and brainstem injuries such as stroke, hemorrhage, and tumors, and as such, in atypical cases or if there are any non-dystonic signs on examination, an MRI should be considered. Blepharospasm can also occur very early in the course of Parkinson's disease and Parkinson-plus disorders such as progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD). Thus, a careful search for bradykinesia, rigidity, posture, and gait changes associated with a parkinsonian syndrome is warranted. Blepharospasm can also be part of a neuroleptic-induced tardive syndrome, so a careful historical screen for exposure to dopamine blocking drugs is a must.

All patients diagnosed with blepharospasm should be encouraged to contact the Benign Essential Blepharospasm Research Foundation (BEBRF). The education and support provided by this organization is well known for improving the quality of lives of those affected by this condition. The treatment of choice for blepharospasm is the injection of affected muscles with botulinum toxin. A practice parameter published by the American Academy of Neurology gave a level B recommendation for both onabotulinumtoxinA (Botox) and incobotulinumtoxinA (Xeomin). OnabotulinumtoxinA and incobotulinumtoxinA are also the FDA-approved options for this indication, but abobotulinumtoxinA (Dysport) may also be considered based on favorable clinical trial results. RimabotulinumtoxinB (Myobloc) is generally reserved for patients who have developed immunoresistance to botulinum toxin type A preparations due its propensity to be associated with unpleasant burning sensation with subcutaneous injections. Unit dosing for these toxins is not equivalent; however, the weight of current literature and practice experience indicates that the two FDA-approved preparations for blepharospasm, onabotulinumtoxinA and incobotulinumtoxinA, can be dose converted in a one-to-one ratio. Because facial muscles are generally quite sensitive to the toxin, and in order to avoid side effects, it is recommended to start with the smallest unit dose per site that is likely to result in some benefit and limit the number of sites to only those that are causing the patient noticeable difficulties. For facial injections, I dilute onabotulinumtoxinA and incobotulinumtoxinA at 25 units per cc allowing for even 0.625 units to be measured with a standard 1 cc syringe. Upper lid and upper lip sites are particularly prone to causing side

Table 45.1 Differential diagnosis of blepharospasm

	Supressibility	Urge	Trick maneuvers	Visible spasm	Response to botulinum toxin	Anatomic distribution
Blepharospasm	–	–	++	++	++	Bilateral
Apraxia of eyelid opening	–	–	+	–	+	Bilateral
Hemifacial spasm	–	–	–	++	++	Unilateral
Facial tics	++	++	–	+	+	Bi- or unilateral
Ptosis	–	–	–	–	–	Bi- or unilateral

effects due to muscle weakness, and a starting dose, no larger than 1.25 units should be employed. Future injections can be considered at a roughly 3-month interval, and site doses can be manipulated in small increments as needed.

The side effects of greatest concern are various forms of lid dysfunction that can result in injury to the cornea due to exposure, unacceptable cosmetic changes, and obscured vision. These are lagophthalmos (inability to close lid completely), ptosis (upper lid droop), and ectropion (out turning of lower lid). Such problems can generally be avoided by careful dosing and avoidance of the midline in the upper lid due to the presence of the levator palpebrae muscle. The best results are generally obtained with the needle directed away from the midline medially and laterally and low on the lid margin (pretarsal part of muscle) using a 30 gauge needle or smaller. It is wise to have the patient followed by an ophthalmologist or optometrist to check for these complications at a time when the injections are having their peak effect. If there is lid dysfunction, moisturizing eye drops should be used liberally, the effected lids can be carefully taped closed at night when sleeping, or a moisture chamber can be employed.

Bruising is another complication of injections that can generally be minimized by avoiding visible veins under the skin, using small gauge needles and in patients that are prone to this complication, holding antiplatelet agents for 1 week prior to injections.. In my experience, patients on anticoagulation that cannot be interrupted can be injected safely for blepharospasm but should be warned about the increased risk of bruising. One should also observe caution when using alcohol to clean the skin around the eye prior to injections. Alcohol is a severe corneal irritant, and every effort should be made to avoid getting it in the eye. Electromyographic (EMG) guidance is not necessary for facial injections and is inadvisable due to the larger size of the needle, increasing the likelihood of patient discomfort and bruising.

Oral medications can be used for adjunctive therapy in patients receiving botulinum injection or as the main therapy in those not receiving injections; however the benefits are generally modest, and side effects often limit dosing. It should be noted that no oral medication is FDA approved for this indication. Benzodiazepines and particularly clonazepam can be helpful and is generally used as a small bedtime dose of 0.25–1 mg. The usual concerns about sedation, ataxia, memory impairment, habituation, and addiction apply. Anticholinergic medications such as trihexyphenidyl in small doses can also be useful in some patients, but the expected anticholinergic effects and new concerns about increasing risk of dementia limit their usefulness. Neuroleptics and atypical neuroleptics have been used in the past but should be avoided due to the risk of tardive syndromes, drug-induced parkinsonism, and metabolic syndrome. Baclofen has been utilized by some, but I have not had any success with it. Tetrabenazine is a vesicular monoamine oxidase (VMAT) inhibitor that reduces catecholamine storage, and it has been approved for the treatment of chorea in Huntington disease. There is limited evidence of its benefit in dystonia, but it is worth considering in severely affected patients. I have tried small daytime doses of zolpidem (5 mg two to four times daily) based on published case reports and have had isolated, but at times, dramatic success. It is surprisingly well tolerated, but should be used with caution, particularly in patients who still drive.

Surgical treatments are also an option for the most severely affected patients that do not derive enough benefit from less aggressive and risky therapies. Experience with deep brain stimulation (DBS) as a treatment for dystonia has increased in recent years, and bilateral stimulation of the globus pallidus interna (GPi) has some support in the literature for both Meige syndrome and isolated blepharospasm. The degree of benefit may be hard to predict, and long-term outcomes are not well known. Full and partial myectomy of the orbicularis oculi has established benefits but should only be considered for those with no other good options due to the functional and cosmetic compromise associated with the procedure and the cost. Often an additional plastic surgery procedure is necessary to improve cosmesis and function, but it is not generally covered by insurance.

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Treatment of Cervical Dystonia

46

Cynthia L. Comella

Case Study

The patient is a 47-year-old woman who noted intermittent pulling of her head to the left that began 4 years ago. Initially, this would occur only in stressful situations, but over the past 2 years, she has experienced a "no-no" tremor of her head and pain in the left posterior area of the neck. She was given the diagnosis of essential tremor and referred for evaluation. On examination, the patient has a large amplitude, irregular head tremor in the horizontal plane. When asked to close her eyes and allow her head to move, there is a deviation of her head to the left (torticollis). When she volitionally turns her head to the left, the "tremor" resolves, and when she turns her head to the right, the amplitude of the tremor increases. When she touches the back of her head, the movements are markedly improved. She has a mild extension of her neck (retrocollis) and a tilt of her head toward her left shoulder. Palpation of her neck shows hypertrophy of the right sternocleidomastoid muscle, left splenius capitis, left levator scapulae, and bilateral trapezius muscles. There are no additional neurological findings. She has no history of exposure to dopamine receptor antagonists.

Discussion

The diagnosis in this patient is dystonia, a neurological disorder with sustained or intermittent muscle contractions resulting in involuntary, abnormal postures that may have overlying spasms that can resemble tremor. The symptoms involve one region of the body, the neck, and the diagnosis is a focal dystonia referred to as cervical dystonia (CD) (spasmodic torticollis previously). The absence of additional neurological findings and lack of exposure to any agents that could cause dystonia suggests that this is an isolated or primary cervical dystonia. CD in this patient is complex, combining several axes of head movement: turning (torticollis), extension of the neck (retrocollis), and tilting of the head (laterocollis). She demonstrates several features that are frequently seen in CD, including a sensory trick or touch that improves the symptoms, and pain arising from the abnormal movements. Her primary posture is that of a leftward horizontal turn. Although the initial diagnosis for this patient was essential tremor, the directional preponderance of the movement to the left, the irregular frequency, and the resolution of tremor when turning to the left suggest that this is a dystonic tremor.

Treatment approaches for cervical dystonia include:

A. *Rehabilitation*: The role of rehabilitation techniques has not been well studied for CD. Attempts to "strengthen" non-dystonic muscles in order to counteract the dystonic ones are not effective. However, there is likely a role for exercises that stretch muscles and focus on range of motion of the neck and head in order to loosen or prevent contractures. These exercises are best introduced to the patient by a physical therapist, with the patient independently continuing them at home.
B. *Medications*: Currently, there are no oral medications that have been approved for use in dystonia or CD. Prior to the availability of botulinum toxins, a variety of medications and combinations were used. Of these, trihexyphenidyl, an anticholinergic agent, was one of the few that were evaluated in a placebo-controlled study. However, there were a limited number of patients and most with generalized dystonia. Subsequent clinical experience has shown that anticholinergic agents, while somewhat effective for the dystonia, often cause dose limiting side effects, including dry mouth, urinary retention, cognitive changes, and exacerbation of closed angle glaucoma. Hence this class of medications has largely been abandoned. Baclofen, a GABA-ergic drug, has been used in the past with limited success. Side effects, includ-

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ing sedation, confusion, dizziness, and fatigue, are frequent. Further, the abrupt withdrawal of baclofen can result in hallucinations and seizures. Clonazepam has been used effectively in some patients who experience exacerbations of dystonia when anxious or stressed; however sedation, depression, and the possibility of dependency limit the usefulness of this drug. A variety of additional oral medications have been anecdotally effective, but none has been adequately evaluated. Oral medications are not often used as sole therapy, but can be used as an adjunct to botulinum toxin injections. In some patients, the use of a low dose of anticholinergic, baclofen, or clonazepam may lessen symptoms as the effect of botulinum toxin wanes.

C. *Botulinum toxins*: Botulinum toxin interferes with neuromuscular transmission by blocking the release of acetylcholine from the nerve terminal (chemodenervation), consequently paralyzing or weakening the muscle into which it is injected. There are two serotypes (A and B) and four brands that are available in the United States: abobotulinumtoxinA (Dysport), incobotulinumtoxinA (Xeomin), onabotulinumtoxinA (Botox), and rimabotulinumtoxinB (Myobloc). All of these have FDA approval for use in CD and have demonstrated safety and efficacy. The most important consideration in choosing the brand of botulinum toxin is the familiarity of the injecting physician with the storage, preparation, and dosing of the brand. Comparative studies have not shown one brand or serotype to be superior to another. The preparation, storage, dilution, and dosing of each brand differs. When using BoNT, it is crucial to know the functional anatomy of the neck because the effect of BoNT is largely into the muscle targeted for injection, although local spread may occur. The use of electromyography to localize muscles allows targeted injections and may improve the magnitude of benefit. Likewise, ultrasound has been proposed as a method to visualize neck muscles and inject directly into hypertrophied muscles. Although neither procedure is accepted as beneficial by all neurologists, use of these techniques is generally accepted. The formation of antibodies and secondary non-response affects <2% of patients using any brand of serotype a. Although the formation of antibodies is increase with serotype B, there does not appear to be a correlation between the presence of antibodies and loss of response. It is of note, however, that with the higher acidity of rimabotulinumtoxinB, the injections may be more painful. In the patient described above, muscles that may be contributing to the clinical signs include the right sternocleidomastoid, left splenius capitis, left longissimus capitis/cervices for the left turn of the head, bilateral upper trapezius or semispinalis for the retrocollis, and the levator scapulae in combination with additional muscles ipsilateral to the left laterocollis. Because not all muscles can be injected effectively, the first injection series is into the 2–4 muscles primarily responsible for the predominant movement (left torticollis). The dose of botulinum toxin into each muscle is variable. Larger muscles, such as the trapezius, require larger doses than the sternocleidomastoid muscle. Typically the total dose when initiating treatment is between 150 and 200 units of onabotulinumtoxinA and incobotulinumtoxinA. The starting dose for abobotulinumtoxinA is 500 units and for rimabotulinumtoxinB is approximately 5000 units, divided among 3–4 muscles. Prior to injection, the patient should be informed that botulinum toxin is not a cure for dystonia and that the benefit will wane over time. The aim of toxin injections is to improve posture, reduce pain, and increase range of motion. The patient should be instructed that the effects of the injections will take a few days to begin and up to 4 weeks to maximize. The duration of benefit is approximately 12 weeks, although a substantial number of patients observe a shorter duration of benefit. Side effects from the injection include dysphagia, excessive neck weakness, local pain from injection, and, in some patients, a flu-like syndrome. Side effects following injection are typically mild and last for 1 or 2 weeks. For dysphagia, switching to a softer diet temporarily can be helpful. For neck weakness, support with a soft neck collar may improve the instability.

D. *Surgery*: There are two types of surgery that have been used for CD. Selective peripheral denervation of the spinal accessory nerve with a posterior ramisectomy from C1–C6 was pioneered by Claude Bertrand. This procedure requires special expertise on the part of the surgeon for appropriate patient selection and assessment of CD and in the technique itself. As many as 60% of patients who undergo the procedure have been reported to have some improvement in their CD. Prospective studies however are lacking. Postoperatively, there is a prolonged period or rehabilitation. Some patients will note excessive neck weakness. Following recovery from surgery, there may be recurrence of CD in some patients. Deep brain stimulation (DBS) of the Gpi has largely supplanted selective peripheral denervation. Initially, Gpi DBS was used as a surgical intervention for Parkinson disease. Following multiple reports of efficacy in generalized dystonia, the procedure received a humanitarian device exemption for dystonia about 15 years ago. The procedure involves implantation of fine stimulating electrodes into the Gpi typically with electrophysiological monitoring. Several studies have now demonstrated efficacy in CD. CD patients who do not respond to botulinum toxin injections either due to secondary non-response (antibody mediated) or to head postures in which the muscles are not accessible for injection, such as anterocollis, should be considered for DBS.

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Treatment of Oromandibular Dystonia

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Stewart A. Factor and Laura M. Scorr

Case

This patient was a 54-year-old woman who began having jaw problems 3 years earlier when she noticed she was clinching her teeth and was given a night guard by her dentist. Two years after this she noticed trouble chewing and could not close her jaw fully. Her husband observed that at onset, her jaw tended to open while eating, but not while speaking. She saw an oral surgeon who prescribed cyclobenzaprine and ibuprofen to no avail. She was given nortriptyline 10 mg per day, but while on it, she worsened, with jaw movements occurring while speaking and ultimately jaw opening even at rest. She stopped the medication. She was worked up with an MRI brain and neck, lumbar puncture, and blood work including ceruloplasmin. The MRI scan showed scattered white matter changes. There were no other findings. One month prior to the visit with us, she went to the emergency department because jaw movements became very severe. She was prescribed lorazepam and baclofen, and for 24 h, she felt better. She was then placed on both by her neurologist. She was also taking diphenhydramine to sleep. Mornings were the best time, and movements worsened as the day progressed. She also noticed a trick to close the jaw, placing her hand under her chin. There was no dysphagia. There were also no problems with gait, writing, and typing, no cervical movements, no blepharospasm, no bowel or bladder issues, and no cognitive or behavioral issues.

Medications at the time of the visit were lorazepam 0.5 mg BID, baclofen 10 mg TID, and diphenhydramine 25 mg at night. Other medications tried previously included benztropine 0.5 mg BID for 1–2 weeks, gabapentin 300 mg qHS for 1 week, and prednisone for a few days.

On examination she had severe jaw-opening dystonia activated by talking and eating (see Video 1). She needed to hold her jaw closed to speak clearly. The trick of putting a straw between her upper and lower teeth on the right kept her mouth closed. She also had lingual protrusion dystonia. These movements would intermittently stop when she was not engaged. The rest of her exam was normal.

The diagnosis was a severe case of oromandibular and lingual dystonia. It was quite disabling as she could only eat soft foods because of her inability to chew. It was likely idiopathic because she has not been exposed to dopamine blocking medications and workup was otherwise negative.

Treatment was initiated with botulinum toxin type A (onabotulinumtoxinA). See Table 47.1 for the dosing scheme and adjustments to optimize response as well as percent improvement at peak toxin effect times estimated by the patient. She was treated at 3-month intervals for approximately 2.5 years. The dystonia evolved such that after 2 years, the lingual dystonia remitted, and blepharospasm started to occur. In another 6 months, it was clear the jaw dystonia had also partially remitted to the point where she no longer needed jaw injections. She continued treatment for blepharospasm.

Discussion

This patient has oromandibular dystonia (OMD), jaw-opening type with lingual protrusion dystonia. This is an uncommon form of cranial dystonia, causing involuntary movements of the lower facial, masticatory, and lingual muscles. The result is involuntary jaw movements including opening (as seen in this patient), closure (with bruxism), protrusion, retraction, or lateral deviation. Literature suggests

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Table 47.1 Dosing scheme and adjustments to optimize response as well as percent improvement at peak toxin effect times estimated by the patient

Treatment number	Lateral pterygoid dose	Genioglossus dose	Digastric dose	Total dose	% improvement jaw/tongue
1	25 units each	5 units each	0	60 units	25/60
2	50 units each	7.5 units each	5 units each	125 units	25/60
3	60 units each	7.5 units each	10 units each	155 units	80/100
4	60 units each	7.5 units each	10 units each	155 units	50/80
5	70 units each	7.5 units each	15 units each	185 units	50/80
6	70 units each	7.5 units each	15 units each	185 units	50/60
7	90 units each	5 units each	15 units each	220 units	75/90
8	90 units each	5 units each	15 units each	220 units	80/90
9	90 units each	0 units each	15 units each	210 units	80/90
10	90 units each	0 units each	10 units each	210 units	90/100

jaw-closing dystonia is most common, but we have seen many more jaw-opening cases in our clinic. Common additional facial movements involve grimacing, lip pursing, or platysma contractions. When the tongue is involved, as in this patient, it usually presents as tongue protrusion or curling and rarely occurs in isolation. Such patients can be severely impaired in relation to eating, speaking, and swallowing, and the movements may be associated with pain and tongue, cheek, and lip mutilation. Embarrassment is also common and can lead to social phobia. In many cases the dystonia is action-induced occurring with speaking and/or eating or with playing a brass musical instrument (so-called embouchure dystonia). In others it may be present at rest. In our case it progressed from action-induced to occurring at rest. Jaw-opening dystonia can vary in severity from mild to uncontrollable opening leading to temporomandibular joint subluxation. Jaw-closing dystonia can range from virtual inability to open the mouth to just intermittent bruxism. OMD may also be a cause of stuttering. As with other dystonias, these patients often discover tricks (geste antagonistique) that temporarily alleviate this movement, i.e., as in this case biting on a straw, touching the chin, and holding something like a cigarette or pencil or toothpick between the lips. Most cases are idiopathic, and many patients report a precipitating event, best known being a dental procedure, although the causal nature remains unclear. Secondary forms include drug-induced (tardive dystonia) and severe OMD may be a sign of Pantothenoate Kinase 2 (PANK2) disease, neuroacanthocytosis, Lesch-Nyhan disease, X-linked dystonia parkinsonism (aka Lubag), and Wilson's disease.

Idiopathic OMD generally occurs in adult life, usually in the sixth decade or beyond. Women are more commonly affected than men. Isolated OMD comprises about 3% of all focal dystonias, and its prevalence has been estimated in several studies to be 0.3 per 100,000 worldwide and as high as 68.9 per million in the USA. It can also occur as part of a segmental or generalized pattern of dystonia, which increases estimates of prevalence. As many as 50% of patients with blepharospasm are estimated to have spread of their dystonia to the lower face involving the oromandibular region. When

Table 47.2 Dose ranges for jaw and tongue muscles with onabotulinumtoxinA

Muscle name	Dose range
Jaw openers	
Lateral pterygoid	15–100 units per side
Digastric	2.5–20 units per side
Jaw closers	
Medial pterygoid	15–100 units per side
Masseter	20–75 units per side
Temporalis	10–60 units per side
Tongue	
Genioglossus	2.5–15 units per side

OMD occurs in a segmental pattern with blepharospasm, spasmodic dysphonia, cervical dystonia, and upper limb dystonia, this syndrome is often called "cranial or craniocervical dystonia," or "Meige syndrome." Patients are frequently misdiagnosed as temporomandibular joint syndrome (TMJ) or having a functional disorder, and this leads to underestimation of cases and undertreatment. These patients are likely to have increased level of depression, social anxiety, and impaired quality of life. Our patient experienced a spontaneous remission which is rare and tends to occur within the first 5 years of onset, but there is often a recurrence.

Treatment of OMD is challenging. Typical oral medications used for dystonia include benzodiazepines (e.g., clonazepam, diazepam), anticholinergics (e.g., trihexyphenidyl, benztropine), and GABAergic drugs (e.g., baclofen, tizanidine). Their impact on OMD is limited. For those patients with a tardive dystonia, tetrabenazine or other VMAT2 inhibitors can be useful. Botulinum toxin injection is the treatment of choice for most patients with OMD. In order to be successful in relieving the OMD, the injector must be very familiar with the muscular anatomy of the jaw and appropriate doses per muscle (see Table 47.2 for our dose ranges for each muscle). Jaw closers include the medial pterygoid, masseter, and temporalis muscles, and symmetric contraction leads to pure closing dystonia or bruxism. Jaw openers include lateral pterygoid and digastric muscles. Symmetric contraction leads to jaw opening, protrusion, and TMJ subluxation with pain. Asymmetric contraction

of openers or closers leads to deviation (ipsilateral if medial pterygoid is involved, contralateral if lateral pterygoid is involved) in combination with opening or closing. Simultaneous or alternating movements of openers and closers may result in jaw tremor or alternating opening and closing. Lingual protrusion dystonia is caused by the genioglossus contraction, which can be symmetric or asymmetric.

Injection of jaw and tongue muscles requires EMG guidance. The pterygoid muscles are adjacent to each other as are the digastric and genioglossus. Precise localization is paramount for appropriate injection of these muscles in OMD. The injections are completed with the patient supine or in a reclining chair. The methodology utilized here is our approach. However, there are other possibilities utilized by some neurologists and otolaryngologists.

Method for lateral pterygoids (Fig. 47.1): This muscle has two heads. The origin of the superior head is the infratemporal surface and crest of the greater wing of the sphenoid bone. The origin of the inferior head is the lateral surface of the lateral pterygoid plate. The two portions merge, and the muscle narrows and stretches horizontally as it approaches the insertion which is ostensibly at the temporomandibular joint. Its action is to pull the head of the condyle out of the mandibular fossa along the articular eminence and swinging the jaw to open. The lateral pterygoid can be accessed with a needle placed below the zygomatic arch and through the masseter muscle and the mandibular notch. The depth of the notch varies in patients, so staying closer to the zygomatic arch is preferred. Patients may have to open the mouth a small amount for the needle to slip through. Point the needle slightly dorsal toward the tragus and have the patient hold the jaw open partially. As one approaches the muscle, you will hear the activation. We use the 1.4 inch EMG needle as the muscle is deep. We generally perform a single injection. Withdraw the plunger first to assure one is not in the internal maxillary artery.

Method for medial pterygoids (Fig. 47.2): This muscle also has two heads, but the major portion originates as the deep head from just above the medial surface of the lateral pterygoid plate. Its fibers then pass downward, lateral, and posterior and insert into the lower and back part of the medial surface of the ramus and angle of the mandible. It's function is to elevate the mandible (thereby closing the jaw). It also plays a role in protrusion of the jaw. Injection approach is at the angle of the jaw. Pointing the needle up and at a dorsal angle of about 30–40 degrees slip it under the mandible (use a finger to guide it). If the needle slips to the exterior of the mandible, the injection will end up in the masseter. Have the patient bite down. As the needle approaches the muscle, the activation will occur. The location of the muscle is close to the angle, so there is no need to go deep. If you do then you could end up passing the needle through it and missing the target. Again a single injection will suffice.

Method for genioglossus and digastric (Fig. 47.3): Genioglossus is a fan-shaped extrinsic muscle that represents a major portion of the body of the tongue. Its origin is the mental spine of the mandible, and its insertions are the hyoid bone and the base of the tongue. The actions are to protrude the tongue. It also stabilizes and enlarges the upper airway. The digastric muscle has two bellies, anterior and posterior, on the lateral aspect submandibular floor, superficial to the

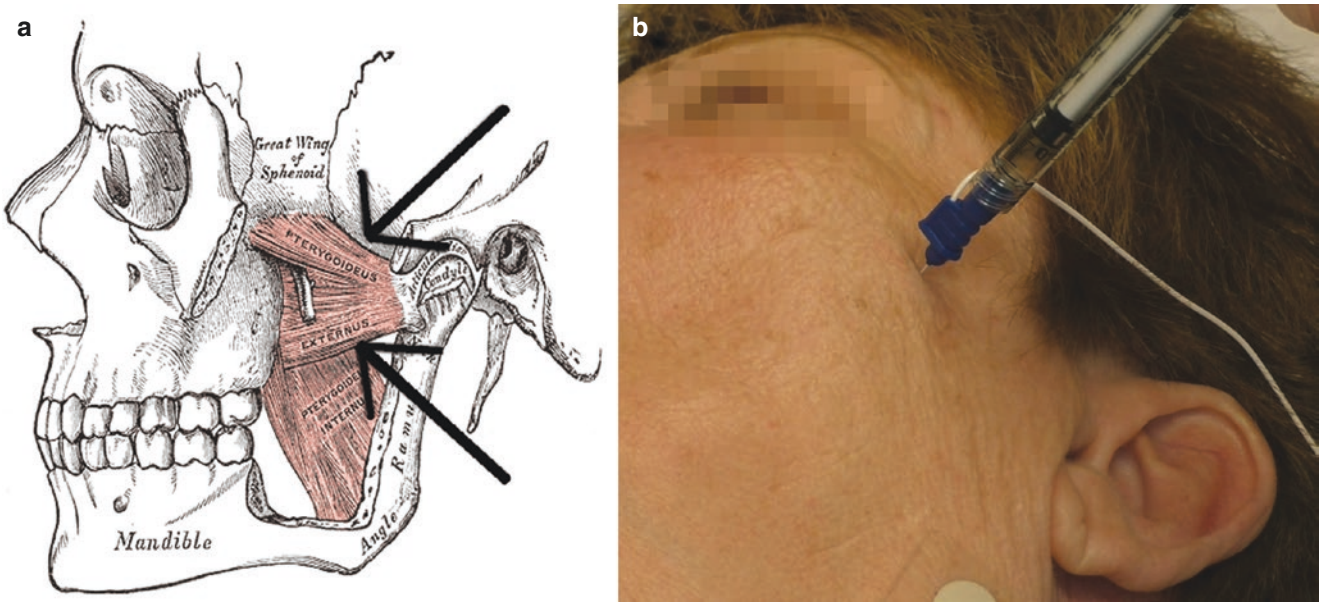

Fig. 47.1 (**a**) Shows anatomy of the lateral pterygoid muscle (see arrow). (**b**) Demonstrates needle placement for injection of the lateral pterygoid muscle. Note the location (inferior to zygomatic arch), angle (toward the tragus), and depth (this muscle requires deep injections – the needle is 1.4 inches)

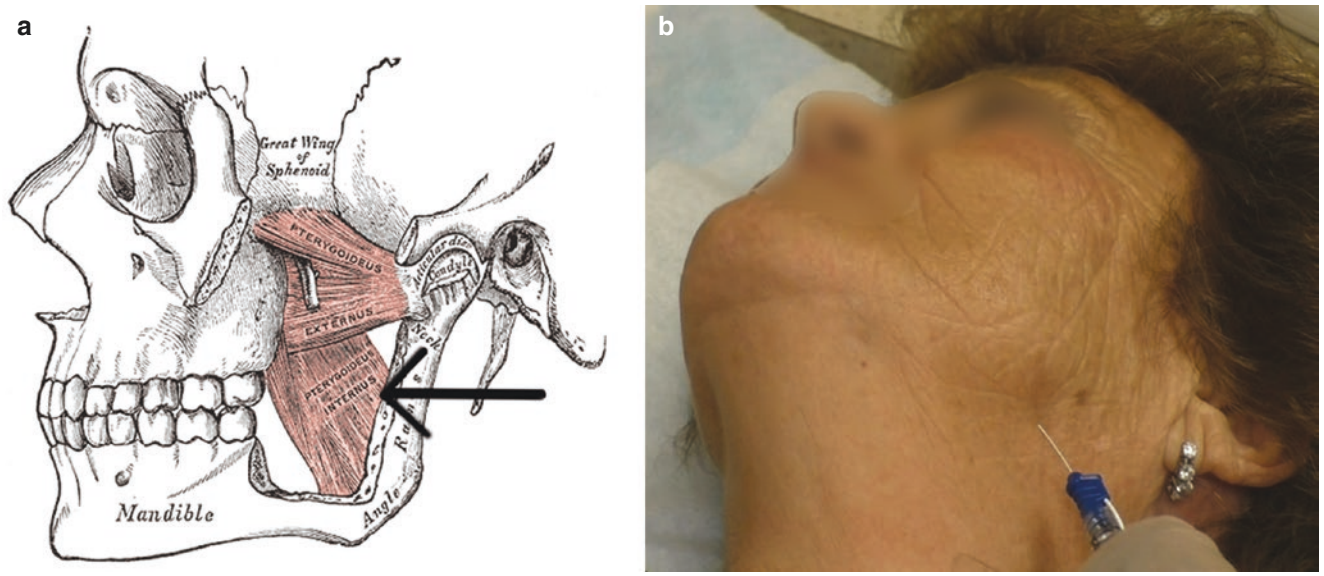

Fig. 47.2 (**a**) Shows anatomy of the medial pterygoid muscle (see arrow). (**b**) Demonstrates needle placement for injection of the medial pterygoid muscle. Note the location (at the angle of the mandible), angle (superior and anterior), and depth (this muscle requires superficial injections inside the mandible – the needle is 1.4 inches)

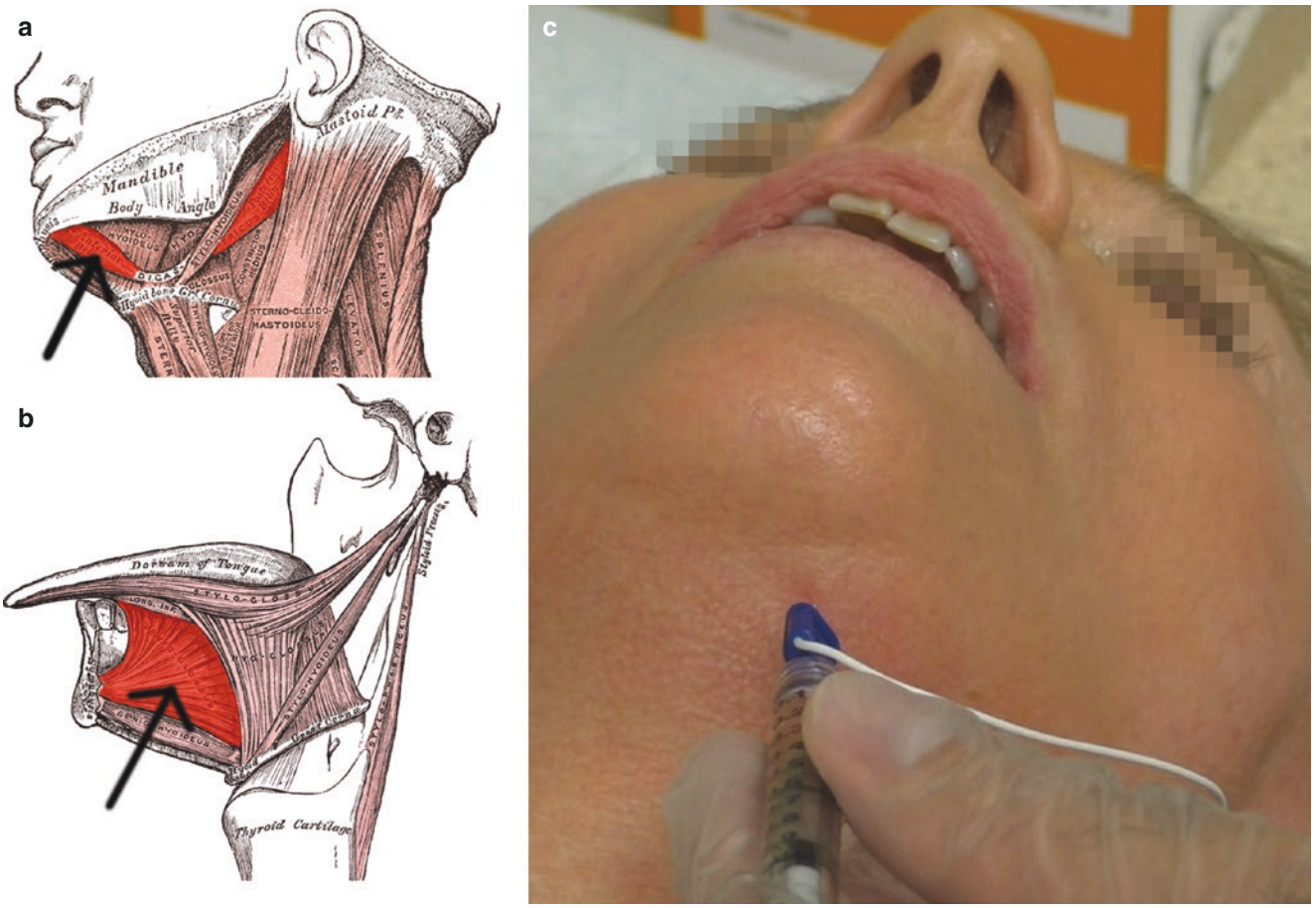

Fig. 47.3 (**a**) Shows anatomy of the digastric muscle. (**b**) Shows the anatomy of the genioglossus muscles. (**c**) Demonstrates needle placement for injection of genioglossus and digastric muscles. Placement is 1–2 fingers breathe dorsal from the mandible and 1–2 cm lateral. In this figure the needle is deeper in the genioglossus. The digastric is more superficial

genioglossus. The anterior belly arises from the digastric fossa of lower border of the mandible, close to the symphysis, and passes downward, lateral, and backward. It is the anterior belly that is targeted for OMD. It opens the jaw. Both have right and left muscles. Digastric and genioglossus muscles can be injected with a single-needle stick. The head tilted back. The placement of the needle is approximately two fingerbreadths back from the midline of the body of the mandible and 1–2 cm lateral. The needle is placed superficially at first within the digastric muscle which can be localized by EMG when the jaw is open. A single injection is sufficient. Then, advancing the needle deeper, it will pass through the mandibular floor, including the digastric muscle, and enter into the genioglossus muscle approximately 2 cm deep. Recruitment is discerned when the mouth is open (there should be no activity), and the tongue is protruded. Again a single injection will suffice.

Method for masseter and temporalis muscles: Although these muscles are superficial and palpable, it is recommended that EMG be used for injection. The masseter is a thick, somewhat quadrilateral muscle, consisting of two heads, superficial and deep. The larger superficial head arises via an aponeurosis from the maxillary process of the zygomatic bone and from the anterior two-thirds of the inferior border of the zygomatic arch. Its fibers pass inferior and posterior, to be inserted into the angle of the mandible and inferior half of the lateral surface of the ramus of the mandible. The smaller deep head originates from the posterior third of the lower border and from the whole of the medial surface of the zygomatic arch. Its fibers pass downward and forward, to be inserted into the upper half of the ramus. The deep head of the muscle is partially concealed, anteriorly, by the superficial masseter and posteriorly by the parotid gland. EMG is helpful because the muscle is covered by a substantial amount of soft tissue, and the target can be missed. The dose can be given as a single dose (this is what we do) or divided into multiple injections. The temporalis origin is on the skull, parietal bone, and superior temporal surface of the sphenoid bone. The insertion is on the coronoid process if the jaw which is on the ventral portion of the mandible. It serves to pull the mandible up and close the jaw. Injection with EMG can be spread to multiple sites closer to the origin.

When injecting the jaw and tongue, there is the potential for serious adverse effects. It is best to start low and work the dose up slowly. The initial dose depends on the severity of the movement. We always tell patients it may take several sessions to find the correct doses. The most serious adverse effect is dysphagia with tongue and medial pterygoid injections. This is usually mild and reversible but may last weeks. Injection of the lateral pterygoid can cause soft palate weakness with nasal regurgitation of fluids.

Once a stable dose is found, after 1–3 sessions, long-term responsiveness is expected with minor adjustments for side effects if necessary. The dose ranges per muscle we use are listed in Table 47.2. These are based on experience and may differ from some published ranges. The doses are for onabotulinumtoxinA only because we (and others) have the most experience with this formulation. Further study is needed for all toxin types. When a patient appears to be going into remission, it is reasonable to spread the time between injections and if no wearing off of the toxin is seen then holding the treatment as we did in this case. For patients who do not respond adequately or become resistant to the toxin, then deep brain stimulation may be considered. (Chap. 53).

Suggested Reading

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Treatment of Laryngeal Dystonia

48

Christy L. Ludlow

Case

A woman of 78 years was seen for voice testing and consideration for therapy on referral to a speech pathologist by an otolaryngologist. The otolaryngologist's referral reported that her laryngeal examination by laryngoscopy indicated no abnormalities. She was accompanied by her son who explained that the onset of her voice problem was gradual. He did most of the communicating for her as she would not go out of the house or answer the phone because of her speech difficulties.

When the patient tried to speak, it took her several seconds to start voicing with a great deal of effort. Her voice was rough and strangled in quality, and she was only able to utter a few syllables at a time before giving up her speaking attempts. Whenever the speech pathologist asked her a question, she turned toward her son for him to answer. She seemed depressed and blinked her eyes whenever she tried to speak, but no eye blinking was noted at rest indicating movement "overflow" while speaking. Her intelligibility was significantly reduced because of her voice disorder.

On nasoendoscopy, no abnormal movements were noted during quiet respiration. On each attempt to phonate, tight closure of the ventricular (false) vocal folds completely obscured the true vocal folds so that closure and vibration of the vocal folds for voice could not be observed. Evaluation of her voice function showed a high laryngeal resistance on aerodynamic testing, reduced maximum phonation time to only 1–2 s, and reduced pitch and loudness range. No measures of voice stability (jitter and shimmer and fundamental frequency) could be analyzed because of aperiodicity of vocal fold vibration. Although she could clear her throat, she could not extend phonation beyond 1 or 2 s. Throat palpation indicated a high tense laryngeal position before attempting voice for speech. The patient could whisper with instruction.

A trial of voice therapy to reduce symptoms of muscular tension dysphonia was recommended. Therapy consisted of laryngeal massage to lower and relax the laryngeal position prior to and during voice, using chewing with humming to produce a more relaxed phonation and learning to slowly exhale while initiating voicing. After three sessions, her tension was reduced, and she was better able to phonate. At that time intermittent voice breaks became evident on vowels in words, similar to adductor spasmodic dysphonia, suggesting that she had symptoms of both muscular tension dysphonia and adductor spasmodic dysphonia. It was explained to her that she may have adductor spasmodic dysphonia, and information was shared with her and her son about the disorder. She was referred back to the otolaryngologist for bilateral injections of botulinum toxin type A (BOTOX) into the thyroarytenoid muscle. She was injected with two units of botulinum toxin type A (BOTOX) into each thyroarytenoid muscle using EMG guidance. On follow-up with her son 24 h later, no problems were reported. The son called back 5 days later to say that his mother was doing much better and was able to talk with friends and family both on the phone and face to face. The son thought she sounded like her old voice, and both he and his mother considered the treatment a success.

Her son then called 2 months later to say that the benefit was wearing off. She was scheduled for another botulinum toxin type A (BOTOX) injection. A similar injection was administered, but she had limited benefit following the second injection with symptoms of both adductor spasmodic dysphonia and muscular tension dysphonia clearly still evident. A third session of injection was scheduled under anesthesia with visual confirmation to assure that the injections were placed in each of the vocal folds. Although she had some breathiness for a few days after the injections, she did not have a significant benefit. A voice reevaluation showed

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continued voice breaks on vowels with muscular tension on voicing and some spasmodic activity in the supraglottal musculature affecting the ventricular folds and pharynx on nasoendoscopy. Her eye blinking occurred in association with attempts to phonate, although no blinking was noted at rest indicating that it was not blepharospasm.

A referral to a neurologist for consideration of Meige syndrome was suggested as the patient likely had involvement of pharyngeal muscles, and pharmacologic management might be considered. The patient continued to have limited benefits from additional botulinum toxin type A (BOTOX) injections over the next 6 months and refused speech therapy.

Discussion

Laryngeal dystonia includes a group of idiopathic laryngeal motor control disorders including adductor breathing dystonia, adductor spasmodic dysphonia [ADSD], and abductor spasmodic dysphonia [ABSD]. These disorders are identified by the exclusion of other laryngeal disorders, the characteristics of the voice during speech or breathing, and vocal fold movement abnormalities observed on nasoendoscopy during breathing and speech.

Adductor breathing dystonia (ABD) is a very rare disorder where the vocal folds are adducted on inspiration causing stridor. This disorder appears as long as the patient is awake, disappearing in sleep, and usually appears in middle age. Sometimes the symptoms are reduced when the patient is placed in a partly supine position. Low-dose bilateral injections of botulinum toxin type A (BOTOX) into the thyroarytenoid muscle in the body of the vocal folds (2 units each side) can reduce inspiratory adduction and stridor although it can also weaken the voice. ABD is a form of dystonia and must be distinguished from paradoxical vocal fold movement disorder (PVFMD). PVFMD is episodic with stridor and shortness of breath due to adduction of the vocal folds on inspiration often resulting in emergency room visits but without a drop in O_2 saturation readings. This is a more common disorder in young adolescents and adults, often exercise induced, and exacerbated by anxiety and can be treated by speech pathologists teaching the patient to use sniffing and controlled prolonged exhalation along with education and lifestyle management to control the episodes.

Identification of patients with spasmodic dysphonia first requires excluding other laryngeal disorders such as laryngeal paresis or paralysis, laryngitis, or lesions such as nodules, polyps, or carcinoma by an otolaryngologist using nasoendoscopy or laryngoscopy to view the larynx. Voice symptoms of ADSD are patient complaints of vocal effort, strained voice quality, and intermittent voice breaks on vowels in sentences. Most patients have some reduction of voice breaks on shouting, singing, and laughter and are without voice breaks on whispering. Although intermittent hyperadduction spasms of the vocal folds during vowels in speech can be observed on nasoendoscopy, this is not required for diagnosis as symptoms sometimes are reduced during examination by nasoendoscopy. It may be that the presence of a nasoendoscope in the hypopharynx and laryngeal vestibule can serve as a "sensory trick" that sometimes reduces dystonia. Symptoms are less manifest during prolonged phonation of vowels and are most evident on connected speech loaded with glottal stops and vowels. Having the patient repeat sentences such as, "We eat eels every evening," "Are the olives large," and "Tom wants to be in the army" and listening to the sounds that are underlined for voice breaks is useful for identifying symptoms. The severity of symptoms can vary greatly; some patients may only complain of speaking effort, have no evident strain, and have a small catch on a vowel once in three sentences and no symptoms on prolonged vowels, shouting or singing. On the other hand, the more severely affected patients, similar to the one reported here, have great difficulty initiating voice and problems in shouting and singing although crying, laughing, and throat clearing may be less affected. The range in severity makes diagnosis difficult, and many patients can see several physicians before being diagnosed.

Abductor spasmodic dysphonia (ABSD) is very rare, affecting about 10% of patients with spasmodic dysphonia. Voice symptoms are prolonged breathy breaks on voiceless consonants including "p" as in "pet," "t" as in "time," "k" as in "camp," "s" as in "sea," "f" as in "fan," "h" as in "help," and "th" as in "theme." Some patients can occasionally have asymmetry of vocal fold movement during speech, but nonspeech tasks such as whistling show normal, symmetric vocal fold movement. The breathy breaks make the patient's voice sound somewhat breathy in quality, but a prolonged vowel is usually normal without breaks, and the symptoms are most evident during sentence production. These patients also complain of a great deal of effort during voice production. As in ADSD, symptoms are not always evident on nasoendoscopy but are intermittent on words containing voiceless consonants showing prolonged opening of the vocal folds during voiceless consonants before closing for vowels. Having the patient repeat sentences loaded with voiceless consonants such as "He had half a head of hair," "The puppy bit the tape," and "She speaks pleasingly" and listening for breathy voice breaks on the sounds underlined can be helpful.

There are no diagnostic tests for the laryngeal dystonia. Identification difficulties are due to the common association of ADSD with other types of voice disorders such as muscular tension dysphonia and voice tremor. At least a third of patients with ADSD also have voice tremor which can alter

the degree of benefit from botulinum toxin type A (BOTOX) injection. Voice tremor is most easily identified on prolonged vowels with regular modulations in voice pitch and loudness at around 4 to 5 Hz. Severe voice tremor can also produce voice breaks on prolonged vowels or on vowels in speech when the vocal folds hyper-adduct during voice, breaking the voice. As speech usually contains about four to five syllables per second with one vowel per syllable, voice tremor can induce breaks on vowels similar to ADSD in speech. Asking the patient to produce a prolonged vowel for at least 10 s is needed to determine if voice tremor is also present. It is important to determine if patients have both voice tremor and ADSD as these patients do not usually show the same degree of benefit from botulinum toxin type A (BOTOX) injections as reliably as patients with ADSD. Further, the majority of patients with essential voice tremor alone are usually not benefitted by botulinum toxin type A (BOTOX) injections.

Muscular tension dysphonia (MTD) is considered a disorder of voice function where patients have developed increased tension in their larynx; it is not a form of dystonia. Some are thought to develop as a result of compensation for vocal fold paralysis, but even after the paralysis resolves, the patient continues to use compensatory effort. Others are thought to follow sensory irritation of laryngeal tissues, laryngitis, and a period of stress or are idiopathic. Symptoms often resolve with voice therapy aimed at teaching the patient to reduce laryngeal tension. Laryngeal massage and retraining voice production can be beneficial after a few therapy sessions in many cases, although some are treated one time by botulinum toxin type A (BOTOX) along with voice therapy. Differentiation between ADSD and MTD is highly controversial and has been a major difficulty to effective management of these patients.

As shown in Fig. 48.1, the relative numbers of patients with each disorder differs, and they can co-occur. Furthermore, some symptoms are similar across these disorders. Distinguishing them usually requires voice recordings on different tasks as well as nasolaryngoscopy (Table 48.1).

Various treatments are effective to different degrees in these disorders (Table 48.1). Close to 90% of patients with ADSD report benefit from small amounts of botulinum toxin type A (BOTOX) injection into the thyroarytenoid and lateral cricoarytenoid muscles bilaterally. The degree of benefit is inconsistent both between patients and within patients from one injection to another. Often patients report the best benefit follows the first injection, and subsequent injections can show less consistent effects. Otolaryngologists experience in doing percutaneous injections with EMG guidance is important for success, although other otolaryngologists are successful using per oral approaches to inject the vocal folds under visual guidance. Either technique can be successful in experienced hands, although variation in the most effective

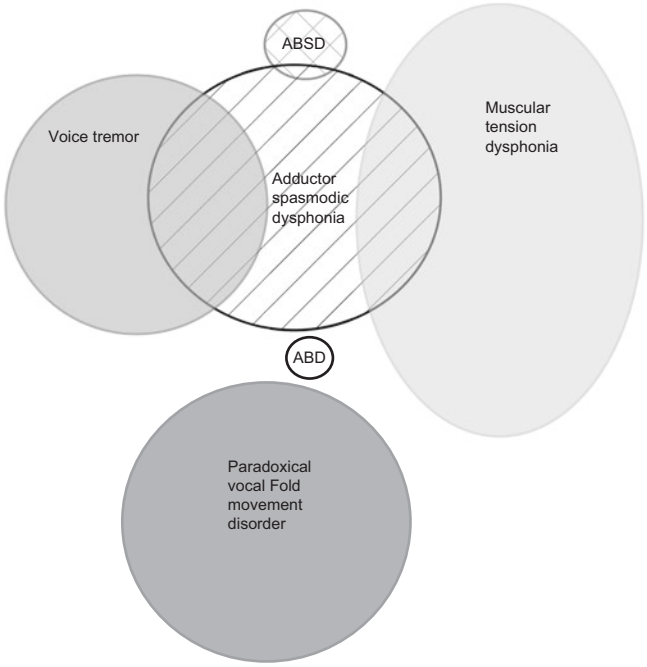

Fig. 48.1 A schematic diagram showing the relative numbers of patients with each of the laryngeal dystonias and related disorders. The laryngeal dystonias are shown on the left side of the schematic, and functional disorders such as muscular tension dysphonia and paradoxical vocal fold movement disorder are more to the right of the diagram. Disorders that can co-occur are shown overlapping to the same degree that they co-occur. ABD is adductor breathing dystonia; ABSD is abductor spasmodic dysphonia

dosage between patients is common with both techniques. Voice clinics at large medical centers usually see greater numbers of patients for botulinum toxin type A (BOTOX), and training in EMG and BOTOX injection are provided during laryngology fellowship training.

Some patients benefit from very small reinjections given at 2-month intervals such as 0.75 units in each thyroarytenoid muscle which maintains the patient's voice symptom-free. Effective injections of botulinum toxin type A (BOTOX) do not need to produce paresis or paralysis of a vocal fold to be effective; in fact, in most cases the best benefit is when a small injection reduces spasm but does not impair vocal fold movement during opening and closing the vocal folds. Other patients may require increasing dosages over time even though they have no evidence of antibodies to botulinum toxin type A (BOTOX). Some require bilateral injections as high as 3–5 units on each side. During repeated injections, a patient's symptoms may become less responsive, and changing from bilateral small dosages to larger unilateral injections of the thyroarytenoid muscles in the vocal folds of around 5–10 units can have benefit. The most effective dosage for a patient usually is worked out over two or three treatments.

Table 48.1 Symptoms and treatments for forms of laryngeal dystonia

Disorder	Speech or breathing symptoms	Laryngeal movement abnormalities	Frequency and other disorders to rule out	Treatment
Adductor breathing dystonia	Stridor on inhalation Airway hunger Symptoms reduced during voice and speech No abnormalities on expiration or during sleep	Both vocal folds move to the center of the larynx during inspiration causing intermittent stridor and airway obstruction	Very rare, onset in middle age. Must differentiate from paradoxical vocal fold movement disorder which is episodic, usually exercise induced in young adults and adolescents	Bilateral injections of 2 units of botulinum toxin type A (BOTOX) into the thyroarytenoid and lateral cricoarytenoid muscles
Adductor spasmodic dysphonia	Effortful strained speech with voice breaks during vowels in words in connected speech symptoms are reduced on shouting, crying, and laughter and absent during whisper	Intermittent vocal fold hyper-adduction during vowels in words producing voice offset perceived as breaks Normal vocal fold range of motion for whistling, sniff, and breathing	Differentiate from essential tremor affecting pharyngeal, laryngeal, and head movements at rest and during prolonged vowels. Differentiate from muscular tension dysphonia with effortful strained voice that affects all sounds without breaks in vowels with symptoms the same on prolonged vowels, speech, and shouting and absent during whisper	Either bilateral injections with botulinum toxin type A (BOTOX) of 2 units into the thyroarytenoid and lateral cricoarytenoid muscles or unilateral injections of botulinum toxin type A (BOTOX) of 5–10 units into the thyroarytenoid and lateral cricoarytenoid on one side
Abductor spasmodic dysphonia	Intermittent prolonged breathy breaks during voiceless consonants p, t, k, f, h, s, and th	Intermittent vocal fold hyper-adduction during voiceless consonants interfering with the onset of vowels in speech. May have some asymmetry of vocal fold movements during speech, but normal vocal fold range of motion for whistling, sniff,and breathing	Differentiate from functional dysphonia which is constantly whispered or breathy on all speech. Differentiate from vocal fold paresis or paralysis	Injection of the posterior cricoarytenoid muscle on one side with 3–5 units of botulinum toxin type A (BOTOX). See the patient on a return visit 2 weeks later to determine the degree of airway opening before injecting the opposite side with 3–5 units of botulinum toxin type A (BOTOX)

Selective laryngeal adductor denervation is an effective long-term surgical approach to controlling ADSD. The surgery involves denervating the branch of the recurrent laryngeal nerve to the thyroarytenoid muscle on each side and then reinnervating the thyroarytenoid muscle with branches from the ansa cervicalis bilaterally. Once the muscle becomes reinnervated, it rarely produces spasmodic activity. Reinnervation can take 6–9 months, and until then, the patient may have a breathy voice and aspirate liquids during swallowing. However, once the thyroarytenoid muscle becomes reinnervated, the voice becomes stronger without breaks. Follow-up in such patients shows a long-term benefit over 4 years. The key to success is accurate identification of patients with symptoms of only ADSD. This treatment is not helpful in patients with voice tremor in addition to ADSD and is not appropriate for ABSD.

For treatment of patients with ABSD, botulinum toxin type A (BOTOX) injections are placed in the posterior cricoarytenoid muscle, the only muscle that opens the vocal folds. Care must be taken not to denervate the posterior cricoarytenoid bilaterally reducing the airway opening causing a need for a tracheotomy. To prevent this, most otolaryngologists inject the posterior cricoarytenoid muscle on one side and have the patient return 2 weeks later to assess the airway opening before providing a small injection to the opposite side if needed. In some patients the cricothyroid muscle may also be involved and may need to be injected. In general, only about 50% of patients with abductor spasmodic dysphonia show a benefit from botulinum toxin type A (BOTOX) injections.

For patients with voice tremor alone, botulinum toxin type A (BOTOX) injections are successful in about a third of patients. Overall benefit depends upon whether or not the tremor is limited to the vocal folds during speech. If the pharyngeal musculature or head tremor is involved, treatment of the vocal folds is not helpful. Some patients evidence vocal fold tremor at rest during both inspiration and expiration and are also difficult to benefit. Those patients with vocal fold tremor only on exhalation and voice seem to have a better response to botulinum toxin type A (BOTOX) injection. Medications used for essential tremor of the limbs, including primidone and propranolol, are usually not effective for voice tremor.

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Treatment of Dystonic Writers' Cramp

49

Victor S. C. Fung

Case History

A 35-year-old right-handed dentist presents with a 1–2 year history of progressive difficulty with writing.

He has noticed that his writing has become increasingly laboured and stilted, to the point that it has become difficult even to write his name. With prolonged writing, he experiences discomfort or mild pain over the dorsum of the hand as well as extensor aspect of the forearm. To make writing easier, he has been forced to alter his pen grip by using his index and third finger to press it against his palm, removing the tip of the thumb from the pen, as it tends to "roll," by which he meant it tends to slip off. He had not noticed any involuntary movements or posturing when writing except for involuntary flexion of the thumb, present only for the past 2 weeks, during which time he has been taking levodopa/benserazide 100/25 twice daily as a therapeutic trial. On questioning, he reports being worse at the end of the day, but even in the early part of the day, he can write no more than a sentence or two before his writing becomes difficult. He is still able to type and perform work procedures normally with his right hand, and aside from writing, no other activity been affected. He has been a prolific writer all his life, with rewriting his notes having been his preferred mode of study, and he had always taken pleasure in writing, including collecting and writing with fountain pens. He initially saw an osteopath who diagnosed tennis elbow and subsequently a physiotherapist who diagnosed dystonia. He reported that he has been psychologically devastated and extremely distressed by his symptoms and disability which have eroded his confidence to the point that he does not like going to work. He was the product of a normal pregnancy and delivery, had normal developmental milestones and is otherwise well. There is no family history of neurological disorder.

On examination, when asked to write with a normal pen grip, he can do so quite neatly but develops progressive involuntary flexion of the interphalangeal more so than metacarpophalangeal joint of the thumb, so that his thumb tip eventually slips off the pen. There is a slight tendency for the index finger to extend. He occasionally interrupts his writing unnaturally in the middle of a word by lifting the pen off the paper. With prolonged writing with the left hand while being asked to rest his right hand on the table, he develops mirror dystonia with flexion of the right thumb more than index finger extension, but he does not develop posturing when writing with the pen held perpendicularly between the extended fingers of his right hand (Video 1). The remainder of his neurological examination is normal. Specifically, there is no tremor when writing, abnormal posturing with the arms outstretched, akinesia or impairment of fractionated finger movements. There are no Kayser-Fleischer rings.

MRI brain is normal. Blood tests including thyroid function, serum copper and caeruloplasmin are normal.

Discussion

Writers' cramp is a term used as a synonym for a task-specific dystonia that affects writing. It can occur as a focal dystonia but also as part of segmental, multifocal or generalised dystonia. When manifesting as focal isolated dystonia, only writing is affected in about 50% of cases, whereas in the remainder, other tasks or actions are also impaired. The dystonic muscle activity can arise predominantly from a few selected muscles, in which case writing will produce distinctive abnormal posturing, for example, excessive flexion of the thumb as in the patient described in this chapter or, as another example, extension of digit 2 causing it to lift off the pen. The abnormal postures that develop during writing are

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stereotyped in a particular individual but will vary between individuals. Sometimes the dystonia will affect multiple forearm muscles in which case progressive painful co-contraction during writing can be observed or palpated but without obvious abnormal posturing. As with all forms of dystonia, writers' cramp can be associated with or even dominated by tremor. Patients may have a sensory trick such as touching or holding the writing with the non-writing hand to reduce the dystonic cramping or tremor.

Patients with writers' cramp usually complain of difficulty with writing, including signatures or filling out forms. Pain or tightness in the forearm, wrist or, less commonly, hand is common due to the progressive dystonic muscle spasm but only when writing and not at rest. Typically, symptoms begin within writing the first few sentences (i.e. within minutes of starting to write) rather than only after prolonged writing (e.g. half an hour into an examination), and the patient cannot write without taking frequent rests. In about 50% of cases, the patient may also complain of difficulty with other tasks such as stirring with a spoon, using a screwdriver or using a key. There may be the complaint of tremor. Tremor or abnormal postures at rest can occur but are very uncommon, except in the setting of degenerative or lesional dystonia. Resting symptoms such as pain, paraesthesia or numbness should not occur and raise the suspicion of an alternative or coexistent diagnosis, e.g. peripheral nerve entrapment. Similarly, writers' cramp does not cause weakness. Occasionally, patients present with the symptom of upper limb pain or discomfort without volunteering that it is limited to writing or specific tasks, and this aspect of the history needs to be elicited by the physician.

The patient needs to be examined during writing, as this may be the only activity which produces an abnormality. During normal writing there is semi-rhythmic contraction and relaxation of groups of forearm muscles corresponding to the production of pen strokes followed by relaxation before the next stroke is produced. In patients with writers' cramp, observe or palpate for sustained or tonic contraction of forearm muscles during writing. It is useful to ask the patient to write a standard sentence such as "The quick brown fox jumps over the lazy dog" four or five times. It may be useful to time how long it takes for later comparison.

Many patients can be observed to develop stereotyped abnormal posturing of the wrist or specific fingers during sustained writing which may lead to difficulty keeping the pen on the page or fingers on the shaft of the pen, e.g. flexion of the interphalangeal joint of digit 1 causing the tip of the thumb to slide up the shaft or slip of the pen, extension of digit 2 causing the index finger to lift off the pen and ulnar deviation of the wrist causing the patient to pause and lift the pen off the page during writing to avoid dragging the nib across or putting excessive pressure on the page. Sometimes more proximal joints such as the elbow or shoulder can be involved, e.g. the elbow developing progressive extension during writing.

As with examination of all forms of dystonia, it is important to keep in mind whether the abnormal posturing observed is primary (being produced by the abnormal dystonic muscle contraction) or compensatory (in the case of writers' cramp, to allow the patient to keep the pen on the page or grip on the pen). For example, dystonic posturing of the interphalangeal joint of the thumb might lead to compensatory forceful flexion of the metacarpophalangeal joint to keep the thumb against the pen, or dystonic elbow extension might lead to compensatory shoulder elevation to allow the wrist and hand to be held in a more natural position during writing.

There are a couple of examination tricks which can be used to try to distinguish dystonic from compensatory abnormal posturing. One is to look for mirror dystonia in the writing hand when the patient attempts to write with their opposite hand. The patient is asked to rest the hypothenar eminence of the writing hand on the desk in the mid-supination/pronation position or to rest the forearm on an elevated object such as a tissue box and let the dangling hand and fingers stay relaxed. In around 50% of patients, during writing with the opposite hand, abnormal dystonic postures and/or movements will develop in the resting hand which reflect the primary dystonic contractions rather than compensatory manoeuvres. A second trick is to ask the patient to hold the pen perpendicularly and loosely between the proximal phalanges of digits 2 and 3 and to attempt to write and observe for dystonic movements and postures.

The patient should then be asked to draw Archimedes spirals clockwise and anticlockwise and also hold the pen in the writing position on the page or with the tip of the nib just above a dot, to see if abnormal postures and movements develop during these tasks as well. A complete neurological examination should of course be performed to exclude evidence of impairments in other neurological systems, focusing especially on the presence of tremor, akinesia, ataxia, pyramidal or signs of peripheral nerve dysfunction in the writing hand.

It is uncommon for a patient to present with the isolated complaint of difficulty with writing other than in writers' cramp. Some differential diagnoses that should be considered are listed in Table 49.1.

Adult-onset, focal isolated dystonia manifesting as writers' cramp is idiopathic in the vast majority of cases, and the yield from investigations is very low. As a general rule, all patients under the age of 50 presenting with dystonia should have screening with serum copper and caeruloplasmin to help exclude Wilson's disease. Cerebral imaging including iron-sensitive sequences should be considered to exclude the remote possibility of underlying structural pathology as the cause and to exclude unexpected basal ganglia or cerebellar abnormalities which would trigger further investigation. For

Table 49.1 Differential diagnosis of writers' cramp

Diagnosis	Comment
Neurological	
Primary writing tremor	Tremor may be isolated to writing or may have associated milder postural tremor
Essential tremor	Associated postural and/or intention tremor should be present
Apraxia	Will almost always have other symptoms or signs related to disease causing the apraxia
Parkinsonism	Complaint usually of micrographia rather than inability to write should have other signs of parkinsonism
Cerebellar ataxia	Complaint usually of messy writing should have other signs of ataxia
Weakness of intrinsic hand muscles	Look for wasting and weakness
Sensory loss in hands	Rare without other symptoms but can occur with sensory ganglionopathy or central cord pathology
Entrapment neuropathy	Rarely presents with writing difficulty, e.g. thoracic outlet syndrome, or entrapment neuropathy may be coexistent, e.g. carpal tunnel syndrome
Musculoskeletal	
Tendonitis/ enthesitis	Pain and tenderness usually localises over affected tendons or provoked by contracting against resistance

patients who have writers' cramp as part of a generalised or combined dystonia, investigations should be as indicated by the other clinical features. Writers' cramp has rarely been reported as the presenting feature in a number of diseases, including dopa-responsive dystonia, monogenic dystonia and spinocerebellar ataxia.

The treatment of choice for dystonic writer's cramp is botulinum toxin injections administered under electromyographic guidance. Results from several small but well-conducted clinical trials support a Level B recommendation (moderate evidence for efficacy). Approximately two thirds to three quarters of patients will experience some benefit, but three quarters will experience hand weakness as a side effect. Taking both into account, approximately one half of patients will derive sufficient net benefit to elect to continue long-term treatment. This response is less than in other forms of focal dystonia such as cervical dystonia or blepharospasm but still a significant proportion. With ongoing treatment, responders will often be able to extend the injection intervals to 5–6 months or even more, whereas it is uncommon for the injection interval to be able to be extended beyond 4 months in cervical or cranial dystonia.

Muscle selection is based on clinical observation of the dystonic postures that develop during writing and anatomical knowledge of the muscles likely to be producing those postures. The wrist and finger extensors usually respond to approximately half the effective dose in the flexors and are more likely to develop symptomatic weakness if higher doses are used (personal observations). Effective doses in muscles will vary between patients, and the absolute dose per muscle in mouse units will also depend upon the preparation of botulinum toxin being used (e.g. onabotulinum toxin versus abobotulinum toxin). Patients should be warned that it may take several injection trials before the optimal muscles and doses can be determined. During this phase, it is essential to examine patients mid-cycle to assess the degree to which targeted muscles have been successfully weakened, the change in dystonic postures postinjection and whether there has been spread of toxin to uninjected muscles in order to plan how to modify subsequent injections.

As with other focal dystonias, the response to oral medications in writers' cramp is in general disappointing, although no randomised controlled trials have been reported. It is my practice to have all patients with writer's cramp undergo a trial of levodopa (300–600 mg daily in 3 divided doses) for at least a month as rarely writers' cramp can be the presenting feature of dopa-responsive dystonia secondary to heterozygous GTP cyclohydrolase 1 mutations. Additional oral medications that can be tried are as for other forms of dystonia. Dystonic movements or tremor occurring as part of the dystonia are more likely to respond than sustained dystonic contractions (personal observations).

There are a small number of studies reporting short-term benefit in writers' cramp following motor and sensory retraining. In the case of motor retraining, performance of non-specific hand and finger movements via manipulation of therapeutic putty was as effective as specific writing and drawing exercises. Sensory retraining involved learning and practising Braille. The clinical trials all required 30–60 min of practice daily, and long-term outcomes are unknown.

In refractory cases when handicap is significant, functional neurosurgery with lesioning or deep brain stimulation of thalamic targets has been reported as beneficial.

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Treatment of Musicians' Dystonia

50

Steven J. Frucht

Case Report

A 44-year-old professional percussionist was referred for evaluation of difficulty playing the Indian tabla drum. Having trained as a classical percussionist using drumsticks and mallets, he began studying Indian tabla 20 years prior as a hobby. The Indian tabla is a set of two drums of unequal size, played in the seated position using only the hands and fingers. Two years prior to evaluation, he spent a summer in India playing tabla 8–10 h per day. Soon thereafter he became aware of difficulty with his right index finger, limited only to the task of playing tabla. He noticed a lack of control of the finger and then became aware that it would curl as soon as he began to play. On his own he discovered that placing his right index finger next to his thumb eliminated the tendency of his index finger to flex. He also obtained benefit from taping the right index finger or putting it in a splint. Examination (Video 1) revealed exquisite task-specific flexion of the index finger when playing, with a prominent sensory trick. After discussion of possible treatment options, he decided not to begin treatment, as he preferred to try and accommodate around the problem.

Five years later he returned for follow-up. In the intervening period, tabla dystonia had worsened to the point that he could no longer effectively play the instrument. Dystonia remained specifically limited to the tabla with no dystonia using mallets or during any other tasks or positions. He no longer obtained benefit from his prior sensory trick. Examination (Video 2) revealed marked progressive curling of the right index finger to the extent that effective playing was impossible. He enrolled in a clinical trial of incobotulinum toxin type A, using a novel trial design that allowed for an initial injection and booster injections at 2 and 4 weeks. Dr. David Simpson performed the injections using a combination of high-resolution ultrasound and electrical stimulation (e-stim) to ensure exact targeting. 7.5 units of incobotulinum toxin type A was injected into the flexor digitorum superficialis (FDS) of digit II, and 5 units of incobotulinum toxin type A was injected into the flexor digitorum profundus of digit II. A noticeable improvement in dystonia was seen at his follow-up visit 2 weeks later (Video 3) at which time a booster injection was performed with 5 units to FDS of digit II. At follow-up 2 weeks later, dystonia was further improved (Video 4), and a small booster injection was administered (2.5 units to FDS of digit II). Follow-up 2 weeks later (6 weeks after initial visit, Video 5) revealed dystonia had resolved. He was able to play with complete freedom and facility and viewed this result as miraculous. He will be followed until his dystonia returns, and a similar injection strategy will be employed. (Fig. 50.1).

Discussion

Musicians' dystonia is an unusual and fascinating example of a focal task-specific dystonia. In 1830, Sir Charles Bell first described focal task-specific dystonia triggered by writing, later called "scrivener's palsy." Hammond, Duchene, and Gowers later described musicians with task-specific dystonia. German neurologists coined the term "geigenneuroses" or occupational neuroses in the early twentieth century to refer to this condition, implying a psychological cause. Not until David Marsden's seminal observations in the 1970s did focal task-specific dystonia become established as an organic central neurologic disorder.

Musicians' dystonia affects men out of proportion to women (4:1), with a typical symptom onset in the late 1930s. Professionals and amateurs may be affected, and while virtually every instrument has been described, certain instruments

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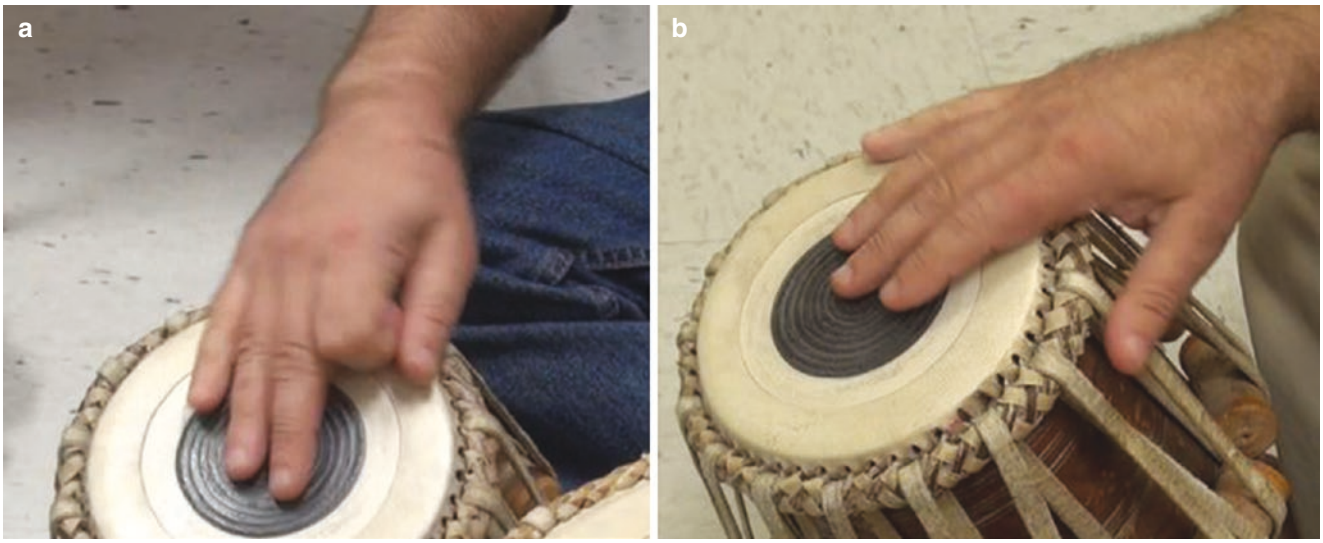

Fig. 50.1 (**a**) A still photo from a video taken at his second visit to the clinic (when botulinum toxin was first administered). The right index finger is flexed at the distal and proximal interphalangeal joints as he plays the Indian tabla; (**b**) a still photo from a video taken on his visit to the clinic 6 weeks later, showing complete resolution of index finger dystonia

such as piano, violin, and guitar are more commonly implicated. The hand that bears the greater technical burden (right hand in pianists and guitarists, left hand in violinists) is usually affected. Dystonia may affect one finger, as in our patient, several fingers, or may be complex affecting the wrist, forearm, or shoulder girdle. Once present symptoms rarely remit even with prolonged rest. Dystonia may spread to involve other tasks or even involve the other hand although this is uncommon.

The evaluation of the musician who presents to the neurologist begins with a careful history and examination. A thorough history is indispensable in distinguishing dystonia from conditions such as overuse syndrome, entrapment neuropathy of the ulnar or median nerve, or cervical radiculopathy that are common in injured musicians. Musicians' dystonia is always painless, usually begins as a sensation of loss of automaticity and typically progresses over weeks to months. Isolated techniques such as scales or arpeggios may be affected initially, with gradual spread over time to involve other skills. Dystonia may fluctuate in severity, but remissions or spontaneous improvements are rare. Time away from the instrument typically does not help, and dystonia returns the moment playing resumes.

A complete neurologic examination should be performed with specific attention to rule out pain on palpation of muscles (suggesting focal tendinitis), atrophy, or focal weakness. A diagnosis of musicians' dystonia *cannot* be made without observing the patient play. Patients should be asked to demonstrate particular passages that bring out dystonic movements. When more than one finger is involved, special care should be paid to try and determine if one finger is the trigger for dystonia. Most important, primary dystonic movements must be distinguished from movements that patients make unconsciously as they attempt to compensate for dystonia. This distinction between primary and compensatory movements is critical for selection of muscles for injection of botulinum toxin, as inadvertent injection of compensatory muscles will worsen functional performance without addressing the underlying dystonia (Table 50.1).

Table 50.1 Clues to the diagnosis of musicians' dystonia

Features consistent with the diagnosis	Red flags that suggest an alternate diagnosis
Insidious onset over weeks to months	Prominent pain
Initial feeling of loss of automaticity	Prominent numbness or paresthesia
Specific techniques or passages involved	Evidence of weakness
One finger or several adjacent fingers involved	Symptoms improve with rest
Rest does not help	Fluctuating symptom course
Symptoms and signs present from the moment of playing Sensory trick	Signs present on exam only after extended play

Available treatment options for musicians' dystonia include oral medications (e.g., anticholinergics), rehabilitative approaches such as constraint-induced movement therapy, injections of botulinum toxin, and stereotactic surgery. The decision whether to treat and with which modality should be individualized, taking into account the practical circumstances facing the performing artist. Musicians by definition earn their livelihood with their hands. Most are loath to admit injury for fear that they will miss work or be labeled as disabled. By the time they are seen in the office,

most musicians have already pursued mechanical modifications and retraining/practice approaches, etc. Stereotactic surgery is an invasive approach and has been applied to this patient population by only one surgeon in Japan. The mainstay of treatment for musicians with upper limb dystonia remains injections of botulinum toxin by a neurologist with experience treating musicians.

In clinical practice, patients with other forms of focal dystonia (spasmodic torticollis, blepharospasm, spasmodic dysphonia, writer's cramp) receive injections at 3-month intervals. This interval reflects the early experience injecting patients with preparations of botulinum toxin that had high levels of contaminating proteins, leading to neutralizing antibodies and diminishing clinical responsiveness. We designed our current approach to address specific challenges that musicians face. A 70% improvement may be acceptable for a patient with spasmodic torticollis, but for a performing artist, this is insufficient. Using a three-month injection cycle, most patients with blepharospasm or cervical dystonia achieve their maximal benefit after the third or fourth injection cycle. For performing musicians whose livelihood depends on being able to play, a year's delay is usually unacceptable. Further, trying to target all of the involved muscles, and estimating doses which will produce benefit without causing problematic weakness, is nearly impossible during one visit. For these reasons, our current clinical approach (now in trial format) is to treat patients in stepwise fashion, targeting single muscles with doses of incobotulinum toxin which may not produce maximum therapeutic benefit but which are unlikely to produce problematic weakness. Incobotulinum toxin has the added advantage of having few contaminating proteins, possible reducing its immunogenic potential. The combination of high-resolution ultrasound and electrical simulation in the hands of an experienced injector (Dr. Simpson) is indispensible for ensuring optimal results.

Musicians' dystonia is a fascinating and challenging movement disorder. As most musicians "live to play," rather than "play to live," the emotional and psychological impact of the disorder can be significant. Better treatments are needed for this challenging disorder.

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Treatment of Generalized Dystonia

51

Susan B. Bressman

Case

A 34-year-old woman was seen for evaluation of involuntary pulling of her head to the right. The neck contractions began 5 years earlier with a mild deviation to the right and occasional superimposed jerking movements and then progressed to overt deviation with near continual repetitive turning movements. There was partial relief when she rested her head against a high back chair. On detailed questioning she also reported bilateral arm tremor and writing problems, starting at about age 14. There were no other complaints, including any change or difficulties with gait, speech, or swallowing. She recalled one cousin with arm tremor and writing problems. Symptoms were not diurnal or better after a nap. Further there was no preceding trauma or exposure to dopamine blocking drugs.

On exam she had cervical dystonia with hypertrophy of the left sternocleidomastoid and right splenius muscle. In addition, there were irregular downward repetitive jerking movements of both arms when holding them out prone in front of her. When she wrote there was diffuse tightening of upper and lower arm muscles, her elbow elevated, and she had difficulty maintaining her grip. Finally, there was a subtle abnormality of her gait consisting of mild but definite flexion of her trunk with rounded shoulders. The remainder of her examination was normal. Specifically, reflexes were normal, there was no parkinsonism, and there were no K-F rings. Her MRI was normal.

Because she had dystonia affecting her neck, arms, and trunk, her "distribution" meets criteria for generalized distribution. Further, because there were no findings on her examination except dystonia, her syndrome could be further characterized as isolated dystonia (previously called primary dystonia); finally, there was no history to suggest an exposure or other causal event; thus the etiologic category was thought likely to be "idiopathic" or genetic. The latter was especially suspected because onset was in adolescence and also because there was a possibly affected cousin.

Her cervical contractions (and increasing pain) were the most debilitating component of her dystonia and the focus of therapy. Botulinum toxin (BT) chemodenervation was discussed with her and considered likely to help; however, because of the early onset and widespread involvement, we first tried carbidopa-levodopa, to determine if dystonia was "dopa-responsive." Starting with ½ 25/100 BID, the dose was increased over 4 weeks to 2 tabs TID. There was no significant change, the levodopa was discontinued, and botulinum toxin injections were initiated with moderate relief. Other medications were added, both because the injections provided only partial relief but also because of more widespread dystonia. These medications included baclofen (with mild benefit at 10 mg TID), trihexyphenidyl (not tolerated beyond 5 mg TID and eventually discontinued), and clonazepam (maintained on 1 mg BID).

After 10 years, her dystonia progressed with worsening flexion contractions of her trunk, now significantly affecting her gait as well as spreading to her voice (adductor dysphonia) and lower face. DBS was discussed, and she met with a neurosurgeon, but she remains reluctant to pursue. Further, clinical-genetic testing had been discussed several times over the course of her illness; she was not initially interested in counseling or testing. However, after her daughter developed symptoms of cervical dystonia, she agreed to both. DYT-*TOR1A* (DYT1) and DYT-*THAP1* (DYT6) screening was performed, and she was found to carry a previously described *THAP1* (DYT6) missense mutation. A *THAP1* mutation was considered more likely than *TOR1A* because of the prominent cervical involvement with late spread up to the voice and lower face, although phenotypes for these genes overlap.

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Discussion

Generalized dystonia is a clinical subtype of dystonia characterized by extensive involvement of multiple body regions and thus distinguished from the more limited focal or segmental distribution subtypes (see Table 51.1 for clinical etiological classification scheme). Criteria defining generalized distribution have evolved over the years. Initially all limbs and the trunk were required. Subsequently the definition required somewhat less extensive involvement of "crural" (both legs or one leg and the trunk) plus at least one other region. Most recently, under the 2013 classification, generalized dystonia no longer requires legs to be involved; instead, current criteria require the trunk and two other body regions. This change in definition was made to convey the notion that generalized implies widespread involvement, which may occur without affected lower body regions.

Generalized dystonia often starts in childhood or adolescence, usually starting in an arm or leg and then spreading to a generalized distribution over 3–5 years. Occasionally, as in this case, dystonia distribution may progress over many years, and the patient may not come to the attention of a neurologist until adulthood. This is especially true when onset is in the arms, and symptoms are not disabling. Regardless of age of onset or presentation, a critical component of management is performing a detailed history and examination. Information gleaned from the history and examination helps determine the clinical subtype and narrows the etiological search, setting the stage for subsequent workup and a treatment approach. The initial step in this process is determining whether there are clinical signs other than dystonia; if there is only dystonia (with or without tremor – which is considered part of the dystonia phenotype), the dystonia is categorized as isolated (previously primary). If there are signs other than dystonia or tremor, such as parkinsonism or ataxia, then dystonia is considered combined or complex (Table 51.1). Subtyping is further refined by adding information about temporal features (e.g., rapid onset, in the setting of fever/metabolic stress), drug or other exposures, trauma, and family history. Once this information is gathered, decisions about further etiological workup, such as imaging, lumbar puncture, and genetic testing, can be made.

Table 51.1 Dystonia classification

Axis 1: Clinical characteristics
Age of onset
Infancy (birth–2 years)
Childhood (3–12 years)
Adolescence (13–20 years)
Early adulthood (21–40 years)
Late adulthood (>40 years)
Affected body region
Focal: One body region
Segmental: Two or more contiguous regions
Multifocal: Two or more noncontiguous regions
Hemidystonia: Multiple regions on one body side
Generalized: Trunk and two or more body regions (with or without leg)
Temporal pattern
Disease course (rapid onset, static versus progressive)
Variability (persistent, action-specific, diurnal, paroxysmal)
Associated features
Isolated versus combined
Isolated dystonia: Dystonia with or without tremor
Combined dystonia: Dystonia with other movement disorder; presence of other neurologic or systemic manifestations (also called complex)
Axis II: Etiology
Nervous system pathology
Evidence of degeneration
Evidence of structural (often static) lesions
No evidence of degeneration or structural lesion
Inherited/acquired
Inherited (autosomal dominant, autosomal recessive, X-linked recessive, mitochondria)
Acquired (perinatal injury, infection, drug/toxic, vascular, neoplastic, trauma, psychogenic)
Idiopathic

There are many causes of generalized dystonia, and consideration of the long list in a real-life clinical setting can be daunting. A reasonable approach is to use the classification scheme to break down the list into three major groups: acquired, genetic, or idiopathic (Table 51.1). For each of these groups, one can also assess whether there is brain pathology, which is clinically evaluated with MR imaging.

Common acquired etiologies of generalized dystonia are hypoxic –ischemic encephalopathy and tardive syndromes. The latter is important to distinguish as it implies a more specific therapeutic approach. This includes careful review of previous and current medications, tapering the offending drug if the patient is still taking, and potential use of clozapine or tetrabenazine. Genetic etiologies are numerous and ever increasing in number. A recent paper classifying genetic forms of dystonia identified 38 fully established genetic causes, and another genetic study using exome sequencing compiled 225 potential loci. A practical approach (see proposed dystonia classification in Marras et al., suggested reading #7) divides the genetic etiologies into the clinical groups mentioned above: (a) dystonia is isolated, occurring as the sole abnormality (except for tremor); (b) dystonia is present, but there is also another movement disorder such as parkinsonism or myoclonus; and (c) dystonia occurs along with other neurological abnormalities such as ataxia, dementia, and/or systemic features such as cirrhosis. It is important to remember that these clinical-genetic groups are fluid; as we have learned more about the phenotypes associated with dystonia genes, we also have learned to reject absolutism in

defining phenotypes. One recent example is DYT/PARK-*ATP1A3*. The originally defined syndrome displayed dystonia and parkinsonism, distinguished by rapid onset (RDP). Over time the phenotype has expanded to include many other abnormalities including alternating hemiplegia, seizures, and severe developmental delay.

Once dystonia is categorized clinically and a genetic etiology considered, a diagnostic workup ensues. How one pursues that workup, however, has evolved and recommendations have changed over the last decade, mirroring genetic advances. Most clinicians agree that a first approach rests on clinical-historical findings and the directive to quickly identify etiologies having effective specific therapies. An example is the opening case of this chapter which portrayed a patient with familial, adolescent onset, isolated, persistent, and generalized dystonia having a normal MRI. This restricted phenotype is associated with only two genes, *TOR1A* and *THAP1* (with former being more common), and a THAP1 mutation was eventually identified. Yet we treated her first for the "combined" dystonia of dopa-responsive (DRD), despite the fact that many typical DRD features, such as diurnal worsening, hyperreflexia, subtle parkinsonism, or foot/leg involvement, were not observed. The decision to treat with levodopa was based on (a) the recognition that there is an expanding range of phenotypes of DRD (and isolated dystonia as in the opening case indeed was a possible phenotype) and (b) the therapeutic imperative to not ever miss the diagnosis of dopa-responsive dystonia.

Although the evaluation of isolated persistent generalized dystonia is fairly limited, once there are (1) signs other than dystonia, or (2) unusual temporal characteristics such as an acute onset, or (3) an abnormal MRI (which is a usual first study in generalized dystonia), a more complicated etiological search ensues. Again, clinical clues pointing to specific etiologies, especially those with effective treatments, drive the approach to work up. For example, if Kayser-Fleischer rings are identified, specific testing for Wilson's should be performed. More often there are a number of potential genetic disorders under consideration. If so, the usual next step would be CSF studies (including neurotransmitter metabolites), along with urine and blood metabolic screening (including organic acids, amino acids, copper, ceruloplasmin, lactate, pyruvate, manganese, ferritin, biotinidase, creatine, vitamin E, uric acid, cholestenol, beta-galactosidase). Results of these screens should narrow the differential for subsequent targeted genetic testing. Increasingly, however, a less specified approach, using diagnostic and whole exome sequencing (WES), has been adopted. The timing of WES relative to other diagnostic tests is evolving, especially as costs drop, with a trend for earlier utilization in the diagnostic process. Various companies have developed broad dystonia gene panels, and one advantage is that even if initially negative, data can be reanalyzed as the field advances.

As the workup proceeds, and depending on the severity and impact of dystonia on the patient's life, a therapeutic approach needs to quickly develop. If a treatable etiology is identified, then specific targeted therapy (e.g., tetrathiomolybdate and zinc for Wilson disease) can be instituted. However, aside from DRD (where specific therapy often brings the patient to a normal or near normal state), additional symptomatic therapy may be required. Symptomatic treatment is also considered for all other generalized dystonia patients whether dystonia is acquired, genetic, or idiopathic.

The approach to symptomatic therapy is determined by several factors, probably most importantly the degree of motor disability and any coexisting pain; other considerations include age, comorbidities (especially depression and anxiety), and social factors. Ultimately, of course, the patient's wishes direct the treatment plan. For the *THAP1* patient described in this chapter, painful torticollis was the main clinically relevant symptom, and after DRD was excluded, BT chemodenervation was the mainstay of therapy with moderate benefit. Similarly, BT can be helpful in other scenarios of generalized dystonia when denervation of selected muscles (e.g., hand, shoulder, foot, facial) can produce clinically meaningful improvement.

Often, as in our patient, oral therapies are tried. The only oral therapy shown to be effective in dystonia patients in a prospective double-blinded fashion is the anticholinergic trihexyphenidyl. Recent studies, including rodent DYT1 models, support striatal cholinergic dysfunction as a unifying pathophysiological mechanism underlying dystonia, and further bolsters use of an anticholinergic. The dose of trihexyphenidyl needs to be carefully titrated up, starting with 1–2 mg/day, and increased as tolerated, usually in a TID schedule; children often tolerate higher dosages and may demonstrate considerable benefit. Our patient developed peripheral and central side effects including forgetfulness and confusion, and the drug was discontinued. Other classes of oral meds are used, albeit without controlled trials, and include baclofen, benzodiazepines, tetrabenazine, and clozapine; the latter two are used especially for tardive dystonia; each carries significant risk of side effects and needs to be carefully monitored (see Table 51.2).

The key therapeutic question that requires consideration for any patient with generalized dystonia is whether he or she is a candidate for deep brain stimulation (DBS). In our *THAP1* patient, the initial clinical picture was dominated by torticollis, and BT was helpful; there was considerable pain and anxiety as well, and clonazepam (along with psychological counseling) was beneficial. However, once it became clear

Table 51.2 Medical therapies for dystonia

Drug	Dose per day	Remarks
Carbidopa-levodopa	In children start at 1 mg/kg and increase to efficacy, usually 5 mg/kg; in adults usually effective at 2–3 tables 25/100 but up to 6 tabs	Usual first medication in children as screen and RX for dopa-responsive dystonia but can be used for other dystonias
Trihexyphenidyl	Increase as tolerated, beginning with a low dosage (2.0 mg at bedtime), titrating slowly up to 40–50 mg/day (given TID) in children; usually not tolerated above 20 mg/day in adults	After levodopa trial first medication for children with generalized dystonia; often also tried in adults but limited by central and peripheral anticholinergic side effects. Peripheral side effects may be ameliorated by pyridostigmine 30–120 mg/day
Diazepam	10–60 mg/day usually given TID	Mainly as add-on but can be especially helpful for painful contractions
Clonazepam	1–4 mg/day usually given BID	Similar to above; often helps to achieve comfortable sleep
Tetrabenazine	12.5 mg titrated up slowly to 25–100 mg/day, usually given TID	Used as second tier primarily for tardive dystonia and myoclonus dystonia but needs to be closely monitored for akathisia, depression, parkinsonism
Clozapine	12.5 mg titrated to >200 mg/day usually given BID	Used primarily for tardive dystonia and closely monitored for sedation and agranulocytosis
Baclofen	15–120 mg/day usually given TID	May be helpful for any dystonia but especially for dystonia with spasticity

that medical therapies were not controlling symptoms, which included worsening gait due to axial contractions, DBS was considered. Most patients with disabling generalized involvement have only partial or moderate relief with medical therapies, and bilateral GPi DBS now has been shown in a growing literature to provide significant benefit overall. There is however considerable variability, which may be explained in part by differing underlying etiologies and possibly clinical characteristics (e.g., distribution, whether clonic, disease duration). There is substantial data to suggest that patients with DYT1 (DYT-*TOR1A*) and isolated "idiopathic" generalized dystonia are most responsive to DBS intervention. Tardive dystonia and dystonia due to *THAP1* mutations are isolated dystonias that appear to respond, although not as consistently. Similarly, there is literature supporting the benefit of DBS for a subset of combined or complex generalized dystonias, such as myoclonus dystonia (with or without *SGCE* mutations), X-linked dystonia parkinsonism, and dystonia due to *PANK2*, although patients with combined/complex dystonia have a less robust response compared to those with isolated forms. Patients with dystonia may have a delayed response to stimulation, with improvement beginning in weeks to months. The most common surgical risks are hardware malfunction or infections, which occur in as many as 10% of patients over the course of a lifetime. Mood and cognition do not appear to worsen postsurgically. Speech does not predictably worsen either. Children and adults with dystonia who receive GPi stimulation may respond to low frequencies (60 Hz to 80 Hz), although higher frequencies (130 Hz) with a pulse width of 60 μsec are generally recommended for initial programming.

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Treatment of Status Dystonicus (Dystonic Storm)

52

Lan Luo, Blair Ford, and Stanley Fahn

Case 1

A 13-year-old boy with severe generalized *DYT1* dystonia developed worsening axial and bilateral leg dystonia along with violent and continuous dystonic spasms. About 7.5 years earlier, at the age of 5, his dystonia started with the development of twisting of his left foot after a mild viral illness. His mother noticed that he would run in a "galloping" fashion, with his right foot plantar-flexed. He was unable to run shortly thereafter. As the years passed, he developed inversion and plantar flexion of his left foot along with dystonic spasms of both legs when he attempted to stand and walk. He occasionally would prefer to crawl instead of walk. Eventually, his walking became increasingly impaired, and he was unable even to stand. His legs would frequently jerk or gave way due to the dystonia. In addition, he also developed right hand and arm writer's cramp and dysarthria. He had occasional backward arching of his trunk to the point that his feet would extend above his head when lying supine. He preferred to sleep in the prone position. He became severely disabled, unable to walk, sit, study, or go to school. His only comfortable position was lying on the bed or the floor. He had tried various medications throughout the years, including levodopa up to 300 mg per day, carbamazepine up to 300 mg per day, reserpine up to 1.75 mg per day, benztropine up to 6 mg per day, and lorazepam up to 3 mg per day, all resulting in minimal improvement in his dystonia. He also tried a combination of trihexyphenidyl 75 mg per day and baclofen 80 mg per day, with slightly better response compared to all the other medications. He had a positive family history of dystonia in his mother and maternal uncle.

On the day of admission, he was first seen in the movement disorders clinic and was noted to be diaphoretic with writhing movements of both legs and trunk. He was unable to walk, stand, or sit. He writhed on the floor with continuous axial muscle contractions. He was given 2 mg of lorazepam and became drowsy with mild improvement of his dystonic spasms. He was admitted directly to the pediatric intensive care unit (ICU) and treated with intravenous hydration along with escalating doses of lorazepam and dantrolene. The high doses of lorazepam essentially produced sedation, which provided relief from the severe muscle spasms. Lab work revealed serum creatine kinase level >5000 IU/L. Fortunately, during his hospital course, he did not develop hyperthermia and did not require mechanical ventilation. We intermittently attempted to reduce the dosing of lorazepam to allow him to awaken and determine if he still had the severe dystonic spasms. Eventually, his spasms subsided in the presence of lower doses of lorazepam, and his serum creatine kinase dropped to normal range over 1 week. His truncal dystonia improved enough for him to lie in bed more comfortably, but he still could not sit unsupported due to back arching. Standing and walking also improved during his hospitalization, but he still remained significantly impaired on discharge. After 10 days in the hospital, he was discharged home on trihexyphenidyl 75 mg daily, baclofen 80 mg daily, reserpine 2 mg daily, dantrolene 75 mg daily, lorazepam 6 mg daily, and benztropine 6 mg daily. Home nursing, physical therapy, and occupational therapy were also arranged for him.

Post-discharge, he continued to be severely debilitated by his dystonia, totally unable to stand or ambulate. He spent

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most of his waking hours lying in bed in the prone position. Due to his severe disability and poor quality of life, he returned to the hospital about 2 months after his earlier hospitalization and underwent bilateral globus pallidus interna (GPi) deep brain stimulation surgery. Post-surgery, he experienced further improvement in his dystonia to the point that he was able to ambulate independently even in the presence of mild axial and left leg dystonia and eventually was able to taper off of reserpine, dantrolene, and benztropine. He remained on trihexyphenidyl 75 mg per day, baclofen 80 mg per day, and lorazepam 3 mg per day.

About 8 months after his deep brain stimulation (DBS) surgery, he experienced skin erosion over his left chest wall pulse generator with subsequent development of Staphylococcus cellulitis. However, even after a course of antibiotics and removal of left extension lead, his infection persisted, eventually requiring removal of his left DBS cranial electrode. On the last clinic visit, about 5 years after his initial DBS surgery, with only right-sided GPi DBS in place, he continued to do well with mild left arm and bilateral leg dystonia.

Discussion

Dystonia is defined as involuntary sustained or intermittent muscle contractions resulting in abnormal postures or repetitive twisting movements. Severe exacerbation of dystonia can become a potentially fatal condition called *status dystonicus*. Also known as dystonic storm, status dystonicus is a rare movement disorder emergency clinically characterized by frequent or continuous episodes of severe generalized dystonia, leading to very high levels of serum creatine, and sometimes myoglobinuria due to rhabdomyolysis. Although no consensus diagnostic criteria exist for this condition, patients often develop one or more of the following: (1) bulbar weakness resulting in compromise of upper airway patency, (2) progressive impairment of respiratory function leading to respiratory failure, (3) metabolic derangements, and (4) exhaustion and pain. It can affect patients of any age, but it is most commonly seen in children between the ages of 5–16 years, as in our case. It can emerge in a patient with underlying dystonia or may even be the first presentation of dystonia. Secondary dystonias, especially those associated with cerebral palsy, outweigh primary dystonias as the underlying cause of dystonias leading up to this condition.

Triggers reported in the literature include infections, trauma, surgical procedures, anesthesia, metabolic decompensation, stress, and pain. Medication changes, including the abrupt withdrawal of certain drugs such as lithium, tetrabenazine, or intrathecal baclofen or the introduction of chelation therapy in Wilson's disease, have all been associated with the development of status dystonicus. Dopamine receptor blockers, such as pimozide and haloperidol, which are sometimes used to treat dystonia, can also initiate status dystonicus. Clonazepam also has been found, if not coincidentally, to be a trigger. Infections of any kind can worsen underlying dystonia and eventually lead to dystonic storm.

Other life-threatening movement disorders, including neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia, intrathecal baclofen withdrawal syndrome, and acute dystonic reactions can present similarly to status dystonicus. In neuroleptic malignant syndrome and serotonin syndrome, mental status is usually reduced, whereas mental status is not affected in status dystonicus. Malignant hyperthermia occurs mostly in the intra- or perioperative setting and is characterized by prominent hyperthermia and autonomic instability. Patients treated with intrathecal baclofen pump can experience baclofen withdrawal syndrome exhibiting rebound spasticity, muscle rigidity, autonomic instability, and diminished consciousness about 12–24 hours or within a few days of the interruption in baclofen infusion. In contrast to the generalized dystonia seen in status dystonicus, acute dystonic reactions often present with focal dystonias.

A patient suspected of status dystonicus should have airway and ventilation stabilized in the emergency room and then should undergo immediate admission to the intensive care unit for further monitoring. Refer to Fig. 52.1 for the management of status dystonicus. Many patients experience dystonic spasms of the muscles of the upper airway and respiratory tract leading to airway compromise, thus requiring paralysis, ventilation, and sedation. It is of the utmost importance to continually monitor the respiratory status by performing routine chest X-ray, pulse oximetry, and blood gas monitoring. Respiratory failure can be seen as the result of aspiration pneumonia, dystonic bulbar spasms, truncal-respiratory muscle spasms, diaphragm dystonia, or generalized exhaustion. Sedation involving propofol 0.3–3 mg/kg/hr. or midazolam initially up to 10 μg/kg/min and then at 30–100 μg/kg/hr. and paralysis with non-depolarizing neuromuscular blockades are utilized to relieve exhaustion and pain from dystonic spasms and provide rest for the musculature and the brain. In certain cases, barbiturate anesthesia may be required. Dystonia should be periodically evaluated by giving the patients respite from all paralyzing and sedative agents. Another frequent complication of generalized muscle spasms is rhabdomyolysis, accompanied by metabolic derangements including elevated creatine kinase up to five times the normal range, myoglobinemia and myoglobinuria, electrolyte abnormalities, and acid-base disturbances. Patients in rhabdomyolysis should be treated with intravenous fluids, urine alkalinization, dantrolene, neuromuscular paralysis, and dialysis in the setting of acute renal failure. Vital signs, basic metabolic panel, creatine kinase, blood gas analysis, serum and urine myoglobin levels, and urine output

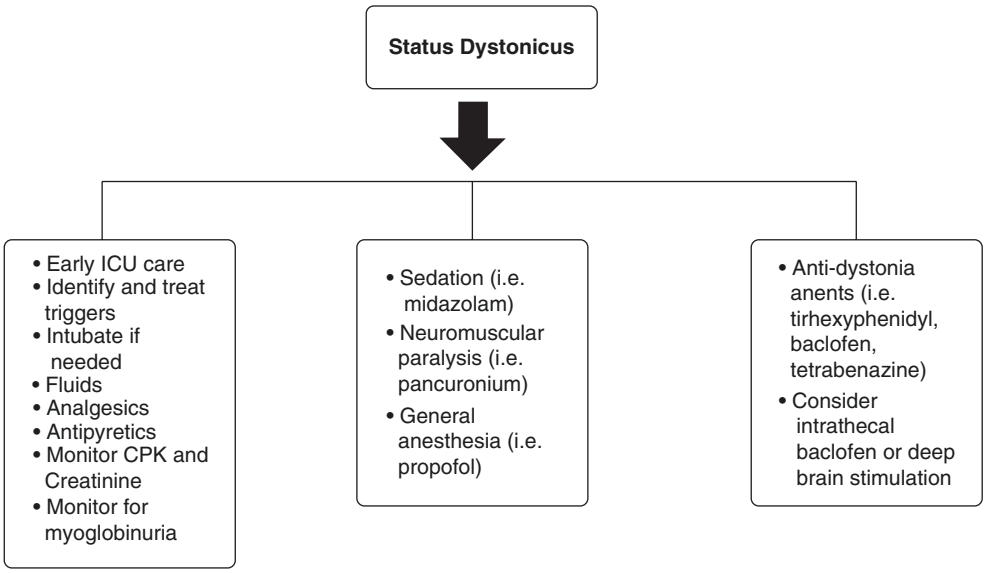

Fig. 52.1 Status dystonicus management

should be continuously monitored. Hyperthermia, stemming from muscle spasm-induced exothermia, can develop and should be managed with acetaminophen and cooling blankets. Any infectious triggers to the dystonic storm should be investigated and treated accordingly.

Once the patient has been stabilized, a combination of dystonia-specific drugs can be used. The current literature on status dystonicus consists of case reports and anecdotal evidence, without any definitive data regarding optimal treatment strategy. Drugs reported in the literature with better success rates include trihexyphenidyl up to 40 mg per day, haloperidol up to 8 mg per day, pimozide up to 10 mg per day, and tetrabenazine up to 75 mg per day. Other drugs used with varying degrees of success are benzodiazepines, anticonvulsants, baclofen, levodopa, benztropine, biperiden, lithium, bromocriptine, chlorpromazine, olanzapine, clozapine, and risperidone. Doses of any of these medications should be advanced slowly and prudently to avoid any side effects or adverse reactions. In cases of status dystonicus due to tardive dystonia, dopamine blockers should be avoided.

Finally, if status dystonicus persists, despite maximal pharmacological therapy, intrathecal baclofen or more often deep brain stimulation should be considered. Continuous intrathecal infusion of baclofen can be an effective treatment for dystonic spasms. Furthermore, quick titration of baclofen is relatively easier in the ICU setting than in the clinic. Reported cases of intrathecal baclofen failure in status dystonicus often arise from baclofen-associated complications or due to tolerance of baclofen. Complications of intrathecal baclofen include overdosage, catheter migration or breakage, and baclofen withdrawal symptoms.

Globus pallidus internus is the preferred target for DBS and is particularly efficacious for tardive dystonia and *DYT1* dystonia. It appears to be effective in the treatment of medically refractory status dystonicus and could potentially lead to weaning off of sedative and anesthetic agents and improvement of dystonic state back to baseline or even better than baseline. However, deep brain stimulation surgery is not without its own complications including skin erosion and infections, electrode breakage, electrode migration, and stimulator malfunction. Additionally, the complication rates may be higher in the pediatric population in which status dystonicus is more frequently found than the adult population.

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Treatment of Dystonia: Deep Brain Stimulation

53

Michael H. Pourfar

Case

A 33-year-old gentleman with a history of mania with psychotic features was treated with antipsychotic medications for 6 years and developed severe dystonia involving his trunk, face, and upper body. Attempts to improve the dystonia, including tapering of neuroleptic and use of tetrabenazine, benzodiazepines, and targeted botulinum injections, were unsuccessful. He required multiple emergency room visits during exacerbations for IV sedation. He was thus sent for consideration of deep brain stimulation. On initial examination, he had marked and generalized dystonia with twisting and pulling back of the torso and arms and persistent grimacing of the face. His Burke-Fahn-Marsden (BFM) score varied on preoperative visits between 56 and 82 depending on his degree of stress. Given the significant disability, we had a lengthy discussion covering the nature of the surgery, risks, and alternatives with particular attention to the variable outcomes associated with DBS for tardive dyskinesias and dystonia, ranging from no improvement to significant improvement but with little likelihood of total resolution of his symptoms. He decided to undergo surgery and had implantation of bilateral DBS electrodes into the globus pallidus interna (GPI) under general anesthesia since the intensity of his movements precluded performing the surgery while awake. Postoperative imaging demonstrated appropriate stereotactic positioning of the electrodes with no complications. This was followed 1 week later by attachment of the electrodes via an extension wire to a pacemaker (implantable pulse generator of IPG) in the chest.

Two weeks after the implantation of the electrodes, he presented for his initial programming. Normally, this would entail a systematic review of all electrodes (as discussed further below). Approaches vary but typical starting parameters involve a pulse width of 90 microseconds (us) and 130 Hertz (Hz) with a stepwise increase in voltage from 0 through 5 volts (v). During this review, we are looking both for immediate benefit (which is not often evident with dystonia) and side effects, particularly flashing lights or phosphenes, that one often finds particularly with the bottom electrode(s) closest to the optic tract, and pulling of the face or arm, which indicates stimulation of the internal capsule, which lies medial and posterior to a well-positioned GPI lead. In this case, however, his dystonia was so intense that he could not sit still for the typically lengthy monopolar review. Unless I find immediate improvement with a given electrode, I typically select the most ventral (i.e., deepest) electrode that is best tolerated. In many cases, this ends up being the second electrode from the bottom (electrode 1- in Medtronic's system). Because I could not practically investigate all electrodes, I thus decided to start with typical parameters of C + 1–3.0 v/90 us/130 Hz and observe him in the office for about an hour. He felt, if anything, that his movements were even worse. Given this impression, I backed off the voltage and sent him home with two different programs, one being C + 1–1.0 v/90 us/130 Hz for both sides (Program A) and a second utilizing the electrode one higher (more dorsal), C + 2–1.0 v/90 us/130 Hz for both sides (Program B). Both programs were set to give him the ability to raise the voltages to a maximum of 2 v. He was to start with Program A and build up toward 2 v in the weeks ahead but change to Program B if he felt he was experiencing a side effect including worsening dystonia, visual symptoms, or uncomfortable sensations.

He built up to 1.5 v with Program A but, as in the office, felt his dystonia was increasing so changed to Program B and built up to 1.5 v, returning a month later with subtle improvement and no apparent side effects. I increased his voltage to 2.0 and recommended he build up toward 3.0 between this visit and the next in 3 months. He returned with significant improvement and I made only a minor increase to 3.5 v. He felt this was too strong and lowered it to 3.3 in the

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weeks ahead but then built it up more slowly to 3.6 v and returned another 3 months later with dramatic improvement, his BFM score now a 44.5 and involving moderate facial movements and mild shoulder twitches. Over the following 2 years, minor adjustments including a slight bump up in F to 145 then 165 Hz were undertaken for residual dystonia with further improvements (BFM reduced to 14.5). He remains mildly dystonic at 5 years follow-up with settings unchanged at C + 2–3.6 v/90 us/165 Hz for the past 2 years.

Discussion

Outcomes of DBS for dystonia are highly variable with the best results usually seen in hereditary forms such as DYT1 dystonia, though even here outcomes can vary quite a bit. For secondary forms of dystonia, including tardive dystonia, the literature is even more mixed. A number of case series, including prospective blinded reports, have demonstrated significant improvement in secondary dystonia, even beyond 5 year follow-up. Despite the mixed results, an average of around 50% reduction in the BFM rating scale at 1 year is a rough guidepost of anticipated response based on several reported results. When discussing this figure with patients, however, it is important to emphasize that it reflects a considerable heterogeneity of both dystonia etiologies and outcomes such that predicting individual outcomes is not presently possible. The potential for non-response is real as is the potential for surgical complications, which ranges between 1% and 5% at most experienced centers. The most devastating, but fortunately rare, complication is a symptomatic intracerebral hemorrhage resulting in permanent neurological deficits, while a more frequent though still rare complication is an infection potentially requiring removal of all implanted hardware. Given the lack of routinely effective medication options for severe dystonia, DBS nevertheless remains an important tool in the management of refractory cases. There are few hard and fast guides as to who will improve beyond the broad primary versus secondary categorization as mentioned above. The presence of fixed contractures from long-term dystonia poses a limitation in terms of potential improvement in mobility, and there is some evidence to suggest, in DYT1 patients at least, that younger age and shorter duration of symptoms at time of surgery is associated with greater degrees of improvement. Significant abnormalities on brain imaging, as might be encountered in some secondary forms of dystonia, should give pause, particularly if the basal ganglia are prominently involved. Figure 53.1 reviews a proposed broad approach to the selection of DBS candidates for dystonia.

In terms of programming for dystonia, there are a variety of proposed algorithms that can be applied irrespective of the nature of the dystonia (see Fig. 53.2). The typical

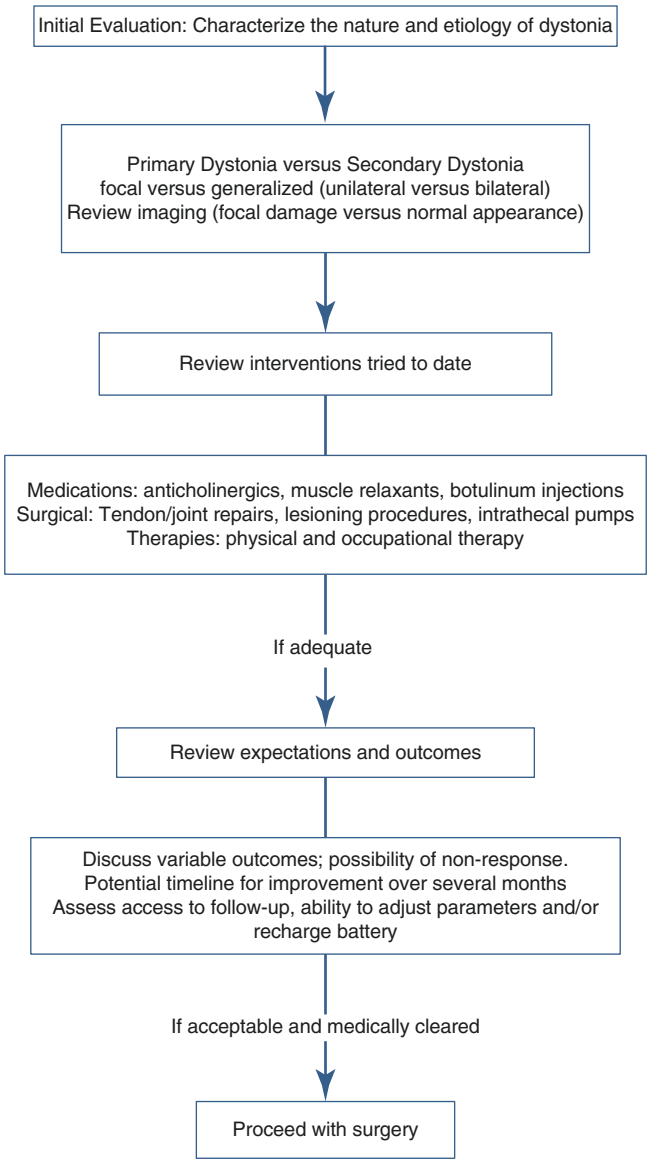

Fig. 53.1 Proposed algorithm for evaluating dystonia patients prior to deep brain stimulation

approach has been to perform a monopolar review, looking at each electrode individually, generally using a PW between 90 and 120 us (though older literature often used even higher PW) and a frequency between 130 and 185 (although there is also evidence for efficacy using lower F in the 60 Hz range, particularly for DYT1 dystonia). Because settings can be quite high in dystonia – at least compared to other indications like Parkinson's – some centers opt to use a rechargeable battery to avoid frequent replacement, especially in children who might require replacements every couple of years with currently available non-recharging batteries. However, a case-by-case approach is probably best since it is difficult for some individuals to routinely recharge. Whether one uses a single IPG that accepts both leads or two separate IPGs is also a matter of

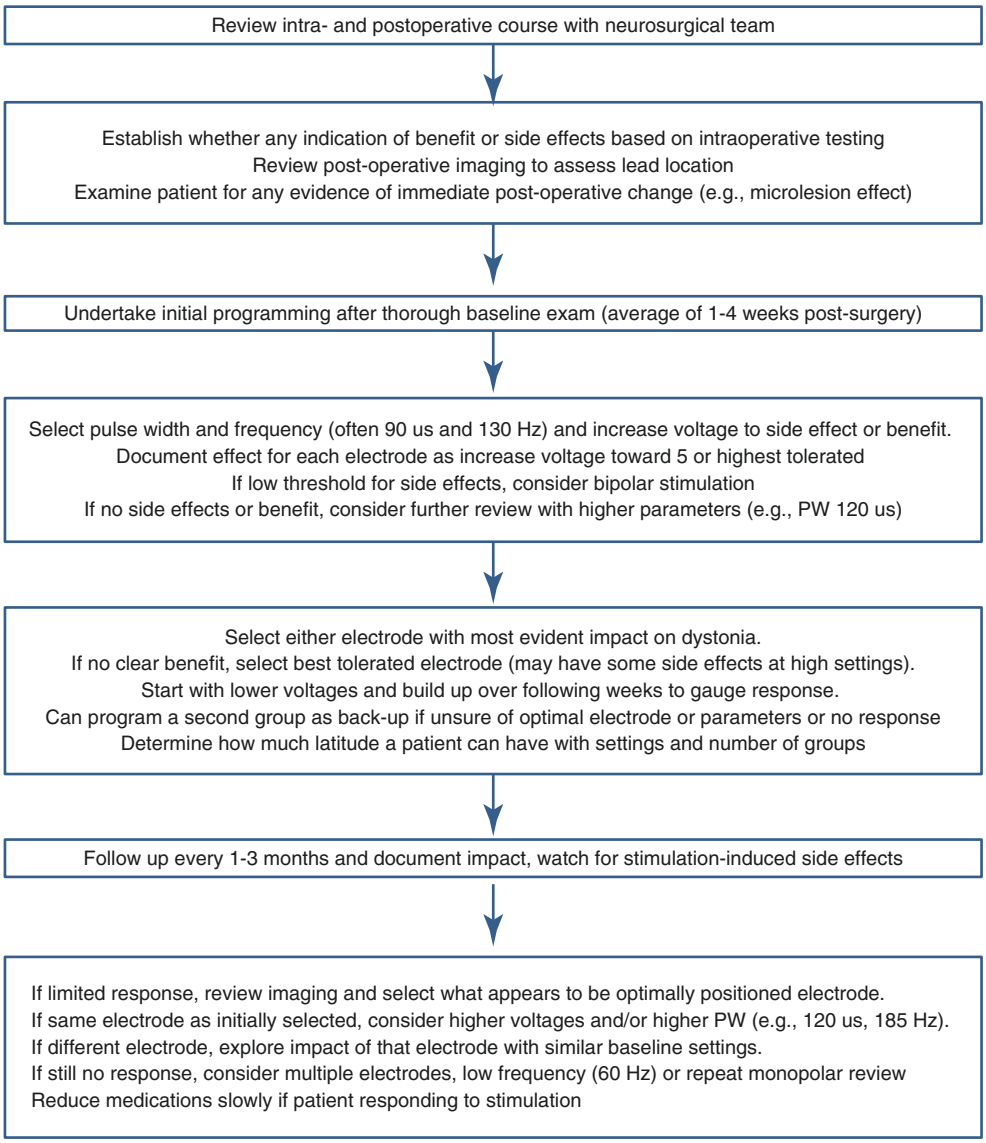

Fig. 53.2 Proposed algorithm for management of DBS for dystonia

patient and surgeon preference. It does not have a big impact on programming save for the relatively minor aspect that dual channel (i.e., one battery for bilateral electrodes) necessitates use of a single frequency for both sides. Whatever IPG is settled upon, my general programming approach is to begin with 90 us and 130 Hz and push the voltages to around 5 v or sometimes even higher to establish thresholds for either visual or capsular side effects. If lucky, we find an electrode that appears to improve the symptoms acutely, which is more often the case with symptoms like tremor in Parkinson's. But for dystonia, we usually do not appreciate any immediate impact beyond side effects. These side effects can include worsening of dystonia (as was noted here) as well as increased slowness and walking difficulties. Some experienced programmers will pick one electrode based on a gestalt impression of tolerability and start with a setting somewhere below the capsular threshold, whereas others will give the patient different contacts to explore over time using different pre-programmed settings. When there is no immediate response with one particular electrode, I often look closely at the postoperative imaging with the neurosurgeon to glean which electrode is in closest proximity to the lateral part of the motor territory of the GPI, typically a few millimeters from the pallidocapsular border. In our experience, it often translates to 1- depending on the depth of the bottom electrode (visual side effects with 0-, which is often close to the optic tract can help reinforce this impression). In this case, the patient had no immediate improvement and maybe a little worsening with 1- so a second option, looking one contact higher, was also offered, and this proved both the better tolerated and more effective electrode with time. Waiting several weeks or even months, assuming there are no side effects and a trend toward improvement, is often

necessary to avoid unnecessarily premature changes in parameters. In this case, the gradual improvement encouraged continued exploration of these general parameters. If there were no improvement by 3 months, considerations could include exploring an adjacent electrode (alone or with 2-), increasing the PW to 120 us, and increasing (or decreasing) the frequency or some combination thereof depending on tolerability. If no benefits are appreciated despite these changes, looking at intraoperative imaging with a DBS neurosurgeon and potentially revisiting the monopolar review sometimes help refocus on additional programming options. In cases where no benefit is seen despite extensive programming of well-placed electrodes, changing from GPI to STN DBS has been associated with improvement in some patients. This should only be considered after a complete assessment of GPI lead location and extensive programming efforts.

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Treatment of Myoclonic Dystonia

54

Marie Vidailhet

Case

A 36-year-old man was seen for jerky movements of the arms and the trunk with severe disability. The jerks were first observed at age 17 and worsened over the years. At the time of examination, the patient was markedly disabled as the jerks interfered with most of the activities of daily life including writing, feeding, and drinking.

On examination, the patient had severe brief, shock-like jerks of the upper limbs that worsened during voluntary movements with some jerks in the neck, trunk, and face. He reported that the jerks improved with alcohol. He also had mild dystonia with retrocollis, blepharospasm, and writer's cramp. Neurological examination was otherwise normal. He had healthy unrelated parents and no family history. He had a mutation on the epsilon-sarcoglycan gene. The patient was treated with clonazepam 2 mg/day for a few weeks but did not tolerate the treatment because of drowsiness. He was then treated with progressively increasing doses of zonisamide up to 150 mg a day with a marked subjective and objective improvement of myoclonus. He was able to perform the activities of daily life, but he developed a mood disorder with irritability and had to stop the treatment with re-emergence of the severe myoclonus. At age 36, he underwent bilateral internal pallidus stimulation (frequency 130 Hz, pulse width 60 microseconds, 3.2 V) with a good tolerance and 80% improvement of myoclonus and dystonia and no adverse psychologic effects and remains stable.

Discussion

Myoclonus dystonia (MD; DYT11) is a rare, childhood-onset, movement disorder that generally occurs in the first or second decade of life with a combination of myoclonus and dystonia. According to the recent revised classification of dystonia, MD belongs to the group of "combined dystonia." Myoclonus is usually the main and most disabling feature. It predominates in the arms and neck but may involve the trunk, lower limbs (about 25% of the cases), and rarely the face or voice. The myoclonic jerks are brief, less than 150 ms (Fig. 54.1), often present at rest, but are mainly triggered or aggravated by posture, action, and stress. Writing, drinking, eating, and other daily activities are markedly impaired. Myoclonus can worsen during the course of the disease (even in old age) and involve body regions that were previously unaffected, independently from the evolution of dystonia. Dystonia is usually mild and often manifests as cervical dystonia or upper limb dystonia (e.g., writer's cramp). Trunk and lower limb dystonia is rare. Myoclonus is often markedly improved by alcohol. Neurological examination and brain imaging (MRI) are normal. Behavioral disorders such as obsessive-compulsive behavior, depression, anxiety, alcohol addiction, and impulsivity have been described in some patients. Mutations of SGCE gene coding for epsilon-sarcoglycan account for 30–50% of MD cases. A positive family history is frequent (autosomal dominant inheritance with maternal imprinting), but sporadic cases due to de novo mutations are observed. Patients with similar phenotypes may or may not have mutations of SGCE gene. The pathophysiology of MD is still unknown with a subcortical origin of myoclonus. Dysfunctions of the basal ganglia and the cerebello-thalamo-cortical networks have been incriminated and, more recently, cortical functional abnormalities have also been suggested.

A broad range of oral medications for myoclonus dystonia have been tried with limited efficacy and poor tolerability. The most effective drugs are benzodiazepines (some

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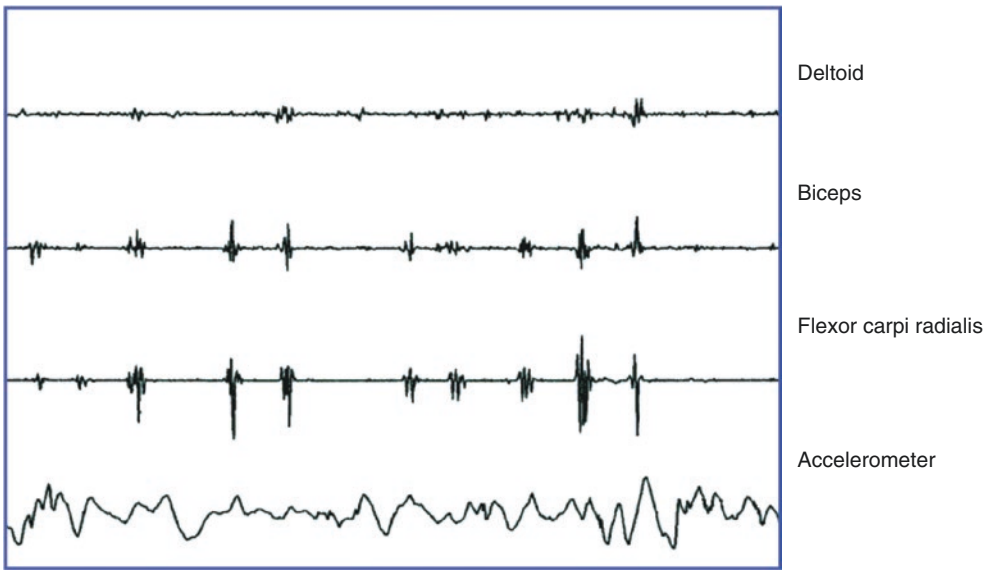

Fig. 54.1 EMG demonstrating shock-like myoclonus, short duration <100 ms

beneficial effect on myoclonus) and anticholinergics (on dystonia), although clinical benefit is rarely satisfactory and adverse effects (somnolence and memory difficulties) are frequent. Many other drugs including dopaminergic agents, tetrabenazine, sodium oxybate, and antiepileptics such as valproate, barbiturates, piracetam, levetiracetam, carbamazepine, and gabapentin have been proposed with little or variable benefit. These drugs were assessed in open-label studies, small series, or case reports, but not in controlled studies. Local injection of botulinum toxin may be helpful for cervical or upper limb dystonia, with a therapeutic strategy similar to those used in isolated focal dystonia. However, disability in everyday life activities is mainly related to myoclonus, with marked limitations in social life, at school, and at work, loss of self-esteem, withdrawal, and depression. Recently, a double-blind, placebo-controlled crossover study demonstrated that zonisamide at a target dose of 300 mg/day in adults improves myoclonus severity and myoclonus-related functional disability in patients with myoclonus dystonia. Zonisamide may thus be considered as a therapeutic option for patients with mild to moderate myoclonus dystonia. However, a beneficial effect is obtained in only 75% of the patients, with partial improvement. The tolerance profile is not perfect as frequent asthenia (65%), and some mood swings, including depression and impulsivity (35%), were observed.

The efficacy of zonisamide appeared to be lower than that reported with bilateral deep brain stimulation of the internal part (GPi) of the pallidus for MD. Series of patients were reported with bilateral thalamic (same target as for essential tremor) or pallidal (GPi) stimulation with marked (over 60–90%) improvement in the severity of myoclonus. GPi deep brain stimulation is associated with motor and functional improvement of both myoclonus and dystonia and marked improvement of quality of life, with a long-term follow-up of more than 10 years and good tolerance. Programming settings are individual, but generally the beneficial effect appears within the first few weeks with rapidly progressive improvement. Stimulation parameters are in the range of those used in isolated generalized or focal dystonias. Age is not a prognostic factor as both children and adults may experience marked beneficial effect. DBS provides the greatest treatment of myoclonus dystonia and should be considered in severe cases to allow a "close to normal" life. Nevertheless, it remains an invasive treatment, with some "maintenance" (battery depletion, rechargeable batteries, visible bulk under the skin, fear of device damage). With both drug treatment and deep brain stimulation for myoclonus dystonia, the degree of beneficial effect is not related to the genetic status (some of the patients do not harbor a mutation on SCGE) but is more related to the phenomenology (predominance of myoclonus and hyperkinetic movement disorders).

In some patients, psychiatric disorders are part of the spectrum of myoclonus dystonia including obsessive-compulsive disorder, compulsivity, generalized anxiety disorder, social phobia, and alcohol dependence.

Children and adolescents experience writing difficulties related to myoclonus, and their attention may be diverted toward motor control, with subsequently learning disorders. Parents and health professionals should take into account the risk of educational underachievement. Early school support,

computer use, and teachers' awareness are essential to improve academic and professional success and social integration. Young adults may seek genetic counseling. Women with myoclonus dystonia may have normal pregnancy and delivery, even when treated with deep brain stimulation, and they may benefit from epidural anesthesia.

There are patients who do not have typical myoclonus dystonia but may appear similar in that they have a tremulous/jerky pattern of dystonia, leading to misdiagnosis. In these cases, in contrast to MD, the same muscles demonstrate a combination of myoclonus and dystonia: irregular jerks (often of longer duration >150 ms) are superimposed upon sustained dystonic contractions emphasizing that the "jerks" are, in fact, part of the spectrum of dystonia and not a separate phenomenon. Dystonia and myoclonic jerks are observed in the neck, trunk, or limbs. These patients were described in the past as "myoclonic dystonia" (e.g., jerky/tremulous dystonia) to give a more evocative "vision" of the phenomenology, with hyperkinetic, phasic features. Some of these patients were referred to as having "dystonic tremor" as the jerks appeared to be more rhythmic (tremulous) than in myoclonic dystonia. According to the 2013 consensus update of dystonia, this movement disorders are now referred to as "isolated" dystonia (which includes dystonic tremor as irregular jerky dystonia). These patients have a normal neurological examination and normal brain imaging and may or may not have a family history and, in some, a genetic disorder (e.g., GNAL mutation with jerky cervical dystonia and limb dystonic tremor).

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Treatment of Dopa-Responsive Dystonia

55

Joseph Jankovic

Case

This 10-year-old girl was referred to the movement disorders clinic by her pediatrician because of an abnormal gait. Her parents became concerned about gait and balance problems when she first started to walk but did not bring it to the attention of the pediatrician until age 2.5 years at which time she was diagnosed with cerebral palsy. She otherwise had normal developmental milestones. Although several family members were previously diagnosed with either cerebral palsy or Parkinson's disease (PD), no diagnostic testing was ever performed. On initial evaluation in the movement disorders clinic, she was noted to have striking fluctuations in her symptoms, manifested by clear deterioration in motor symptoms over the course of the day so that she was essentially normal in the morning but by noon she was noted to have inversion of the right and then left feet, followed by stiff and scissoring gait and rapid deterioration in her balance. She was wheelchair bound at dinner time and essentially bedridden by bedtime. Examination in mid-afternoon revealed that she was an engaging and highly intelligent girl with dystonic lower limb posturing which markedly impaired her gait. She had slowness of rapid succession of movements in the feet and, to lesser degree, in the hands, slight rest and postural tremor in both hands and feet, increased muscle tone in the legs, and brisk deep tendon reflexes. A trial of carbidopa/levodopa, 25/100 mg three times per day, resulted in complete resolution of all motor symptoms within 5 days. This benefit continued over the next 3 years without the emergence of motor fluctuations or dyskinesias.

The family history indicated that the patient's 8-year-old sister had mild gait and balance difficulties, attributed by her pediatrician to "toe-walking" and cerebral palsy. One 6-year-old brother was normal. The patient's mother had some features of depression and obsessive-compulsive behavior but no evidence of movement disorder except for mild dystonic writer's cramp. The mother's sister, however, had adult-onset, slowly progressive, tremor-dominant, levodopa-responsive PD.

Because dopa-responsive dystonia (DRD) was suspected, a DNA test for mutations in guanosine triphosphate (GTP) cyclohydrolase I (*GCH1*) gene was obtained and showed heterozygous point (single-base change) mutation, confirming the diagnosis of DRD. It is, however, important to note that the commercially available test screens for only the most common of over a hundred mutations identified in the *GCH1* gene and, therefore, a negative test does not necessarily exclude the presence of *GCH1*-related DRD. The test provides results not only of deletion analysis in the *GCH1* gene but also DNA sequencing in this gene and the tyrosine hydroxylase (*TH*) gene. Cerebrospinal fluid analysis showed reduced levels of neopterin, biopterin, 5-hydroxyindoleacetic acid (5-HIAA), and homovanillic acid (HVA) but normal levels of phenylalanine. Furthermore, the marked improvement in all motor symptoms with levodopa supported the diagnosis of DRD in this case.

Discussion

This case illustrates the typical features of DRD (Table 55.1). Even before genetically confirmed, the diagnosis of DRD was suspected based on the typical clinical presentation, including the diurnal variation, the CSF findings of low levels of neurotransmitter metabolites, and the dramatic and sustained response to low-dose levodopa. Neuroimaging studies are usually not helpful in the evaluation of patients with suspected DRD as MRI of the brain is usually normal, DaTscan shows normal dopamine transporter receptor density, and PET studies usually show normal fluorodopa uptake. The latter two studies may be helpful, however, when

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Table 55.1 Clinical features in DRD

Abnormal gait
Postural instability
Distal limb (especially foot) dystonia (equinovarus posture)
Dystonic extension of the big toe (striatal toe) striatal toe
Dystonic writer's cramp
Rest and postural tremor
Bradykinesia
Rigidity
Hyperreflexia and ankle clonus
Oculogyric crises
Oromandibular, cervical, and truncal dystonia (scoliosis, camptocormia)
Myoclonus
Restless-leg-like symptoms
Ataxia
Hypotonic weakness
Diurnal variation
Depression, anxiety, and obsessive-compulsive behavior?

there is a suspicion of PD where the studies are usually abnormal. If routine, commercially available, testing does not reveal the genetic diagnosis, whole-exome or whole-genome sequencing may be needed.

First described by Segawa in 1971, DRD has since been well characterized clinically and genetically. Although initially classified as DYT5, the new nomenclature of genetic movement disorders has reclassified this disorder as DYT/PARK-GCH1 to draw attention to the *GCH1* and *TH* genetic defects resulting in the combination of dystonia and parkinsonism. Other genes in the dopamine synthesis pathway, such as *PTS* (pyruvoyl tetrahydropterin synthase) and *SPR* (sepiapterin reductase) may cause DRD as well.

The average age at onset of DRD is between 6 and 10 years of age; it may be, however, suspected as early as infancy and may not present until late adulthood, typically in a form of parkinsonism. DRD is more common in females than males (the reported female-to-male ratio is about 4:1), and the *GCH1* mutation penetrance is 2–3 times higher in females than in males.

Although it most typically presents as dystonic inversion of the foot while walking and progressive deterioration in gait and balance as well as rapidly evolving generalized dystonia in a few years, its presentation may be quite heterogeneous. For example, DRD may be initially noted only during exercise or in the evenings, but it may also present as a paroxysmal dystonia. Diurnal fluctuations of dystonia, manifested by worsening of symptoms as the day progresses and marked improvement after sleep, is one of the most characteristic features of DRD but is present in only about 50% of all cases. Although psychiatric symptoms, such as depression, anxiety, and obsessive-compulsive behavior, have been reported to occur quite frequently in patients with DRD, it is not clear whether psychiatric comorbidities occur more frequently than expected in patients with DRD or their relatives. Rarely, coexistent tics and Tourette syndrome have been reported in patients with DRD. DRD is often misdiagnosed as cerebral palsy, juvenile parkinsonism, "foot drop," or psychogenic gait disorder. This may delay the diagnosis by years or even decades.

The most common form of DRD is due to loss-of-function mutations in the *GCH1* gene, localized to chromosomal region 14q22.1–22.2. This results in tetrahydrobiopterin deficiency, a cofactor for aromatic L-amino acid hydroxylases, including TH, essential for dopamine synthesis (Fig. 55.1). In addition to amino acid substitutions and missense mutations, deletions in either *GCH1* introns and exons or the promoter region have been found in DRD patients. Besides mutations in the *GCH1* gene, there are many other gene abnormalities that may lead to the DRD phenotype as mentioned earlier (Table 55.2).

Because of relatively low penetrance, the parents of the affected child and other relatives may be asymptomatic carriers of mutations in the *GCH1* gene and may not exhibit any symptoms of DRD or may have a quite different phenotype in terms of age at onset and clinical presentation. Furthermore, other family members may present with adult-onset, levodopa-responsive PD. This suggests that mutations or variants in the *GCH1* gene not only lead to impaired dopamine synthesis but also may predispose some individual to nigrostriatal degeneration.

The wide intrafamilial variability in clinical expression of DRD is illustrated by another of our patients, an 88-year-old man and a member of a large Texas family with *GCH1* mutation, described originally in 2001 (Hahn et al.). He presented with parkinsonian symptoms at age 44, manifested chiefly by progressive gait impairment (more spastic than parkinsonian), bradykinesia, dementia, hallucinations, and dysautonomia (urinary incontinence, orthostatic hypotension). His motor symptoms responded well to levodopa but he experienced moderate levodopa-induced dyskinesia. Other family members had otherwise typical DRD phenotype but without diurnal variation except for increased afternoon fatigue. Of the 11 family members evaluated (age at evaluation: 10–73 years), carbidopa-levodopa 25/100 mg was administered to 6 subjects, all of whom had improvement in their motor symptoms with 2–3 tablets per day. A novel mutation (37-base pair deletion) in exon 2 of the GCH1 gene was demonstrated in 11 family members.

Because of the robust response to levodopa, which has not only therapeutic benefits but also diagnostic implications, an empiric trial of levodopa should be considered in any child with dystonia. It should be noted, however, that

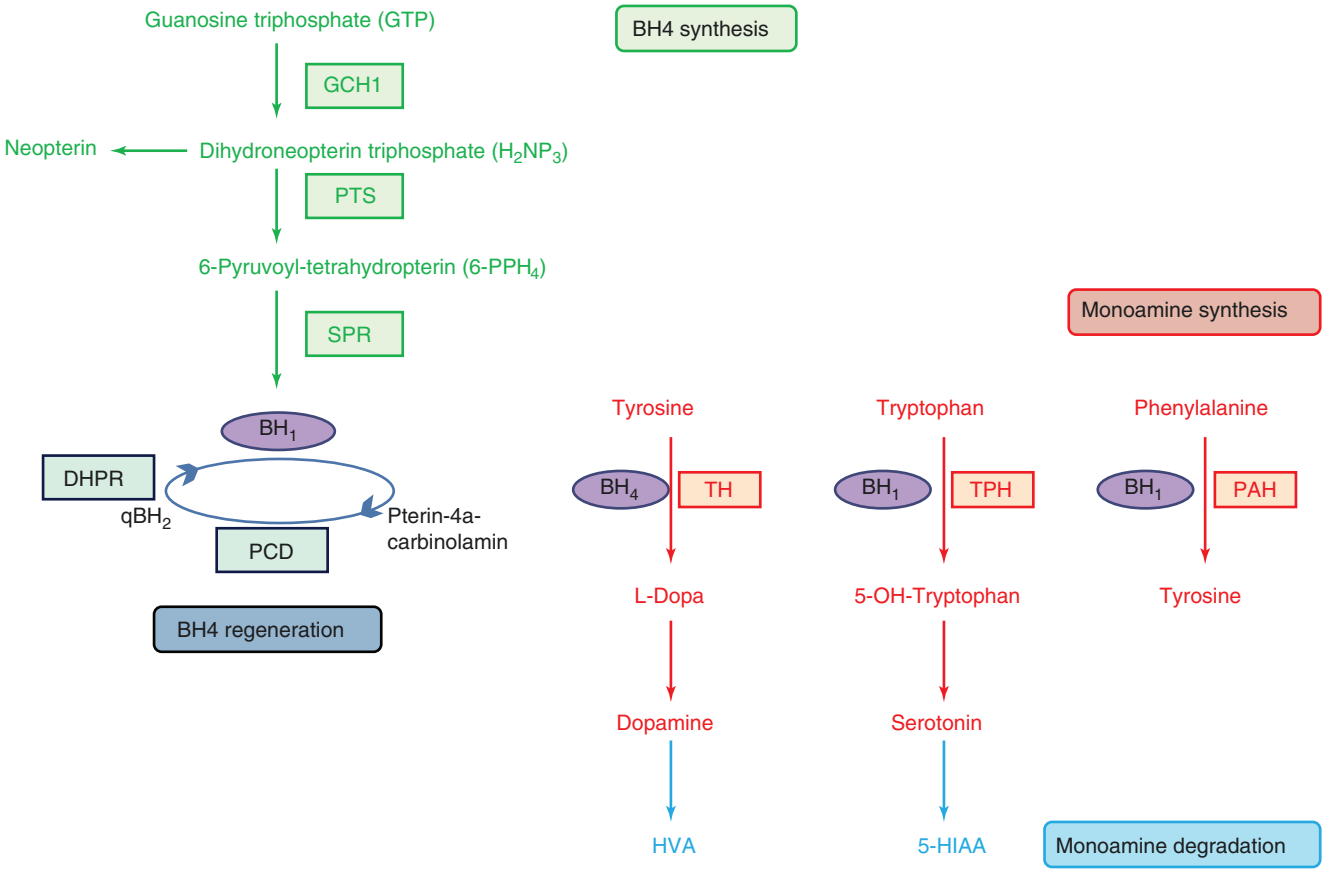

Fig. 55.1 Impaired synthesis of dopamine due to defects in *GCH1*, *PTS*, and *SPR* genes. *Abbreviations:* AADC aromatic l-amino acid decarboxylase, BH4 tetrahydrobiopterin, DHPR dihydropteridine reductase, GTP-CH-I GTP cyclohydrolase 1, HVA homovanillic acid, 5-HIAA 5-hydroxyindoleacetic acid, PAH phenylalanine hydroxylase, PCD pterin carbinolamine dehydratase, PTP 6-pyruvoyl tetrahydropterin, qBH2 quinonoid dihydrobiopterin, TH tyrosine hydroxylase, TPH tryptophan hydroxylase, SPR sepiapterin reductase

Table 55.2 Differential diagnosis of DRD

Juvenile PD
Rapid-onset dystonia parkinsonism
X-linked dystonia parkinsonism (Lubag)
Huntington disease
Wilson disease
Camptocormia
Mutations in *GCH1, TH, SPR, ATM, SPG11, Parkin, DJ-1, PINK1, FBOX7, ATP1A3, PRKRA, Ataxin 2, Ataxin3,* and *PLA2G6* genes

other disorders with DRD phenotype may respond to levodopa, including juvenile PD, and disorders due to mutations in genes coding for other enzymes in the dopamine synthesis pathways (Fig. 55.1, Table 55.2). Carbidopa/levodopa is typically initiated as quarter or half of a 25/100 mg tablet once or twice daily, and marked improvement is usually noted within several days. The dose may be increased gradually, but it would be highly unlikely that the patient will require more than 10 mg/kg or 25/250 mg three times per day. In contrast to juvenile or young onset PD in which majority of patients develop levodopa-related motor complications within 3–5 years of initiation of therapy, less than 20% of DRD patients exhibit wearing off effect or levodopa-induced dyskinesias, and these are rarely troublesome. In most cases of DRD, the motor symptoms are well controlled with levodopa, but despite optimal therapy, about 20% may have residual dystonia and about 10% still experience some parkinsonian symptoms. Levodopa does not appear to cause fetal abnormalities when taken during pregnancy, and if the symptoms are otherwise interfering with the patient's functioning, it is reasonable to continue levodopa during pregnancy. In addition to levodopa, patients with DRD also improve with dopamine agonists and anticholinergic medications. Surgical treatment, such as deep brain stimulation, is rarely ever contemplated in patients with DRD but has been reported effective in some medically refractory cases of TH deficiency presenting as DRD phenotype.

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Part VI

Chorea

Treatment of the Motor Features of Huntington's Disease

56

Samuel Frank

Case 1: Early HD

A 36-year-old man who works as a chef was diagnosed with symptomatic HD in the past year with the presence of involuntary movements. He has been accidentally cutting himself at work and requests a medication to reduce the movements. On examination, there was mild chorea of all limbs and the trunk. There was neither a history nor ongoing issues with depression.

In this case, even though the chorea is mild, it is presenting a functional problem in light of his occupation as a chef. The decision as to whether to start a medication should be discussed with every patient with a focus on the goals of therapy. To maintain optimal functioning in this case, and since he has no other medical issues, he is a good candidate for a VMAT2 inhibitor such as tetrabenazine or deutetrabenazine. There are many choices in this situation, including the use of D2-blocking agents; olanzapine and aripiprazole have been studied most extensively, but risperidone, haloperidol, and others are commonly used as well. Refer to the table for starting uses, common starting doses, common maintenance doses, and common side effects.

Case 2: Mid-Stage Issues

A 45-year-old woman with HD for 5 years has progressively increasing chorea and dystonia. She is having more falls and she eats too quickly resulting in mild swallowing issues, but no choking. She has a history of well-treated and relatively mild depression.

In this case, there are many motor and non-motor manifestations that require consideration in the management of chorea and motor symptoms. Mild depression is not a contraindication for the use of tetrabenazine or deutetrabenazine, but her mood would require close monitoring by clinic staff and caregivers. In one small study, aripiprazole improved mood and reduced chorea. Neuroleptics may be a good option, but caution may be advised due to swallowing issues. Falls may be caused by ataxia, imbalance, or chorea in HD but may also increase with the use of some medications such as neuroleptics. A non-dopamine-based medication such as amantadine may be a good option to address multiple issues in this case. Allied health interventions would also be important to include in her management. Physical therapy, occupational therapy, and speech and language pathology specialists are critical components of the team to care for patients with HD.

Case 3: Advanced HD

A 57-year-old man with HD has not walked in a few years. When he was first diagnosed, about 20 years ago, his chorea was marked and required multiple medications. However, as he progressed, more dystonia developed and became the predominant movement disorder, and the medications to suppress chorea were ultimately stopped since they were not needed because chorea became less pronounced as the disease progressed. In the past 6 months, caregivers at his chronic care facility noticed the emergence of large-amplitude movements, particularly when he would initiate voluntary actions. The movements are described as large enough that when he tries to turn over in bed, he has fallen over the side of the bed. Some of his caregivers are reluctant to provide care, because when the patient tries to "help," the large-amplitude, uncontrolled ballistic-like movements have injured staff.

This patient requires use of medications to suppress chorea for his own safety as well as the safety of the staff. VMAT2 inhibitors, neuroleptics, amantadine, benzodiazepines, and riluzole may all be considered. Assuming there are no other medical issues, tetrabenazine or deutetrabenazine

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would be the first choice for these movements. These medications may reduce chorea and in higher doses may also suppress other hyperkinetic movements as well without worsening swallowing. A neuroleptic such as olanzapine, aripiprazole, or risperidone would all be reasonable choices, also depending on the situation. For example, olanzapine would be appropriate if weight loss is also occurring. Any of the neuroleptics could be used if there are behavioral issues. In addition to medication interventions, an improved environment such as appropriate padding should be placed on and near the patient to protect him. For patients such as this one, low beds and pads next to the bed should be considered. Environmental modifications may be as important as the medical interventions when managing motor issues, particularly in more advanced cases of HD. Careful skin observation and care is also critical to maintaining patient comfort and safety.

Case 4: Westphal Variant

A 26-year-old man with HD symptoms since his teen years has only mild, intermittent chorea in his trunk and rarely in his right arm. He has severe dystonia of the trunk with leaning to the left, and there is reduced range of motion in all limbs with flexion contractures at the knees, elbows, wrist, and fingers. There is some but limited range of motion on passive movement. He has an intermittent tremor in the right upper extremity. Muscle stretch reflexes are easily elicited and there is spontaneous clonus in the lower extremities.

This patient does not require medications to suppress chorea and in fact may require the discontinuation of any medications that reduce dopamine effect (D2 blockade or VMAT2 inhibition). Amantadine and benzodiazepines (such as clonazepam) are often used for patients in these situations. If there are focal areas that are painful or interfere with dressing or hygiene, therapeutic botulinum toxin injection can be considered. To address some of the bradykinesia and dystonia, anti-parkinsonian medications can also be used. In patients with more dystonia than chorea, physical therapy, occupational therapy, bracing/orthotics, and education of the nursing staff become a critical component of care to maintain comfort and safety. For troublesome clonus, baclofen, tizanidine, and/or diazepam that act on the spinal cord.

Discussion

Chorea is the hallmark and a major motor sign of HD. However, other movement disorders may be present, including dystonia, myoclonus, ataxia, or tremor. All motor issues need to be addressed from time of diagnosis and through the various stages of progression of disease. As of early 2017, there are two FDA-approved drugs for HD, tetrabenazine and deutetrabenazine. Both are vesicular monoamine transporter 2 (VMAT2) inhibitors. These medications may address chorea, while other drugs may address other motor issues including dystonia, myoclonus, ataxia, dysphagia, or paucity of voluntary movements. The management of motor symptoms in HD requires individualization, focusing on goals and a team approach. Allied health fields and environmental changes also play a critical role in maintaining the safety and functioning of patients with HD. There are many medications that have been used for chorea off label, parkinsonism, and other manifestations of HD, but the removal of medications also needs to be considered with every patient as the disease progresses. It is important to minimize the use of medications that may have been started for one purpose but lead to a longer-term side effect. For example, myoclonus can be caused or worsened by some antidepressants, gabapentin, or opiates. Dystonia, parkinsonism, and akathisia may be exacerbated by the use of neuroleptics.

The medication choices are limited in class for the movement aspect of HD, but treatment choices should be considered in the context of the complete picture of HD. In patients with early HD and mild chorea who have more refractory depression requiring medication beyond a TCA, SSRI, or SNRI, a supplementary medication such as aripiprazole can be considered. In that situation, the additional medication to address depression may also have a positive impact on the motor features. In mid-stage disease, balance and swallowing problems may arise and the use of a neuroleptic may be avoided, unless the balance issues are related to the presence of chorea.

Assessing the need to treat chorea may take a team approach. Due to the lack of awareness of chorea, for example, patients may not complain about the movements themselves. To fully address motor issues, the input from caregivers and other members of the household may be critical. Another approach is to ask not about the chorea itself but rather the consequences of having chorea. Providers should ask about knocking objects off a table or bumping into walls with an arm. Assessing if there are bruises or superficial abrasions on the limbs may be another clue that chorea that requires treatment.

Huntington's disease is a progressive disease and the motor manifestations change over time. The use of medications should be periodically re-evaluated, considering which medications are appropriate to add, but also removing medications if possible. In addition, if the motor manifestations are incompletely addressed, providers can consider changing medications to another class (Table 56.1).

As with any disease process, the medication and allied health field interventions need to be tailored to the individual patient. In addition to addressing the motor issues

Table 56.1 Medications commonly used to treat the motor aspects of HD

Drug	Indication	Common starting dose	Common maintenance dose range	Common side effects
Tetrabenazine	Chorea	12.5 mg daily	37.5 mg–75 mg divided TID	Depression, akathisia, anxiety
Deutetrabenazine	Chorea	12 mg daily	24–48 mg divided BID	Somnolence, dry mouth, diarrhea
Olanzapine	Chorea, weight loss, behavioral dyscontrol	5 mg qhs	10–20 mg qhs	Weight gain, akathisia
Aripiprazole	Chorea, depression	5 mg qhs	10–20 mg qhs	Akathisia
Amantadine	Chorea, bradykinesia, tremor, dystonia	100 mg daily	300 mg–600 mg divided TID	Livedo reticularis, leg edema, confusion
Clonazepam	Anxiety, dystonia	0.5 mg qhs	0.5–2 mg daily, divided BID	Somnolence
Risperidone	Chorea	0.5 mg daily	1–4 mg daily, divided BID	Somnolence, dystonia
Botulinum toxin	Focal dystonia	100–400 units q3 months		Weakness, flu-like reaction

immediately present, treating patients with HD requires a periodic re-evaluation of the purpose and safety of all interventions. The field of treating HD is also evolving and emerging treatments should always be considered. Given the current and future options, we will continue to make HD an increasing treatable disease.

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Treatment of Irritability and Aggression in Huntington's Disease

57

Karen E. Anderson

Case

The patient was a 47-year-old man with advanced Huntington's disease (HD). He worked for many years as a mid-level programmer at a software company, where he was shy and reticent but by all accounts a very good employee. At age 30, he developed subtle abnormal movements. He had undergone at-risk (asymptomatic) testing for the HD gene mutation expansion years before since his father died of HD at age 50 and knew he carried the HD genetic expansion mutation. After receiving confirmation that he would, 1 day, develop HD, he elected not to marry or have children. Clinical assessment confirmed he had signs of HD at age 32. In the next 5 years, he developed worsening chorea in his face and extremities, new-onset depression and anxiety, and sleep difficulties. Subtle cognitive deficits had a negative impact on his work performance. He had trouble doing more complex coding and often took 10 or 12 h to do 8 h worth of work. He was transferred to a supervisory position, which did not have as many technical requirements, but, due to personality changes, which included rigid behaviors, irritability, and angry outbursts, he was unable to continue working and at age 34 he went on disability. In the ensuing 5 years, he became more and more rigid about his schedule for watching television shows, foods he would eat, and how his large collection of film DVDs was organized. He was unable to part with useless items like empty cologne bottles and old magazines. His chorea worsened, his gait and balance became more of an issue, and he had some choking episodes. When his brother hired a housekeeper to help mitigate some of the clutter in the patient's home, he flew into a rage because "she moves my things around and I will not be able to find them." The housekeeper quit after 2 weeks because the patient followed her around constantly, asking her the same question repeatedly, "Where is my *Sound of Music* DVD?" even though she pointed its location out to him several times an hour.

His brother, frustrated by the squalor in the patient's home and unable to manage the outbursts, which now interfered with family visits and events, brought him in to see a psychiatrist. The first visit was very challenging, ending when the patient demanded to know "where are my DVDs!" and threw a water bottle at a fellow in the clinic. He was subsequently taken to the emergency room by hospital security for evaluation.

In the emergency room, he was given 5 mg haloperidol and 2 mg lorazepam intramuscularly after he punched a security officer and spat on the psychiatrist. He was admitted involuntarily to the psychiatric floor, where he was started on an SSRI antidepressant to help with both the perseveration and the irritability. Due to frequent agitation and physical aggression toward other patients and staff in the first couple of days on the unit, olanzapine 10 mg BID was added, with PRN 5 mg haloperidol po or IM available for more severe outbursts. A nursing aide noticed the patient consistently became restless and sometimes agitated around midafternoon. Adding in a snack and beverage, to prevent hunger and dehydration, was helpful in preventing these episodes. Nursing also noted the patient was spending long amounts of time in the toilet and did not have daily bowel movements. Dietary changes were instituted which, along with the increased hydration, helped to decrease constipation. This also improved irritability and restlessness. The patient spent much less time in the restroom and more time in common areas on the unit. He continued to perseverate, mostly on his movie collection. His brother tried bringing in some DVDs for the patient's enjoyment, but this led to a verbal outburst when he became convinced that his brother was stealing DVDs from him. After a week on the inpatient unit, the patient's outbursts were much better controlled.

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Side effects from this regimen, likely due to the olanzapine, were improved sleep at night, more daytime sedation, constipation, and increased appetite with a 5 pound weight gain, which was helpful since the patient had been losing weight. His chorea was mildly reduced, likely due to dopamine blockade from the olanzapine, but he had a couple of falls resulting in severe bruises. A routine electrocardiogram at this time point showed QTc prolongation, likely due to the olanzapine, with a change from normal baseline of 439 milliseconds at admission to 463 milliseconds, which was in the abnormal range for a male. Due to the risk of a cardiac event with the elevated QTc, olanzapine was decreased to 5 mg BID. The patient did well with this dose and the QTc reverted to 439 milliseconds. Unit staff continued to watch for environmental modifications that could benefit the patient. They found that reminding him to take a blanket or sweater to the day room, which was in a colder part of the unit, decreased his irritability during groups held there. They also encouraged other patients to simply walk away from him if he became upset during a conversation, rather than arguing. This prevented him from engaging in intimidating behaviors toward others, including shouting and cursing.

He was discharged to home after 2 weeks, still on the SSRI and olanzapine 5 mg BID. His brother hired a caregiver to be with him during the day 5 days a week, and the family provided some supervision on weekends, because the patient continued to fall and to choke at meals, so that he was not safe to be on his own for extended periods while awake. After 2 months, the perseveration improved to the point where the patient did not become agitated when his helper cleaned the home, as long as no DVDs were moved. The aide was instructed to offer the patient snacks, even if he did not ask for them, and to encourage him to use the toilet. The aide kept a record of his bowel movements and made dietary changes (adding more fruit, encouraging him to do safe exercises as able) to prevent constipation. At a follow-up clinic visit 2 months later, he was doing so well that the olanzapine was reduced to 5 mg QHS. The patient expressed remorse for assaulting the fellow in clinic, to whom he apologized, and the security officer in the emergency department. After several more clinic visits, the patient and his brother agreed to completely stop the olanzapine. He did fairly well with this change for the first week, but after a loud and threatening verbal altercation with the postman over a missed package, his brother felt the behaviors were becoming a problem again. The aide also said he could not continue to take him on outings if the loud public outbursts continued. Olanzapine was restarted at 2.5 mg QHS. The patient was more alert than he had been with 5 mg QHS but did tend become irritable when stressed. The family and hired caregiver were able to manage this through behavioral interventions. These included redirecting him to another activity when he became upset, walking away from the patient when he was agitated to avoid a direct confrontation, anticipating and avoiding triggers for irritability (such as hunger or tiredness), and providing small rewards when he went for an entire day without any outbursts. He continued on the SSRI, which was felt to help not only the irritability but also perseveration and overall mood. His chorea did worsen after decreasing olanzapine, but not to the point where it was thought that any other treatment for chorea was warranted.

Discussion

Irritability is an extreme emotional response to an event and/or lack of normal control over emotions. It is usually episodic and can be accompanied with an internal sense of impulsivity, frustration, and agitation. Both internal and external factors may trigger irritability and consequent aggressive outbursts. Environmental triggers are not always obvious, making environmental modification and behavioral interventions challenging. Patients with HD, who commonly have limited awareness of many symptoms, including irritability, may not remember the episodes of aggression or may deny these problematic behaviors. Irritability and ensuing aggression can cause patients to harm themselves or others. It worsens social isolation by making it difficult for family and friends to spend time with the patient. When these symptoms occur in the home, they can traumatize children, who may be at risk for HD themselves, and cause the spouse to leave the marriage and abandon the patient. It can make placement in long-term care impossible, since most facilities do not welcome a patient who may injure staff or other residents. Irritability and aggression are two of the main reasons highly sedating medications are given to people with HD, and these symptoms are often a cause of permanent institutionalization.

Environmental interventions (Table 57.1) for irritability and aggression include minimizing overstimulation, making sure patients have adequate hydration and caloric intake, and following consistent, predictable schedules. Behavioral interventions may be useful, particularly in patients who are relatively intact cognitively. These include providing small rewards for good behavior and redirecting or "changing the subject" when patients become agitated. As was seen in this case, irritability and aggression often occur with other psychiatric symptoms. When perseverative symptoms occur, they can worsen irritability if patients are prevented from acting on them. Agents used to treat irritability and aggression often decrease perseveration, improving behavior overall. There have been no placebo-controlled, randomized

Table 57.1 Behavioral/environmental interventions for irritability in HD

Intervention	Comments
Decrease overstimulating environment	People with HD may find normal environments to be overstimulating
Assess for physical discomfort	Particularly important in patients who have poor insight or cannot communicate well
Provide adequate hydration and calories	Dehydration may occur due to chorea; people with HD often need double the usual calories to maintain weight and prevent feelings of hunger. More advanced patients may have difficulty recognizing when they are hungry or thirsty, or may forget to eat and drink without encouragement
Do not argue with patient who is agitated	Train staff to "pick their battles" and to walk away from arguments rather than trying to win them
Provide small rewards for good behavior	Helpful in patients who are able to understand and remember reward paradigm, e.g., earning "tokens" that can be used to purchase small items
Distract patient if becoming agitated	Change the topic of conversation, walk the patient into a another room, hand him/her something distracting, like a cookie
Establish and follow routines	Minimize surprises, if in an institution, attempt to keep staffing predictable

Table 57.2 Drug dosing

Drug class	Approximate maximum daily dose
Antidepressants	
Sertraline	200 mg
Citalopram	40 mg
Escitalopram	20 mg
Mirtazapine	45 mg
Antipsychotics[a]	
Olanzapine	20 mg
Haloperidol	40 mg
Risperidone	8 mg
Quetiapine	800 mg
Antiepileptics	
Valproate	2000
Carbamazepine	400
Lamotrigine	400
Benzodiazepines	
Lorazepam	4 mg
Clonazepam	4 mg

[a]Consider dosing antipsychotics at night to avoid daytime sedation

treatment studies for irritability in HD (see reviews by Groves 2011, van Duijn 2010). Several classes of medication (Table 57.2) are used in clinical practice to address this problem, but only a few small studies exist. It is difficult to compare these studies, since varying criteria for entry and assessment scales were incorporated into the study design. There are single-case reports on the use of an SSRI, olanzapine with valproate, and haloperidol with lithium and nabilone, a cannabinoid. It is difficult to assess treatment response from these reports.

An expert survey, conducted with HD clinicians from Europe, North America, and Australia, demonstrated that SSRIs were the most common choice for treatment of mild to moderate HD irritability. Antipsychotic medications were a common alternative as first-line treatment. Antiepileptic drugs were endorsed less frequently as a first-line option. Buspirone, mirtazapine, propranolol, or TCAs were not recommended as first-line drugs, but each was cited as an alternative monotherapy drug by a small number of respondents. Benzodiazepines were used most frequently as adjunctive treatment.

This case illustrates that neuroleptics are sometimes needed in high doses for initial treatment of irritability and aggression, particularly when there are safety concerns related to the behaviors. It is important for clinicians to reassess the need for neuroleptics once the behaviors have improved, and to attempt to decrease these medications when possible, to reduce side effects, including sedation; QTc prolongation, which can lead to severe cardiac events such as torsade de pointes; worsening of gait; and cognitive impairment. Tardive dyskinesia, a risk with all neuroleptics, can occur in HD and may be very difficult to assess given the underlying chorea. Weight gain, which is a limiting factor in many psychiatric patients, may benefit HD patients, who tend to lose weight due to the illness.

In summary, treatments for irritability and aggression have not been well studied in HD. Education of family and other caregivers can be helpful in minimizing these behaviors. Clinical experience indicates that antidepressants, usually SSRIs, are the first line of treatment if symptoms are not severe. For more severe cases, an antipsychotic drug is a better choice, due to sedating quality and faster onset of action. Treatment of these symptoms can help to alleviate some of the burden placed on patients and family members by presence of irritability and aggression in an already disabling condition.

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Treatment of Hemiballismus

58

Oksana Suchowersky and Aakash Shetty

Case

A previously healthy 65-year-old-woman was seen in the emergency room with abrupt onset of involuntary movements involving the right side of the body, which were interfering with daily activities. Blood work showed normal CBC, electrolytes, calcium, and HgA1C. MRI of the brain (including DWI imaging) did not show any acute infarctions or structural lesions, but the etiology was thought to be most likely vascular. The patient was started on tetrabenazine 12.5 mg bid and was asked to follow up in 1 month. She was also assessed for stroke risk factors.

Examination (Video 1) demonstrated random continuous irregular movements involving the proximal and distal right extremities, face, and trunk. These movements are characteristic of chorea with occasional larger amplitude movements signifying hemiballismus.

Discussion

Ballism is derived from the Greek verb meaning "to throw "and is characterized by large-amplitude random, continuous, coarse flinging movements which are predominantly proximal. When these movements involve one half of the body, it is referred to as hemiballismus.

Chorea is characterized by involuntary abrupt, brief, nonsustained, jerky, irregular movements that flow randomly from one body part to another and can be associated with motor impersistence and "hung-up" reflexes. Hemichorea and hemiballismus are a spectrum of the same movement disorder and together characterized as hemichorea/hemiballismus. They share common etiologies, pathophysiology, and management.

In 1865, Jules Luys was the first physician to suggest lesions of the subthalamic nucleus (STN) result in hemiballismus. The relationship of hemiballismus and the STN was re-established by J.P. Martins in 1927 by reviewing case series where 11 of 12 patients with hemiballismus had lesions in the STN. However, with the advent of MRI scanning, recent reports have shown multiple structures may be involved in hemiballismus. In the review by Postuma and Lang in 2003, only 24% of hemiballismus cases were secondary to a STN lesion, while 53% of the patients had lesions in the thalamus, basal ganglia (outside of the STN), white matter, and even cortex. Of interest, 20% of the patients did not have any demonstrable lesions on imaging.

The most common structural lesion causing hemiballismus/hemichorea is vascular. Listed in Table 58.1 are other less common causes, such as tumors, infections, and demyelination. HIV is another important infectious cause of hemiballismus secondary to toxoplasmosis.

Nonketotic hyperglycemia is the most common nonstructural etiology of hemiballismus/hemichorea and typically seen in Asians, the elderly, and women. This is usually associated with T1W hyperintensities in the basal ganglia along with restriction on diffusion-weighted imaging (Fig. 58.1). A variety of autoimmune disorders can present with chorea and/or ballism, which occasionally is asymmetric or unilateral. This is not uncommonly the case in Sydenham's chorea.

It is important to remember that a variety of medications (see Table 58.1) can result in generalized chorea/ballism, which can be predominantly unilateral in patients having predisposing asymmetrical or unilateral structural damage to the basal ganglia.

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Table 58.1 Causes of hemiballismus/hemichorea

Structural lesions	Nonstructural lesions
Vascular	Hyperglycemia
Hemorrhage	Hypoglycemia
Vascular malformation	Hypocalcemia
Ventriculoperitoneal shunts	Hyperthyroidism
Neoplasms (primary, metastatic)	Sydenham chorea
Infections	Antiphospholipid syndrome
Tuberculomas	Systemic lupus erythematosus
HIV (toxoplasmosis)	Influenza A infection/ immunization
Abscesses	Drugs (levodopa, phenytoin, lamotrigine, pentamidine, cocaine, oral contraceptives)
Demyelinating plaques	
Trauma	

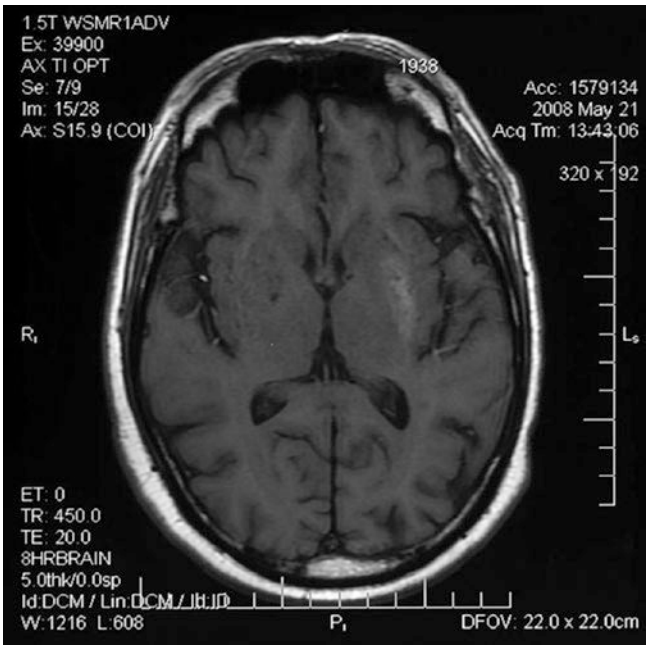

Fig. 58.1 This T1-weighted MRI from another patient demonstrates abnormal signal in the right putamen in a patient with acute left hemiballismus due to hyperosmolar hyperglycemia

Conventional teaching about the classic model of basal ganglia physiology consists of direct (facilitating motor movements) and indirect (inhibiting motor movements) pathways. The STN plays a vital role in the indirect pathway by providing excitatory signals to the globus pallidus interna (GPi), thereby reducing the thalamocortical outflow and inhibiting motor movements. This model has a number of limitations as the STN is not the only anatomical site responsible for hemiballismus. Secondly, lesioning of GPi should worsen hemiballismus but instead improves it, and finally, STN deep brain stimulation (DBS) commonly performed for Parkinson's disease is rarely complicated with hemiballismus. Current studies suggest that the cause of hemiballismus is the result of an altered firing pattern in the GPi, with intermittent bursts and pauses. The pauses appear to be correlated with the hemiballistic movement.

Initially, hemiballismus was thought to have a poor prognosis as it was associated with the development of heart failure, particularly with structural lesions. However, it is now recognized that the condition is self-limiting in most cases and usually responds well to treatment.

Management begins with identifying the underlying cause, with appropriate blood work and imaging, and medical intervention. In cases of hyperglycemia, correction of blood sugar may lead to improvement or even disappearance of the movement disorder. At the same time, care should be taken to prevent injuries to the affected flinging limbs by padding the involved limb and railings. Complications, such as rhabdomyolysis and dehydration, are rare, but preventable and careful monitoring is recommended.

Medical treatment to reduce the hemiballismus involves dopamine receptor blockade or dopamine depletion. Dopamine depleters, such as tetrabenazine or one of the new VMAT2 inhibitors, are used as a first-line treatment and generally considered both fairly safe and efficacious. The patient should be warned of the risk of depression and akathisia. The development of Parkinsonism, particularly with longer-term use in the older population, should be monitored. We recommend starting tetrabenazine with 12.5 mg bid and gradually escalating the dose to 50–100 mg per day in divided doses.

For more severe hemiballismus, or a poor response to tetrabenazine, the atypical antipsychotics, such as risperidone, pimozide, or olanzapine, can be used. The older typical neuroleptics, such as haloperidol, are no longer recommended due to higher side effect profile. All of the antipsychotics carry a risk of tardive dyskinesia. In cases where side effects limit the use of these medications, anticonvulsants such as levetiracetam, topiramate, and valproic acid can be tried. Clonazepam can also be added in the acute stages.

As hemiballismus is typically self-limiting and gradually decreases to chorea before disappearing within 3–12 months of onset, it is important to regularly reevaluate the severity of the movement disorder with tapering of the medications.

Surgical management is reserved for extreme cases of hemiballismus not responding to medical management. Previously, lesioning of the ventral intermediate thalamus (Vim) or GPi was undertaken, but DBS of the GPi or Vim is now more common. Very rarely, anesthesia is required in extreme cases.

In summary, hemiballismus is an uncommon but well-described movement disorder typically encountered in the emergency room. Stroke and hyperglycemia are the most common etiologies. Management first involves identification

and treatment of the underlying etiology and prevention of injury. Hemiballismus typically responds well to treatment with dopamine depleters or dopamine receptor-blocking agents. For patients with intractable hemiballismus, lesional surgeries or DBS involving the GPi can be considered. Hemiballismus carries a favorable prognosis with spontaneous remission in many patients.

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Treatment of Sydenham's Chorea

59

Francisco Cardoso

Case

An 8-year-old girl suddenly developed pain and swelling of right wrist, knee, and ankles associated with a movement disorder in all limbs. One week later, the patient was unable to speak, and as a result of worsening of the involuntary movements, she became bedridden. Twenty days after onset, she was admitted to the Movement Disorders Clinic of the Federal University of Minas Gerais. The most important findings on examination were anarthria, severe and generalized chorea, decreased muscle tone, as well as inability to walk and even sit without assistance. Her medical history was remarkable for the presence of repeated episodes of sore throat, and 2 years before, she had developed arthritis, carditis, and chorea. At that time, she was diagnosed with rheumatic fever and Sydenham's chorea (SC). The chorea had been controlled with haloperidol, but the patient did not comply with penicillin prophylaxis. The diagnosis of the current episode was recurrence of SC, this time expressed by chorea paralytica.

During the admission to treat the episode of chorea paralytica, cardiac evaluation (echocardiography) showed mild mitral insufficiency. Lab work-up included antistreptolysin 336 UI/mL (normal range less than 250), C-reactive protein 7.45 mg/mL (normal range less than 8), and sedimentation rate 35 mm. One week of 30 mg/kg per day of valproic acid failed to improve the patient. Because of the severity of the chorea, this anticonvulsant was withdrawn and she was started on pimozide (4 mg twice a day). Fifteen days after her admission, the patient was discharged. At that time, there was still anarthria, mild chorea, and severe decreased muscle tone, but she was able to sit and walk if assisted. On a follow-up visit 3 weeks later, she was still on 8 mg per day of pimozide; the main clinical findings were dysarthria, decreased verbal output (she stated 6 animal names in 1 min. Normal range for her age and educational level is 11 to 13), and moderately decreased muscle tone, but no chorea was noticed, and she sat and walked unassisted. Eight weeks later, the patient was chorea-free and a gradual decrease of pimozide dosage was started. The neuroleptic was discontinued 4 months after discharge. Forty-two months after the episode of chorea paralytica, the patient remains without neurologic abnormalities and receiving regular penicillin prophylaxis (120,000 IM of benzathine penicillin every 21 days).

Discussion

Sydenham's chorea is one of the major features of acute rheumatic fever. The pathogenesis of this condition involves a mechanism of molecular mimicry where infection with beta-hemolytic *Streptococcus* in predisposed individuals triggers the development of antibodies that cross-react with basal ganglia epitopes.

The first issue to be considered in this case is how to establish the diagnosis of SC. Despite the widespread belief that this condition is limited to underdeveloped areas of the world, there is plenty of evidence showing that SC remains the most common cause of acute chorea in children worldwide, including in the USA. There is no specific biological marker of SC. Even the anti-basal ganglia, also known as anti-neuronal antibodies, do not have a role in daily clinical practice since they are neither specific nor commercially available. Thus the diagnosis relies on meeting the modified Jones criteria of rheumatic fever. In brief, in addition to acute onset chorea, alternative causes of chorea must be ruled out. In up to 80% of individuals with SC, there are other features of acute rheumatic fever, such as carditis and arthritis. For this reason, it is mandatory to order cardiac evaluation, including echocardiography, in patients where there is suspicion of SC. One should bear in mind, however, that in 20% of patients, the presentation is isolated chorea. In this group,

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it is particularly important to rule out alternative causes of chorea. The most common differential diagnoses are systemic lupus erythematosus and vascular lesions. Genetic conditions, such as benign hereditary chorea and mutations of the ADCY5 genes, may also cause chorea in children. However, not only are they quite uncommon disorders but also have a chronic course. The differentiation may not be always straightforward since 30–50% of individuals with SC may persist for 2 or more years, and recurrence, such as in the case herein reported, is observed in 20% of individuals. This patient also had chorea paralytica, a unusual presentation where there is a severe decrease of the muscle tone that prevents the individual from walking or even standing unassisted. William Gowers originally described this form, observed in 8% of patients with SC. Rheumatic chorea also includes non-motor features. In this case, there was decreased verbal fluency but many studies describe other prefrontal signs as well as behavioral changes such as obsessions, compulsions, hyperactivity, and attention deficit disorder.

The recommendations for treatment of SC are based on small series of cases, single-case reports, and opinion of experts. Unfortunately there are no published studies that meet rigorous criteria of evidence-based medicine. Moreover as there are no approved treatments for SC, the guidelines discussed in this chapter are off label.

Anticonvulsants, particularly valproic acid (30 mg/kg per day), are considered the first-line treatment for acute chorea in SC. These agents have an antichoreic action less potent than dopamine receptor blockers. Nevertheless, they are the first choice because of the high risk of development of extrapyramidal side effects (e.g., acute dystonia, tremor, and parkinsonism) of neuroleptics in SC subjects. Another issue is the potential for these agents to induce cardiac arrhythmias requiring EKG monitoring during their use. Neuroleptics are thus reserved for situations where there is failure of treatment with anticonvulsants. Some clinicians also use neuroleptics as first choice for severe cases such as chorea paralytica where it is less likely that valproic acid or other antiepileptic agent will provide meaningful benefit. As to the choice of neuroleptics, the clinician should choose an agent that provides significant blocking of dopamine D2 receptors but with a more acceptable profile of side effects. Taking into account these criteria, there is a tendency not to use haloperidol, given its high risk of unwanted motor effects, and to avoid atypical neuroleptics such as quetiapine and clozapine for lack of meaningful D2 action. In the Movement Disorders Clinic of the Federal University of Minas Gerais, the standard practice is to use risperidone, which has an acceptable risk-benefit ratio. In the reported case, pimozide was used because of the severity of the chorea, requiring an agent with more powerful D2-blocking property than risperidone. Chorea in SC is a self-limited problem with a tendency for spontaneous remission in the majority of patients. Therefore, after 4 weeks of control of the movement disorder, the antichoreic agent should be gradually withdrawn.

Since SC is an autoimmune movement disorder, it is fair to consider the use of immunosuppressive agents. There is one controlled small study suggesting that oral prednisone modestly shortens the time to reach remission of chorea. Small series of cases suggest that intravenous (IV) methyl prednisolone is effective in inducing remission of chorea in severe cases refractory to anticonvulsants and neuroleptics. There are also reports of a few patients who were successfully treated with IV immunoglobulin and even plasmapheresis. For most experts in the field, the role of these latter measures in the management of SC remains uncertain at best. At the Movement Disorders Clinic of the Federal University of Minas Gerais, corticosteroid treatment is reserved to the rare patients who fail to improve with valproic acid and neuroleptics.

Patients with SC are at risk of developing recurrence of rheumatic fever, particularly carditis, its most disabling feature. For this reason, antibiotic prophylaxis is recommended to prevent recurrent *Streptococcus* infections that can lead to new bouts of rheumatic fever. Evidence suggests that this is effective to avoid carditis, but data are less compelling as to prevention of SC. Nevertheless the guideline of the World Health Organization states that this should be done with intramuscular benzathine penicillin every 21 days. A contentious issue is the length of the prophylaxis. Most authorities agree that this should remain in place until age 21 years for people living in areas where rheumatic fever is endemic. In other parts of the world, it is less clear with most clinicians recommending a 6-month use of penicillin. Patients who are allergic to penicillin should be treated with sulfa.

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Part VII

Tics

Treatment of Tourette Syndrome: Medical Therapy

60

Donald L. Gilbert

Case

A 12-year-old prepubertal boy in the sixth grade was seen in late spring for motor and phonic tics first noted intermittently between the ages of 3 and 5 years and present continuously since age 7 years. Current tics included blinking, moving his eye gaze to the left then right, a full facial grimace, rotating his head and neck, bobbing his head forward very quickly, extending both arms followed by clenching his fists, sniffing, grunting, slurping, humming, and making a rooster sound. He acknowledged that he "does" his tics but said, "my brain makes me do it." He described some itching in his throat, briefly relieved by performing his phonic tics, and some tension in the muscles around his eyes, neck, trunk, and forearms preceding motor tics. The rooster sound tic may be repeated if he does not do it "just right." Although the parents were worried for years that tics would result in teasing and bullying, the boy said his peers did not consistently notice or tease him until age 11. The parents stated that the tics currently occur all waking hours, but more frequently if he is nervous, for example, when speaking in front of his class and in the evenings with family when watching TV. During soccer season, the tics subsided when he was dribbling the ball or engaged in a play but occurred frequently when he was on the sideline. They have not interfered with his activities of daily living or participation in gym or sports but slowed down his reading and completing homework this school year. The boy said he tried to hide his tics at school but that this was becoming impossible.

Parents also acknowledged that he was inattentive, easily distracted, and disorganized at school, with declining grades as school became more complex. They described him as impulsive, talkative, and socially immature compared to his peers. His parents denied excessive anxiety or obsessive-compulsive behavior but noticed some preferences for symmetry and even numbers. Review of systems was notable only for difficulty with sleep initiation most nights due to tics and rumination. His medical history was unremarkable and the family history was notable for his mother having obsessive-compulsive tendencies and a maternal uncle with childhood tics.

On examination, he made good eye contact and had normal speech and prosody. His facial and phonic tics subsided during the cranial nerve exam. Motor examination was notable only for mild clumsiness on sequential finger tapping. There was no weakness, spasticity, or hyperreflexia. There was no chorea, dystonia, tremor, or parkinsonism. The remainder of the examination was normal except for the presence of frequent tics. It was explained to the parents that Tourette syndrome is a clinical diagnosis and that blood testing, EEG, and brain imaging are not needed or helpful. Rating scales for tics (Yale Global Tic Severity Scale) and ADHD (Vanderbilt Scale) were completed with both tic and inattention scores in a moderate to marked range.

Since the parents and child both reported that tics were disruptive to classroom and home life and interfered with his concentration and speaking, treatment options were discussed. Medication options were outlined: (1) alpha 2 adrenergic agonists like guanfacine and clonidine; (2) "other" medications like topiramate; and (3) dopamine 2-receptor blocking agents like fluphenazine, haloperidol, pimozide, risperidone, aripiprazole, and ziprasidone. Information on Comprehensive Behavioral Intervention Therapy (CBIT), which combines (1) "awareness training" for tics and premonitory urges, (2) "competing response" implementation and practice, (3) social support, (4) function-based assessment and interventions, (5) education, and (6) relaxation was also discussed. The family expressed concern about access to behavioral therapy, as they were from a small town. They were also concerned about the possibility of short- and long-term side effects of brain medications. As it was nearly summer, and therefore school disruption from tics would

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soon not be an issue, I advised the parents to review the information provided on medications and behavioral treatments, to read more at appropriate ".gov and .org" websites such as the Tourette Association of America (www.tourette.org), to avoid websites with questionable experts selling unproven therapies, and to return in the fall.

The parents did not schedule a follow-up, but after a summer of mild tics, they called the first week of seventh grade because the phonic tics had increased markedly. They were considering home schooling him to help his tics. I encouraged the family to keep him in school and to work with him to gain the self-confidence to acknowledge the Tourette diagnosis to his peers. I also prescribed guanfacine, which is generally well tolerated and sometimes helps with both tics and ADHD. I prescribed 1 mg guanfacine tabs, starting at 1/2 tab at bedtime and increasing by 1/2 tab every 3 days to a target dose of 1 mg AM and PM. As he did not develop any tiredness or lightheadedness, this dose was continued for 2 months until a follow-up visit. At that time, his tics had improved about 25% on the tic scale, and his rating scale score of ADHD symptoms was also diminished.

Discussion

Tics are common in a wide variety of developmental and psychiatric conditions in children. Tourette syndrome is diagnosed when tics develop in childhood and are sustained for greater than 1 year, including multiple motor and at least one phonic (vocal) tics. Typically tics emerge before the age of 10 and wax and wane with multiple tics that migrate in location over time. Boys are affected three times as often as girls, and tics may peak between the ages of 9 and 14, a socially challenging time. The diagnosis is clinical, and it is essential to distinguish tics from other similar movement disorders including complex motor stereotypies, fidgeting, other impulsive behaviors, myoclonus, and drug-induced movement disorders. These distinctions are based on phenomenology and do not require blood tests, EEG, or neuroimaging. Co-occurring ADHD and/or OCD symptoms are present in the majority of children whose parents seek medical attention for their child's tics. It is important for practices aiming to treat persons with Tourette syndrome to have plans in place to address ADHD, OCD, or other developmental disorders or to refer to collaborating psychologists or psychiatrists.

In childhood, ADHD symptoms often precede tics. It is not rare for families to believe that stimulant ADHD medications prescribed for ADHD either caused tics or made tics worse. However, often this is a temporal coincidence, not causal. Controlled clinical trials in children with both ADHD and TS show that in most cases, stimulants improve ADHD symptoms without exacerbating tics. In some children, particularly those who are anxious or exhibit some symptoms of autism spectrum disorder, side effects of stimulants are more common.

For pharmacological treatment of tics, I generally start with guanfacine 1 mg tabs, 1/2 tab at bedtime or in the afternoon increasing by 1/2 tab every 3 days to a target dose of 1 mg AM and 1 mg PM. This may be helpful for ADHD symptoms as well. If guanfacine fails, I will generally prescribe topiramate 50 mg two times per day, starting with 25 mg at bedtime and titrating up by 25 mg weekly. This may also be helpful for prevention of migraines, which are more common in children and adolescents with TS. If these agents are ineffective, any of the high-potency typical or atypical dopamine receptor blocking agents can be used. I will use up to 4 mg daily of fluphenazine or risperidone. For overweight or obese children, I may prescribe ziprasidone 20 to 40 mg daily. Stimulant medication for ADHD may be used concurrently and my preference is to use long-acting forms of methylphenidate with a starting dose of 0.3–0.5 mg/kg/day and maximum dose under 1 mg/kg/day. For distressing and functionally impairing OCD or anxiety, I usually prescribe either citalopram, starting with 10 mg daily, or sertraline, starting with 25 mg daily. Sleep initiation and maintenance difficulties are common in this group of kids. I start with sleep hygiene recommendations as this is often a big problem. If that is unsuccessful, diphenhydramine 12.5–50 mg or clonidine 0.05–0.2 mg at bedtime may be helpful (Table 60.1).

Fortunately, for many children with tics, even those meeting criteria for Tourette syndrome, education about the

Table 60.1 Suggested pharmacological treatments for tics in Tourette syndrome

Medication	Common dosing regimen	Common, possible side effects
Guanfacine 1 mg	Start with 0.5 mg at bedtime, increase by 0.5 mg every 3–7 days to target dose of 1 mg po BID	Light-headedness, fatigue
Topiramate 25 mg	Start with 25 mg at bedtime, increase by 25 mg every 7 days to target dose of 25 to 50 mg BID	Fatigue, word-finding problems, tingling
Risperidone 0.5, 1, 2 mg	0.25 to 0.5 mg at bedtime, increase by 0.25 mg every 3–5 days to target dose of 1–4 mg once daily or divided BID	Weight gain, anxiety, somnolence, dystonic reaction, akathisia
Aripiprazole 2, 5, 10 mg	Start with 1 mg at bedtime, increase by 1 mg every 3–5 days to target dose of 2–10 mg once daily or divided BID	Weight gain, anxiety, somnolence, akathisia
Ziprasidone 20 mg tabs	Start with 20 mg at bedtime, increase by 20 mg every week to target dose of 20–80 mg once daily or divided BID	Somnolence

syndrome and how to manage it socially are all that is needed for the tics. However, in the presence of tics causing self-injury, pain, or substantial social or functional interference, treatment is reasonable. In children with TS, it is vital to obtain perspectives of both the child and parent. A realistic expectation is for reduction in symptoms to a manageable level. Ideally, the clinician should track symptoms using validated rating scales, such as the Yale Global Tic Severity Scale, the Child Yale-Brown Obsessive-Compulsive Disorder Scale, and the Vanderbilt or Dupaul ADHD rating scale, and also address functional interference within school, home, and social domains. Close collaboration with patients and families around issues of treatment choices and benefits, waxing and waning symptoms, treatment costs and side effects, and social and psychological sequelae is important for producing more satisfactory long-term outcomes. A small fraction of pediatric patients go on to have so-called malignant TS with severe and worsening tics in adulthood. Severe tics involving one or several muscles can be treated with botulinum toxin. In some such rare cases, deep brain stimulation has been performed to reduce symptoms.

Suggested Reading

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Treatment of Non-motor Symptoms in Tourette Syndrome

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Jorge L. Juncos and Jagan Chilakamarri

Case I

This 35-year-old right-handed male nurse practitioner sought consultation for possible deep brain stimulation (DBS) for severe tics. He was diagnosed with TS at age 12 and was first seen at the Emory Movement Disorders Program about 10 years ago when the tics were moderately severe. He was lost to follow up until the summer of 2016. In the interim he had difficulty tolerating multiple medications mean to treat the motor and phonic tics. In spite of the poor tic control, he was able to remain employed and married. ADHD-related symptoms were first detected in elementary school but were never treated due to the presence of tics and an initial bad experience with stimulants. He is intelligent and well-adjusted even after having to make multiple adjustments in his life to accommodate the TS symptoms. Over the last 10 years, the tics increased gradually as life- and work-related stressors increased.

Failed treatments included multiple anti-tic medicines and medicines for generalized anxiety disorder (GAD) and obsessive-compulsive disorder (OCD). These included haloperidol for tics and selective serotonin reuptake inhibitors (SSRIs) for OCD. The latter resulted in increased anxiety and behavioral activation. As a teenager, methylphenidate treatment for ADHD aggravated the tics and was stopped. He has a positive family history of essential tremor (ET), and shortly thereafter he developed the first symptoms of ET. Beta-blockers provoked severe orthostatic hypotension, and primidone produced unacceptable daytime sedation. ET thus remains a significant source of disability. There is no history of substance abuse or other medical illness.

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By 2016 the tics had escalated to intolerable and disabling levels. Earlier that year he received a trial of olanzapine (7.5–15 mg) that led to unacceptable weight gain, headaches, and significant daytime sedation; it had little effect on the tics. In spite of sleeping 8 h at night, he was waking up tired every morning. Obstructive sleep apnea was diagnosed via polysomnography and has been on CPAP since. Outstanding sleep issues include persistent tics during sleep and the untreated ADHD symptoms which make it difficult for him to 'settle down' mentally in order to induce sleep and GAD which made it difficult for him to stop worrying about work and life, and most of the time he is not sure what he is worried about.

On examination, the patient is a personable, intelligent, articulate, and attentive young man. He was anxious about his tics and the tremor and how they affect his work (e.g., placing central lines, intubating, etc.). He is not depressed or moody. The tics consisted of loud snorting, throat clearing, and tongue thrusting movements and jerky leg motions. These were brisk and frequent (Q30 s). There were no symptoms to suggest restless leg syndrome or neuropathy. The tics improved but did not disappear during sleep. He gave the impression of always being in a *hyper-aroused* state. That is, his body language conveyed a sense of being too "energized," "vigilant," and impatient. He was surprised to find this out when his wife brought it up when asked by the examiner who concurred with his wife. Beside the tics and tremor, there were no other motor signs of hyperactivity. Behaviors at home included compulsive arranging, cleaning, and getting stuck before starting a project. The Yale Global Tic Severity Scale (YGTSS) score was 36/50, and the functional disability score was 20/50 (lower scores are better).

The rest of the motor exam revealed significant kinetic > postural tremors which have been frequently aggravated by medicines used to treat the tics and the anxiety. Surprisingly, the tremor had not worsened since the introduction of fluphenazine upon his return to Emory (see below). There are no other extrapyramidal symptoms (EPS) such as akathisia,

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chorea, dystonia or rest tremor. The remainder of the neurologic exam was normal.

At Emory he was started on fluphenazine and titrated to a dose of 6 mg/day in two doses. Clonazepam was added (0.5 mg in am and 1.5 mg QHS) to reduce anxiety and worry related to OCD symptoms and to improve sleep. After a month of this combination, the anxiety and the tics significantly improved. Tics went from severe to moderate (YGTSS score of 36 to 24/50). The most impressive results, however, were 50% reductions in anxiety and OC symptoms. ADHD symptoms were only minimally affected. Unfortunately this drug combination continued to produce EDS. Normally we monitor ADHD symptoms with standardized scales, several of which have been abbreviated for effective use in clinic, e.g., the Conners' Adult ADHD Rating Scales, the Brown Attention-Deficit Disorder Scales, the ADHD Rating Scale-IV, and the Adult ADHD Self-Report Scale-V. Most of these scales also have a pediatric version. We also rely on the history, on spousal and parental reports, and when available on school or work reports. In this case his wife was also medically trained.

Because of persistent EDS and weight gain and mindfulness of the prior adverse reaction to methylphenidate, we began treatment for ADHD symptoms slowly introducing dextroamphetamine/amphetamine salts at a dose of 10 mg extended release upon awakening. In 4 weeks we added another 10 mg dose at 10 am. With this there was a resolution of daytime sedation, significant improvement in attentional symptoms at work, and an additional marked improvement in tics (final YGTSS = 10/50 for motor tics and 8/50 for functional tic-related disability). There was also additional improvement in anxiety. On the last examination, there was no detectable anxiety and tolerable levels of residual OCD. By then there were no phonic tics and only a rare and mild motor tics on exam. The tremor was not aggravated by the amphetamine salts or by the final dose of fluphenazine (6 mg/d). In time the amphetamine salts started to dampen his appetite and decrease his weight. The ET remained a major problem.

Within a year he underwent bilateral thalamic VIM-DBS (ventro-intermediate nucleus of the thalamus-deep brain stimulation) which dramatically improved the postural/kinetic tremor (>60% improvement on clinical exam) without any effect on the tics or other symptoms. DBS for TS is no longer being considered.

Discussion

Though tic severity was the major problem in this case, in retrospect, much of the tic severity was fueled by untreated ADHD, anxiety and OCD/OC behaviors (OCBs), and the stress of managing them. Like many of these patients, our patient, although feeling stressed all the time, could rarely point to the exact source of stress when not at work. Thus suspecting the presence of these conditions in a patient with TS, and with the help of an observant wife, we began to open the door to opportunities to expand and improve the results obtained with previously futile tic-reducing strategies now capable of improving the overall quality of life beyond tic control.

ADHD symptoms are not difficult to identify when a hyperactive, impulsive child has difficulties staying on task in school. ADHD symptoms can be difficult to detect in intelligent and industrious persons without hyperactivity or impulsivity. Like this patient, many adults now grew up at a time when there was little awareness of this diagnosis. Symptomatic patients were often regarded as scattered and sloppy. The diagnosis is still difficult to make in adults given the misconception that most forms of ADHD are outgrown in adulthood. On the contrary, we now know there are a number of ADHD phenotypes that will not improve and may worsen with aging. Adults and children often rationalize their symptoms as something else, they tend to have poor self monitoring making them poor reporters of their conditon. In TS, another obstacle to addressing ADHD symptoms is the warning that comes with the label of stimulants indicating that they can aggravate tics. This inhibits many parents and clinician from treating ADHD. Anxiety associated with ADHD is often attributed to other forms of anxiety including that co-existing GAD and OCD which are common in TS. ADHD-associated anxiety is more episodic compared to the more steady anxiety of GAD. ADHD instead presents with a more steady state of *hyperarousal* with low-grade, chronic impatience and irritability with episodic rage disproportional to any trigger. This is similar to the "meltdowns" seen in GAD patients with panic but of shorter duration. Other symptoms of ADHD include chronic insomnia, daytime fatigue, and moodiness, all of which can fuel tics. A less appreciated source of stress in ADHD with tics is the added effort and constant vigilance required to control tics in public. This puts an added burden on the already "overextended attentional bandwidth" of these patients. Intrinsic to ADHD is poor self-monitoring of their own emotional state which can cause additional stress from conflicts in social interactions, marriage, and work.

Introduction of stimulants in TS can indeed aggravate tics particularly if the introduction is done when the tics are out of control. However, there are a number of double-blind, placebo-controlled studies indicating that treating ADHD in patients with TS will lead to overall improvement of ADHD symptoms and tics (see Allen et al., Benaschewski et al., and Hoeskstra et al. in Suggested Reading). In case I, the introduction of stimulant was successful compared to his earlier experience, in part because the tics were already reasonably well controlled. Even in successfully treated cases of ADHD

with tics, the initial titration of the stimulant may lead to a transient increase in tics that can be managed by slowing the titration rate and limiting the maximum dose as needed. In children it is important to validate the parent's concern over worsening tics. This has to be addressed with reassurance and close monitoring.

In retrospect, we learned from the patient that having grown up with untreated ADHD led to problems with self-esteem from perceived defects in his academic-professional competence. There is evidence that this can be avoided with a more timely treatment ADHD. In our view, the ultimate success in treating ADHD was instrumental in allowing this patient to revise his original intention to undergo DBS for the treatment of tics. Interestingly, the indirect *anxiolytic* effect of stimulant in ADHD could not be reproduced solely by the introduction of fluphenazine.

Case II

The patient is a 16-year-old high school student with motor and phonic tics since age 6. She was first diagnosed with TS at age 8 and has been followed in this clinic since the spring of 2016 when she was first started on medications. Two years ago when she started high school, the tics went from manageable to moderately severe. Until then, tics were a minor issue thanks to her resourcefulness and to a supportive family. There is a family history of tics and GAD with mild OCD traits in the mother.

Her tics involve the eyelids (frequent blinks), face (forceful squints), neck and head tossing, and brief tightening of truncal muscles. She has frequent phonic tics consisting of loud squealing sound, grunts, and breathy sounds. The phonic tics are the main source of tic-related disability. She has no vocal tics (e.g., words, phrases) or coprolalia (utterance of obscene words). Her motor tics are far easier to disguise and suppress than the phonic tics. Tics in general are present every hour and become moderately intense with minor stress. They are accompanied by somatic premonitory urges temporarily satisfied by the tics. Her baseline score on the Yale Global Tic Severity Scale (YGTSS) was 26/50. She scored 20/50 in the global impairment subscale, which is in the moderate-severe range. The rest of the motor examination was normal.

She is an excellent student and athletic and has normal intelligence. She has minor signs and symptoms of ADHD, inattentive type. These consist of periodic "daydreaming" and procrastination. There is no hyperactivity or impulsivity. Because of her excellent school work and proclivity for perfection (from the OCD traits below), her academic performance had not suffered until recently. Inattentiveness has been compensated by meticulousness and by spending long hours on homework. These compensatory mechanisms started to break down shortly before coming to Emory and became an additional source of unrecognized anxiety.

During the initial interview, the patient denied symptoms of anxiety, worry, obsessions, or compulsions (OC behaviors/OCD). The mother concurred with this assessment. Apparently over the years, the family had learned to accept behaviors that we ultimately identified as compulsive (see below), as acceptable, and as normal for her. Only through the administration of standardized questionnaires (such as YBOCS and anxiety questionnaire for adolescents), and through the description of concrete examples of such behaviors, did the mother begin to recognize them as connected to the OCB symptoms and potentially relevant to the current tic flare-up. With the help of the above, the mother began to recall other OCB behaviors she had seen in her daughter. Ultimately the patient was able to describe ill-defined feelings of discomfort when certain sensory or cognitive conditions were not met or when certain actions did not "feel just right" nor met an "an unspoken standard." Examples included not being able to eat with metal utensils; only plastic utensils would do. She needed to know that certain possessions, electronics and items of clothing, were in a predetermined location in the house. If moved or lost, she would find it difficult to impossible to continue her other activities until the item(s) in question were found and returned to their assigned location. Other conditions that could trigger this virtual freezing of action included perceived asymmetry, unevenness of lines and edges in objects in her line of vision. They described a semiautomatic link between these perceptions and an automatic "internal churning" that then drove the rituals and compulsions. The rituals had to then correct these *imperfections* in order to alleviate the churning. Most of the time, particularly when stressed, she found very difficult to resist the unspoken rules and mandates that ruled her emotions. The compulsive actions were an attempt to restore "order," and when successful, provide effective, albeit temporary, relief to the churning. Having identified these unspoken rules and cognitive churning, the patient was still unable to see the importance and the connection between these symptoms and the tics. The symptoms were, after all, an accepted part of her life rather that a source of distress. Similarly, the family had learned to accept the repetitive behaviors as a "non-issue" not worthy of attention. As a child the patient was barely aware of the above internal discomfort that we now call *churning* and which is provoked by any perceived violation of the unspoken rules (e.g., do not eat with metal utensils) or by violation of the symmetry standards. These perceptions and actions had little to no language attached to them and were thus difficult to share with anyone. We interpret the internal feeling that she describes *churning*, the emotional/cognitive-laden equivalent to the somatic urges that antecede motor tics. Finally, the patients had no history of depression,

suicidality, or psychotic symptoms. She is sociable with no signs of autism spectrum disorder.

At the end of the initial evaluation, the patient and family were still anxiously focusing on the tics. We thus started treatment with a dopamine blocker, fluphenazine at 1 mg bid. This led to a reduction in the YGTSS motor score from 24 to 16 in 3 weeks. Once the tics were regulated, she experienced less fatigue and was able to complete the semester successfully. Fluphenazine also reduced the anxiety caused by the tic-related disruptions in school and by the need to constantly suppress them in public. There was also a slight reduction in the anxiety associated with the low-grade feeling of inadequacy brought on by the ADHD symptoms (i.e., procrastination and increased time to complete tasks).

To target anxiety and OCBs, venlafaxine extended release was added. At 150 mg/day tic severity decreased to a YGTSS score of 12. There has since been a dramatic change in her outlook on life and her attitude toward school. The original automatic negative thoughts and tendency to *catastrophize* with any rule violation of perception that deviated from "the expected" were reduced by at least 50%. Comprehensive behavioral therapy for TS (CBT) lead to additional improvement in tics and further reductions in the sensory experiences associated with OCBs (see above). One of the first strategies of the psychoeducational approach of CBT is to make the patient and family understand the dynamics of tics and how they are exacerbated by anxiety and family-school stressors. CBT helps address the various unconscious triggers of anxiety (e.g., unwritten rules and expectations). In the case of our patient, the long-term goal (months to 6–12 months) was to determine if CBT, once mastered [with or without follow-up cognitive behavioral therapy], was sufficient to eliminate the ongoing need for fluphenazine for the treatment of tics. ADHD symptoms are being investigated through her school. If significant, this may open another treatment avenue for later consideration. Thus far she has had no problems with drug-induced side effects and continues to do well scholastically and socially.

Discussion

It is particularly difficult to identify comorbid symptoms in TS during a busy movement disorder or psychiatric clinic. This is particularly true when the symptoms are not explicit and visible or when they are deemed as unimportant by the patients and thus not worth mentioning. Sometimes well-intended but uninformed parenting and school systems help facilitate maladaptive behaviors in response to tics. Examples include common attitudes at home like "all the problems are due to the tics" and "he cannot help the tics" or in school, "the tics are just another tool he/she uses to manipulate," etc. So, in addition to aggravating tics, comorbidities have additional chronic, debilitating effect on self-esteem and drain normal coping skills.

Note that the above OCD-related symptoms were elicited only through the repeated use of standardized questionnaires and with the use of multiple examples of similar behaviors and by recruiting the help of a parent. With the use of these extended interviews, the mother finally recognized the OCD symptoms and their connection to tic severity. This allowed her to point out these behaviors to her daughter using clear examples of her own. It took a few weeks of CBT before the patient was able to link the above lifelong churning sensations, the *unimportant* compulsions, and the level of tic severity.

We conclude that in addition to the premonitory somatic urges associated with tics, this patient exemplifies a second type of premonitory more *cognitive urge* linked with compulsion in TS – the self-described churning. We explain this as an emotional-cognitive, low-grade but draining internal feeling of being ill at ease. The feeling is difficult to articulate and is more complex than the premonitory urge linked to tics. It is triggered by any violation of unspoken and fuzzy rules and expectations that must be met in TS-linked OCD in order to avoid the equally fuzzy and inarticulate consequences, mostly a heightened anxiety that then drives compulsions. In a child, a loving, nonjudgmental family can help teach adaptive coping skills to deal with these anxieties even without understanding all the details. Through example and support, they can help a child learn how to dissipate this internal energy effectively with techniques spelled out in CBT manuals (see Odette et al. in selected reading). The family can help shield and channel that *churning* energy before it becomes a fixed maladaptive pattern of behavior. Once outside the home environment, from high school to the workplace and beyond, these conditions are more difficult to address and correct without focused therapy or medication. Fortunately CBT and medications are equally effective in adults.

Common themes in TS-associated OCD are symmetry, counting, fear of losing control, intrusive sexual and other thoughts, etc. OCD symptoms in people without tics tend to be more explicit. Examples of these are fear of contamination and phobias, fear of heights, fear of open places, and religious and targeted obsession (see Cath et al. under Suggested Reading). In the OCD of TS, language and thus explicit thought processes play a lesser role. These experiences are more in the feelings domain rather than ideas domain. Because of this they are hard to articulate and thus perceived as unimportant and easy to dismiss by the child. This premature dismissal exacts a price over time similar to that of the somatic urges that accompany the tics. Both urges and the emotional churning of the inarticulate OCD of TS require an investment of mental energy to control. They lead to an unspoken constant fear of losing control that requires

constant vigilance that can be draining. In case II, the protracted flare-up of tics was in large part a consequence of the breakdown in the protection and support she received from the family during elementary and middle school. Once she entered high school, this protection decreased as she was forced to function more independently. From an ADHD perspective, the increased academic challenges provoked anxiety linked to a secret fear of inadequacy and lack of competence similar to that in case 1. In intelligent individuals this fear can be met in part through industriousness and by learning strategies to work around the core deficiencies of ADHD and its executive dysfunction. The anxiety that this perceived dysfunction creates is additive to that provoked by the tics and any source of anxiety.

In treating anxiety and related symptoms in TS, it is important to remember that the lower doses of SSRIs and SNRIs can treat general anxiety and depression (e.g., fluoxetine 10–20 mg, sertraline 50–100 mg, and venlafaxine 37.5–150 mg/day) but not necessarily the OCD symptoms. Examples of typical agents and doses used to treat OCD symptoms include fluoxetine ≥20–40 mg, sertraline 100–200 mg/day, and venlafaxine 150–450 mg/day. Antidepressant responses can start as early as 2–6 weeks after starting treatment. Anti-OCD effects of SSRIs and NSRIs may take as long as 2–3 months. CBT can treat these symptoms in the absence of these agents and can augment the effect of these drugs. CIBIT is thus an ideal strategy to consider in all patients, particularly in children and in those with poor tolerance to the above agents.

In TS cases with significant ADHD symptoms, early treatment with alpha-2 agonists (i.e., clonidine and guanfacine) can address impulsivity, hyperactivity, rage, sleep problems, and tics. The slow and mindful introduction of stimulants for the treatment of ADHD in TS is illustrated in case I.

These cases illustrate the importance of standardized questionnaires and the use of concrete examples of ADHD and OCD behaviors during patient interviews. These instruments help guide and inform the evaluation and treatment. When there appears to be a disconnect between severity of tics and relative "absence" of comorbidities, we recommend more detailed neuropsychological testing that also include ascertainment for attentional neuro cognitive difficulties such as working memory defects, processing issues, mood disorders, and generalized and other anxiety disorders. Other areas worthy of investigation are sensory and language processing, learning disabilities, issues of social and emotional maturity, and substance abuse. These studies often help uncover symptoms not evident to the patient or the family. They should be administered by a psychometrician familiar with TS. Finally, correction of any sleep disorders is fundamental to addressing any of the above issues.

The type of ADHD exemplified by case II, the inattentive type, is particularly common in girls and more likely to be missed than the combined or hyperactive/impulsive subtypes. Anxiety disorders and OCD symptoms in children have a different phenotype and carry a different narrative than that in adults without tics. In adult TS, OCBs can increase as life gets more complicated and unpredictable. Along with the common social scrutiny from having tics, the early comorbid symptoms (i.e., ADHD between ages 4 and 7 and OCBs between 8 and 12 years) take a toll on emotional resiliency and maturation. This in turn may lead to chronic maladaptive behavior patterns that impair normal coping skills. This unnecessary burden can be avoided with early detection and treatment.

Tics, like tremor, provide an inflated gain to minor changes in emotional state brought on by anxiety and OCD. In this field, questions that require further investigation are: Does the energy invested in controlling OCBs impair the resiliency needed to control tics? Can the effort invested in controlling tics become a stressor itself? How much cognitive "bandwidth" does this effort consume? What happens to ADHD-linked cognitive processes when this "bandwidth" is occupied with the extra effort at controlling tics, anxiety, and OCD? An unexpected change in tic severity may thus serve and the "canary in the mine" point to otherwise hard-to-detect changes in the emotional state of the individual. Better detection and management of anxiety, OCD, and ADHD will provide clear long-term advantages to the QOL of individuals with TS.

When the tics are severe, they should be treated first (or concurrently) in order to facilitate the introduction of other treatments for comorbid conditions. When tics are not severe, consider starting treatment with the most prominent comorbid condition to help reduce tic severity and thus the need for drugs to directly address the tics. These drugs (e.g., antipsychotics, presynaptic catecholamine depletors, central alpha-2 receptor agonists, and benzodiazepines) are typically associated with adverse events that may be higher than those used to treat ADHD and OCD. In particular, dopamine antagonists used to treat tics can lead to sedation, weight gain, extrapyramidal symptoms, and in vulnerable individuals, to cardiac conduction abnormalities and orthostatic hypotension.

Mood symptoms (including suicidality) cannot be ignored as they can present with significant aggression, temper tantrums, and prolonged "meltdowns" followed by significant difficulty recovering from such events. Rage attacks may require the temporary use of antipsychotics (atypical or typical), while the patient is being investigated for conditions like major affective disorder and/or bipolar illness and psychotic illness. Once the more disruptive symptoms are controlled, anxiety and OCD symptoms can be tackled using medications and psychotherapy to prevent relapse. Response to these SSRIs may take weeks, and patients in crisis cannot wait. In addition, agitated patients may exhibit paradoxical activation reactions during the initial titration of SSRIs.

Occasionally Asperger spectrum disorders can co-occur with a tic disorder. These cases are particularly difficult to dissect and treat and should be referred to experts in the field.

The role that CBD oils with or without delta-9-tetrahydocannabinol (THC) may play in he management of TS and related conditions remains controversial and complex. The reader is thus referred to the Tourette Association of America (TAA) web site and to the 2017 review by Shucheng-Wong and Wilens under Suggested Reading for more information.

A major obstacle in the management of tics is overcoming parental misconceptions about the nature of its symptoms. There can also be significant misunderstanding about the behaviors in question on the part of school administrators, teachers, and peers. For instance, a common question from school administrators is: Are tics voluntary or involuntary? Most children view them as involuntary. As they get older, they realize they can be under some voluntary control, but this control is "state dependent," that is, it depends on the environment and circumstances. As children, they may learn to use tics to self-sooth the premonitory urges. This temporizing measure comes at the expense of developing more adaptive measures to control tics such as those taught during CBT (see suggested reading) and when needed, medications. The TAA web site has a wealth of educational materials available to patients, parents, and educators (https://www.tourette.org/) that can inform the community about TS and its treatments. State organization also provides support to patients and families at many different levels.

In TS, the detection and treatment of comorbidities are fundamental to the successful management of tics in a majority of patients. This is probably true even when the severity of symptoms associated with the comorbidities appears "insignificant" during the initial evaluation. Behavioral therapies (CBT, exposure response prevention (ERP), and cognitive behavioral therapy exercises, transcendental meditation)) should be considered early in the treatment of tics, whether accompanied by comorbidities or not. These techniques offer the advantage of less reliance on medications and thus less risk and side effects to the patient. These techniques quickly become a lifelong *toolbox* to deal with life stressors and thus tics. CBT, CBT, and ERP have evidence-based effectiveness in both children and adults. Medications which do help many patients are ideally used in conjunction with behavioral therapy and, when this is not possible, with caution and close monitoring and for only as long as needed.

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Part VIII

Myoclonus

Treatment of Post-Hypoxic Myoclonus

62

Mark Hallett

Case

A 72-year-old man was seen 7 months after a cardiac arrest for what he referred to as "tremor" which began within weeks of the arrest. This affected all limbs and was debilitating. He reported some use of the right hand, such as holding a cup of coffee, but eventually it would start "bouncing." With the left hand: "I can't hold anything." He was not able to walk or stand and required assistance with all activities of daily living. The referring neurologist began treatment with valproic acid, 1000 mg twice per day, which reportedly mildly diminished the jerks, but there was no improvement in his functioning.

The patient came to the office in a wheelchair. There was mild dysarthria, but his speech was easily intelligible. He scored 15/30 on the MOCA. Limb strength was normal, but testing was limited by the myoclonus. At rest, there were occasional myoclonic jerks of the left upper limb and both lower limbs. The myoclonus increased with posture in the upper limbs, especially the left. During finger-to-nose on the left, the myoclonus was severe, involving proximal muscles and of large amplitude. Isometric movements, such as squeezing the examiner's fingers or attempting to push up from the wheelchair, also exacerbated the myoclonus. The lower extremity myoclonus was also exacerbated by movement (see Video 1).

The patient was diagnosed as having post-hypoxic myoclonus (Lance-Adams syndrome). Levetiracetam was added to the valproic acid and escalated to 1000 mg twice per day without improvement, and the patient did not return for follow-up.

Discussion

In this situation, the diagnosis is not much in doubt. After a period of hypoxia (anoxia) and a short latent period, myoclonus developed. Myoclonus is a clinical diagnosis based on the visual appearance of simple, quick muscle jerks. Myoclonus can involve all or part of the body (focal). Each myoclonic jerk can involve the whole body (or whole region affected) or just small parts at a time (multifocal). Myoclonus can be positive, meaning caused by a muscle burst, or negative, meaning a brief lapse of muscle activity. Negative myoclonus is a problem, for example, when patients are trying to stand or walk since these actions require consistent muscle activity to maintain an upright stance. Negative myoclonus during walking leads to what is called bouncing gait. Myoclonus can be spontaneous, reflex-induced, and movement-induced or accentuated. Action myoclonus is often the most disabling feature.

Delayed post-hypoxic myoclonus should be differentiated from acute hypoxic myoclonus which is seen almost immediately after the insult and typically during the period of coma. It is associated with severe brain damage. Clinically it is usually characterized by periodic whole body jerks associated with EEG discharges or a burst suppression pattern. Many of these patients go on to die, but these days with hypothermia treatment, more patients are surviving. Patients with acute hypoxic myoclonus who survive do not usually have post-hypoxic myoclonus, but it can happen.

Delayed post-hypoxic myoclonus was first described by Lance and Adams and is therefore often referred to as the Lance-Adams syndrome. They described the myoclonus, emphasizing action myoclonus and noting both positive and negative myoclonus. They also noted coexistent ataxia, gait disturbance, and seizures. Ataxic limb movements can be difficult to identify in the presence of action myoclonus, so this can be clinically ambiguous. In the typical case, it is really only the myoclonus that is a major problem. Werhahn et al. reported on 14 patients. The duration of coma was

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4–18 days; myoclonus developed within a few days in most, but in others did not appear for several months. They noted that mild cognitive impairment was also present. Followed over the years, the myoclonus and disability had some gradual improvement.

The pathophysiology of post-hypoxic myoclonus is a fragment of epilepsy, a single discharge affecting the motor system. Usually the hyperexcitability is in the sensorimotor cortex with each discharge being very focal, giving rise to multifocal myoclonus. The excitability can spread in the cortex and even across the callosum, the latter giving rise to a symmetrical focal myoclonic jerks in the contralateral limb with an interval of 10 ms due to the transcallosal conduction time. There also can be hyperactivity of the brainstem, likely in the reticular formation, giving rise to whole body jerks. The nature of the brain lesion giving rise to the hyperexcitability is unknown. Hypotheses focus on the cerebellum and the reticular nucleus of the thalamus.

Myoclonus has a typical appearance with clinical neurophysiology, and such studies can be undertaken if there is any difficulty with the diagnosis. EMG discharges associated with the myoclonus are brief; backaveraging the EEG on the myoclonus might reveal an EEG spike, and somatosensory evoked potentials might be "giant" if there is hyperexcitability of the sensory cortex.

The first treatment demonstrated for post-anoxic myoclonus was with 5-hydroxy-tryptophane (5-HTP), a precursor of serotonin. The original case reports were extremely dramatic, comparable to the effect of L-DOPA on Parkinson disease. 5-HTP, however, has a number of side effects, and when it was found that anticonvulsants had similar efficacy, the use of 5-HTP stopped. While the logic of 5-HTP has never been clear, the logic of anticonvulsants is clear given that the myoclonus is a fragment of epilepsy.

The most commonly used anticonvulsants are clonazepam, valproic acid, and levetiracetam (see Table 62.1). Brivaracetam is a new relative of levetiracetam, and its efficacy is not yet clear. It is important to note that phenytoin, gabapentin, and carbamazepine can worsen myoclonus (for unclear reasons) and should not be used. Certainly, there should be an attempt to use just one or few of them, but, for uncertain reasons, it is often necessary to use two or three together. Epilepsy seems more responsive than myoclonus, and this might be because myoclonus may be analogous to an interictal discharge and interictal discharges are not fully suppressed even if seizures are suppressed.

Table 62.1 Anticonvulsants used for myoclonus treatment

Agent	Dose (mg/day)
Clonazepam	3–20
Valproic acid	1000–2000
Levetiracetam	1000–3000
Primidone	500–750
Phenobarbital	60–180
Zonisamide	100–600
Brivaracetam (?)	150 (?)

It is not infrequent that the positive myoclonus will be suppressed, but the negative myoclonus remains. This might well leave significant disability, particularly with gait. In these circumstances, unfortunately, there is no therapeutic strategy that is known to work.

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Treatment of Myoclonus in Degenerative Disorders

63

John N. Caviness

Clinical Case

A 72-year-old woman was evaluated for memory problems and "shaking." She and her husband had noticed 3 years prior that she was more forgetful. More recently, her husband increasingly had to compensate for her lack of memory. However, more concerning to her husband was a lack of judgment and inability to plan. She was a retired math teacher and began to ask her husband to answer simple addition and subtraction problems. He noticed that in the checkbook that she kept, the columns of numbers were misaligned. On one occasion, she mentioned to her husband that there were mean-looking children playing in their backyard. For many years, she would yell and lash out in her dreams. The husband was impressed with the cognitive fluctuations that would occur in his spouse. Within the last year, there were times when her hands shook while holding a glass or plate. At other times, it seemed like her whole upper body jerked. In addition, she seemed to "slow down" over the last few years.

On examination, a mini-mental status assessment score was 24/30, with missing points for memory, attention, and drawing. Gait showed a mildly slow cadence. Cranial nerves, strength, sensation, and reflexes were normal. Repetitive motion rates in the upper extremities were mildly but significantly slowed. Tone was borderline elevated in the upper extremities. Occasionally, there was myoclonus of the upper torso. On finger-to-nose maneuver, there was action myoclonus that exacerbated near the target, jerking the finger away from the nose. Reflex stimulation, including that of the hands or stretching thumb/wrist muscles, did not elicit myoclonus. Neuropsychological testing revealed multiple cognitive deficits consistent with dementia, particularly in frontal/executive dysfunction. Blood and urine evaluation did not reveal a cause for the cognitive deficits. MRI of the head demonstrated mild diffuse cortical atrophy. The nature of the upper extremity "shaking" was investigated with surface electromyography (EMG) polygraphy showing brief (<75 ms) multifocal discharges in distal > proximal upper extremities during muscle activation. EEG back-averaging of these myoclonic EMG discharges from the right wrist revealed a focal cortical transient over the left sensorimotor cortex. These results established this patient's shaking to be cortical myoclonus. The figures show averaged correlates to right wrist myoclonus: accelerometry of right wrist movement (Fig. 63.1), right wrist myoclonus EMG discharge (Fig. 63.2), and a back-averaged EEG transient over the left sensorimotor area at electrode C3 (Fig. 63.3).

A diagnosis of dementia with Lewy bodies (DLB) was made on the basis of progressive dementia, mild parkinsonism, and other characteristic findings including myoclonus. Rivastigmine 1.5 mg twice per day, increased eventually to 3.0 mg twice daily, was started for the chief complaint of memory loss, and there was significant improvement. Levetiracetam was started for the myoclonus and gradually increased to 1000 mg twice per day. This yielded mild-to-moderate suppression of the upper extremity action myoclonus resulting in symptomatic benefit. Over the ensuing years, she experienced worsening of her symptoms. Delusions became more problematic. Atypical neuroleptics were tried for the delusions and hallucinations with only mild benefit. The patient died of pneumonia. At autopsy, neuropathological examination revealed diffuse Lewy bodies confirming the diagnosis, but Alzheimer's disease pathological criteria were not fulfilled.

Discussion

Dementia with Lewy bodies is a leading cause of dementia, second to Alzheimer's disease (AD), and comprises 25% of dementia. Clinically, certain characteristics seem to differentiate it from classic AD such as fluctuating attention, early parkinsonism, early hallucinations and delusions, and

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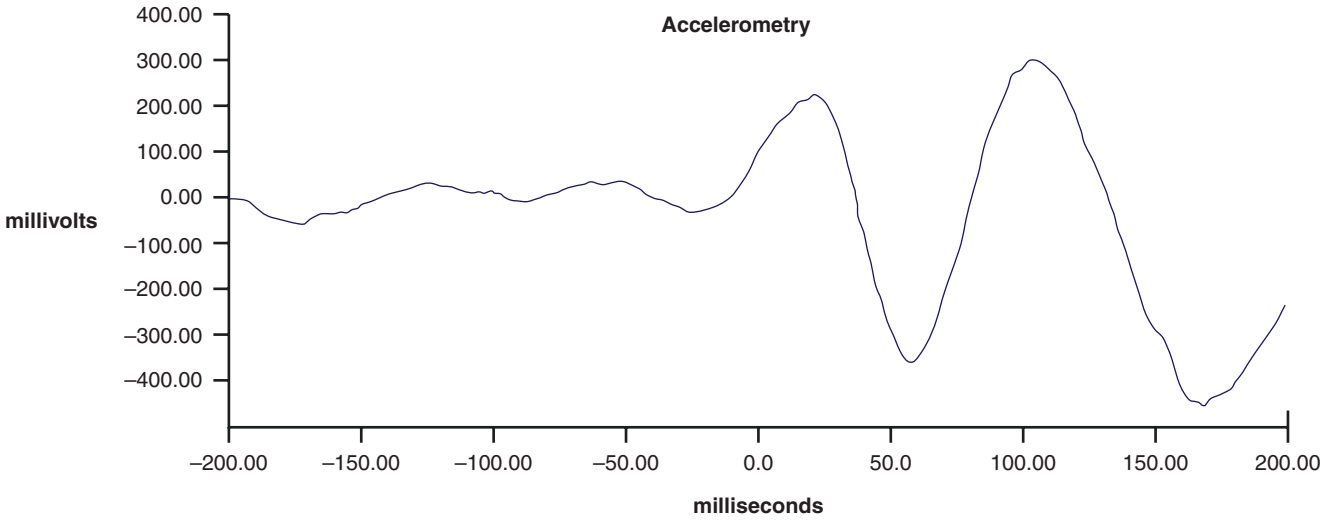

Fig. 63.1 Accelerometer signal on the right wrist during myoclonus. A sudden, brief displacement occurs at the beginning of the myoclonic jerk around time zero. The vertical axis shows microvolts, and the accelerometer is calibrated in units of meters/second^2 per microvolt

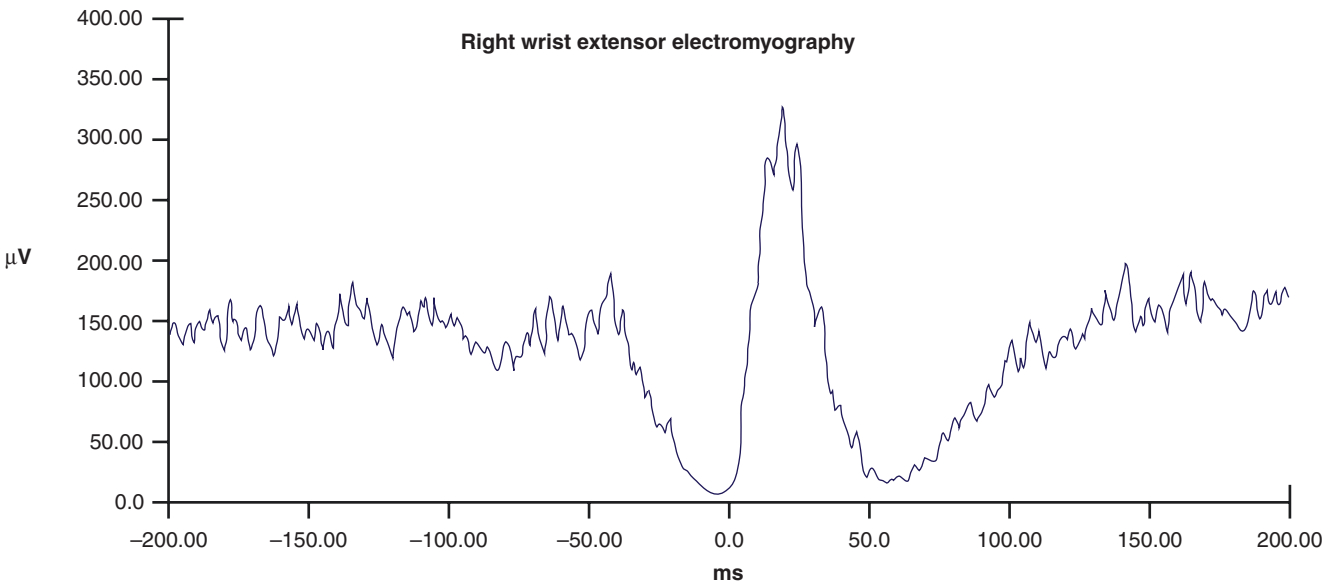

Fig. 63.2 Surface EMG signal arising from the right wrist extensor muscle group during the myoclonus. Note brevity of discharge. The vertical axis shows microvolts, and horizontal axis shows milliseconds with "0" as the onset of the myoclonus

disproportionate working memory impairment compared to retrieval memory problems so prominent in AD. Despite these core features, differentiation between DLB and AD may be difficult. The sensitivity and specificity of DLB clinical criteria fall short of what can reliably distinguish between DLB and AD. Biomarker research should improve diagnosis during life, but the development of such diagnostic biomarkers is still in development. Nevertheless, the combination of dementia, early parkinsonism, hallucinations, cognitive fluctuations, and myoclonus is strongly suggestive of the diagnosis. Additional clinical features may include REM sleep behavior disorder, autonomic dysfunction, and neuroleptic sensitivity. There is a progressive natural history. It is common for the neuropsychiatric features to dominate later in the clinical course. For rapidly progressive clinical presentations, Creutzfeldt-Jakob and AD are in the differential diagnosis.

Treatment strategy in DLB is governed by which of multiple possible manifestations are the most disabling. Memory deficits may be helped by acetylcholinesterase inhibitor therapy. The parkinsonism in early DLB is often mild and not a significant issue. However, significant parkinsonism may be treated with levodopa therapy. Often, anti-parkinsonism treatment is problematic since hallucinations, delusions, and

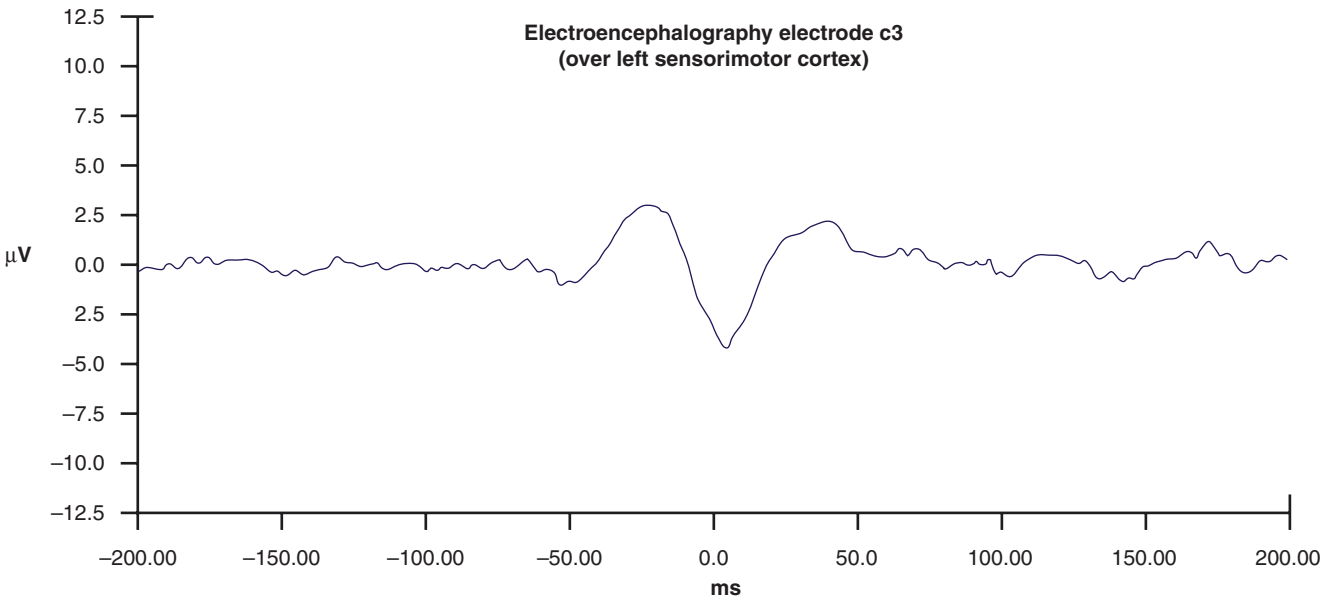

Fig. 63.3 Back-averaged EEG correlation to the EMG signal in Fig. 63.2. Note that the positive-negative discharge precedes time "0" of the myoclonus. The vertical axis shows microvolts. The horizontal axis shows milliseconds with "0" as the onset of the myoclonus

altered mental status may worsen as a side effect of dopaminergic therapy. Moreover, there is often limited clinical benefit with anti-parkinsonism treatment. Behavioral problems and hallucinations may improve with acetylcholinesterase inhibitor therapy. The atypical antipsychotic quetiapine may provide symptomatic benefit, and it may be better tolerated than typical or other atypical antipsychotic medication. If quetiapine is not effective, clozapine can be considered although this medication requires considerable monitoring. Caution must be exercised with regard to any medication that has anti-dopaminergic action, since such adverse sensitivity to such medication, particularly neuroleptics, is characteristic of DLB. Selective serotonin uptake inhibitors may treat mood problems in DLB. Medications with anticholinergic action should be avoided due to risk of worsening memory and mental status.

Myoclonus is defined as sudden, brief, shock-like, involuntary movements caused by muscular contractions (positive myoclonus) or inhibitions (negative myoclonus). It refers to a *symptom* or *sign*, and it does not constitute a diagnosis. Myoclonus may have a variety of etiologies and physiological mechanisms. Accurate characterization of the individual patient presentation of myoclonus has strong implications for diagnosis and treatment. Clinically, myoclonus is often classified as either (A) physiologic (normal), (B) essential (most prominent or nearly most prominent symptom), (C) epileptic (associated with chronic seizure disorder), or (D) symptomatic or secondary to another disorder, neurologic or medical. It is important to keep in mind that numerous medications can cause myoclonus or exacerbate it when underlying neurological disease is present. Since seizures are an important differential diagnosis, electroencephalograpy is recommended. Neurodegenerative disease is a common cause of myoclonus, and such disorders are listed in Table 63.1. In addition, physiologic classification also contributes to diagnosis but also particularly treatment. Physiologic classification categories include (1) cortical, (2) cortical-subcortical, (3) subcortical-nonsegmental, (4) segmental, and (5) peripheral. Treatment is appropriate for those instances where the underlying condition cannot be reversed. Symptomatic treatment of myoclonus is best derived from a defined or presumed physiological classification category of cortical, cortical-subcortical, subcortical, segmental, or peripheral pathophysiology.

Table 63.1 Most common neurodegenerative diseases with myoclonus

Alzheimer's disease
Lewy body disorders
Dementia with Lewy bodies
Parkinson's disease
Hereditary Lewy body disease
Corticobasal degeneration
Multiple system atrophy
Spinocerebellar degeneration
Frontotemporal dementia
Hereditary
Sporadic
Progressive supranuclear palsy

Myoclonus may be a prominent symptom or sign in DLB, occurring significantly in about 1/3 of cases. Myoclonus is common in AD, so it is not a good feature to differentiate these two diseases. When compared to the myoclonus in

Parkinson's disease (PD), DLB myoclonus is larger and more likely to occur at rest. Moreover, in DLB, myoclonus appears earlier in its course. In PD, small-amplitude myoclonus is not as common, late in the course, and often with dementia. The myoclonus pathophysiology in DLB is cortical, presumably from the alpha-synuclein and/or AD pathology within motor cortical areas. The motor homunculus in the cortex is the largest motor representation of the brain. Its activation provides fractionated movements. Thus, the muscle activation myoclonus produces multifocal jerks within body segments and may worsen with goal intention. Such characteristics are typical of the myoclonus in DLB.

Given that the myoclonus in DLB has a cortical physiology, a cortical strategy toward myoclonus treatment in DLB is recommended. However, since these medications can have significant adverse events, it is critical to conclude that the myoclonus is causing enough disability so as to warrant treatment. For most patients, education and reassurance are the main therapies. Since cortical myoclonus pathophysiology has overlap with the treatment of epileptic seizures, antiepileptic medications have been found to be the most effective for cortical myoclonus. There are no controlled studies for the treatment of myoclonus in DLB. However, if the myoclonus is disabling in DLB, levetiracetam can be effective and is the best choice for initial therapy. Since drowsiness may occur as an adverse event, it is best to begin with 250 or 500 mg/day followed by gradual titration upward. The maximum recommended dose is 3000 mg/day. Levetiracetam is minimally protein-bound and excreted in the urine. It has virtually no interactions with other drugs. It is considered the drug of choice in the treatment of myoclonus in DLB. However, mood and even psychotic side effects can occur with levetiracetam. Since such symptoms commonly occur in the natural history of DLB, the clinician should be keenly aware of levetiracetam increasing these symptoms.

Valproic acid is effective in cortical, cortical-subcortical, and subcortical-nonsegmental myoclonus. If an alternative to levetiracetam is needed, valproic acid may be suitable for use in treating the myoclonus of DLB. Valproic acid is usually begun at 125 mg twice daily and titrated to a clinical response. For the treatment of myoclonus, doses of 750–1000 mg/day are usually required. It is contraindicated in patient with significant hepatic dysfunction and urea cycle disorders. It may cause neural tube defects, craniofacial defects, and cardiovascular malformations if taken during pregnancy, but this would not usually be a concern in DLB if the patient is not capable of having children. Valproic acid may increase levels of warfarin, lamotrigine, phenobarbital, and phenytoin. Fatal hepatic failure and pancreatitis may occur in patients taking valproic acid, requiring frequent monitoring. Since valproic acid can be used to treat mood disorders, it may have usefulness for both myoclonus and possible mood disorders in DLB.

Clonazepam is used in cortical, subcortical-nonsegmental, and segmental myoclonus. Clonazepam is typically begun with 0.5 mg three times a day and titrated until there is control of symptoms or problematic side effects appear. Doses of at least 3 mg/day are generally required. Most common side effects are drowsiness but ataxia and personality changes may occur. It is contraindicated in patients with narrow-angle glaucoma or with hepatic dysfunction. Clonazepam can also treat the REM behavior disorder in DLB. Although its ability to treat both myoclonus and REM behavior disorder suggests an ideal treatment for these DLB symptoms, clonazepam can worsen the cognitive problems in DLB. Therefore, close monitoring is required if it is used to treat myoclonus in DLB.

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Part IX

Tardive Syndromes and other Drug-Induced Movement Disorders

Treatment of Tardive Dyskinesia

64

Stewart A. Factor

Case

This patient was a 75-year-old woman seen in 2010 for Tardive Dyskinesia (TD). She had a history of multiple surgeries for breast cancer which were complicated by intractable nausea. This was treated chronically but intermittently (over 20 years) with antiemetics including trimethobenzamide suppositories and promethazine. She developed dyskinetic movements of the face, lips, and mouth 3–4 years prior to the visit, after more than 16 years of dopamine receptor blocker exposure. The movements caused difficulty speaking and were associated with self-mutilation; she would bite her tongue frequently. She also developed respiratory dyskinesia with an irregular breathing pattern and chronic motor restlessness. She also described an urge to move and said she "can't sit still" associated with feeling anxious which worsened after withdrawal of the antiemetics. She was diagnosed with tardive dyskinesia including respiratory dyskinesia and tardive akathisia. The antiemetic medications were discontinued. Two years prior to the visit, she was given benztropine for the movements with no benefit. Clonidine was also tried with no benefit.

She had a 3-year history of depression, diabetes mellitus, hypertension, hypercholesterolemia, and mild cognitive impairment. Medications at the initial visit included benztropine 4 mg PO bid (for 2 years), duloxetine 20 mg bid, clonidine 0.1 mg daily, donepezil 10 mg po daily (for 5 years), lorazepam 1 mg po qid, and gabapentin 300 mg po qid.

Blood pressure was 145/82, heart rate 82. On examination she had orofaciolingual dyskinesia characterized by nearly constant tongue protrusion movements, lateral jaw displacement to either side, lip pursing, and eye closure (blepharospasm). She also had respiratory dyskinesia but no limb movements. The movements were somewhat less frequent with attempts at suppression but could not be suppressed completely. She also had stereotypic rocking of the trunk. She had an antalgic gait because of bilateral leg pain. The rest of the neurological exam was normal.

Discussion

Tardive dyskinesia is an iatrogenic disorder due to treatment with dopamine receptor blocking drugs. The use of atypical antipsychotics has not led to a decrease in this problem; in fact the prevalence is likely growing particularly because of an increase (perhaps threefold) in the number of prescriptions written, particularly for nonpsychotic disorders. Even irregular or intermittent use of such drugs, as in this case, represents a risk. DSM V criteria for TD require exposure for several months except for people over 60 years of age where the exposure is less, but less frequent exposure, as in days to weeks, can still cause TD. Tardive dyskinesia has many phenotypes, the so-called tardive syndromes. By far the most common is orobuccolingual dyskinesia which can be choreic or stereotyped (referred to here as classical TD). This form makes up over half the patients. Some also have generalized movements of the same type. Other types include tardive dystonia, akathisia, tics, and rarely tremor. Many have a mixed movement disorder. The pharmacological approach to therapy varies for the different types (see Table 64.1 and Fig. 64.1). For all, removing the causative agents (already done in this patient) is always the initial step, but there is insufficient evidence that this has an impact according to the 2013 American Academy of Neurology (AAN) practice parameter. In psychiatric patients, switching to a less potent or atypical agent, if possible, is also considered appropriate. Data suggests that even after that step, ~85% of patients have a permanent disorder (may be higher for dystonia) although some improvement can be seen over time (months to years). This patient had classical

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Table 64.1 Drug dosing for TD

Classical tardive dyskinesia	Approximate maximum daily dose	Frequency
Propranolol[a]	80 mg	TID to QID
Amantadine	300 mg	BID to TID
Levetiracetam	3000 mg	BID
Valbenazine	80 mg	QD
Deutetrabenazine	48 mg	BID
Tetrabenazine	75 mg	TID
Clonazepam	2 mg	QD to BID
Ginkgo biloba	240 mg	QD
Tardive dystonia		
Trihexyphenidyl	15 mg (depends on age – could be 40 mg in children and 6 mg in elderly)	
Baclofen	120 mg	TID
Valbenazine	80 mg	QD
Deutetrabenazine	48 mg	BID
Tetrabenazine	75 mg	TID
Clonazepam	2 mg	QD to BID
Tardive akathisia		
Propranolol	80 mg	TID to QID
Mirtazapine	30 mg	QHS
Trazodone	100 mg	QHS
Vitamin B6	1200 mg	QD
Tardive tic		
Clonidine	0.6 mg	BID
Tetrabenazine	75 mg	TID
Tardive tremor		
Propranolol	120 mg	TID to QID
Primidone	200 mg	QD (QHS) to BID
Tetrabenazine	75 mg	TID

[a]Dose for propranolol is in standard formulation; similar dose in the long-acting formulation can be used QD

TD. Because anticholinergics are known to worsen classical TD, benztropine was tapered off over 1–2 weeks; this was followed by tapering clonidine since it had no benefit on the movements. It should be noted that some patients with TD are not bothered by the movements. In these there may be no need to initiate treatment. There are now two treatments FDA approved for TD, valbenazine and deutetrabenazine (both approved in 2017); both are vesicular monoamine transporter 2 (VMAT2) inhibitors, which result in a presynaptic dopamine depletion. Both of these drugs have been evaluated in two large multicenter trials demonstrating significant improvement of the primary outcome measure, the Abnormal Involuntary Movement Scale (AIMS), as scored by blinded video raters, along with several secondary outcomes including patient clinical global rating. This would qualify as level A evidence. Based on this information, these should be considered first choice, but there are other issues to consider, discussed below. Several other medications have been examined in smaller randomized trials for classical TD. They include amantadine, levetiracetam, clonazepam, propranolol, tetrabenazine, and ginkgo biloba. For many movement disorder specialists, tetrabenazine, another VMAT2 inhibitor, has been the treatment of choice despite weak, level C evidence. This was until the valbenazine and deutetrabenazine were approved. There are decades of open-label data for tetrabenazine but only two small blinded trials (one with open therapy but blinded video raters). Although there has been no direct comparison, the two newer drugs, as a result of improved pharmacokinetics, seem to be safer. Amantadine has also been studied in two small blinded trials and has level C evidence suggesting it may be considered, but there is skepticism about the effectiveness. The same skepticism is noted for levetiracetam which had 1 positive 50-subject double-blinded trial and more than 1 open trial. Ginkgo biloba had one 100-subject trial (level B moderate evidence) that actually showed that the reversal of TD was permanent after washout, but this has not been replicated. Clonazepam is used frequently despite one small blinded trial reported in 1990 (level B moderate evidence). The β-adrenergic blocker propranolol is another option. In the 1980s, ~30 patients were treated in an open fashion in case reports or case series and in a small double-blinded trial, and >60% had improvement with small doses. Based on these findings, there was a call for large-scale, long-term placebo-controlled trials through an editorial, but it was never performed. It was believed by some that the efficacy came about because propranolol increased neuroleptic plasma levels leading to suppression of symptoms. However, many of the patients were not on neuroleptics at the time of therapy. Nevertheless, I have used propranolol with success.

Adverse effects, particularly in the elderly, are a significant concern with many of these drugs. For instance, tetrabenazine may worsen depression or cause parkinsonism, akathisia, and orthostatic hypotension. It is also costly. The newer VMAT2 inhibitors, as noted above, seem to have fewer of these side effects, but the risk is not zero, and cost is an issue. The use of specialty pharmacies for these agents is another barrier one may have to deal with. Levetiracetam is associated with somnolence, ataxia, and a decreased WBC. Amantadine can cause anticholinergic effects of confusion, constipation, urinary issues, and others as well as pedal edema and livedo reticularis. Clonazepam is associated with somnolence and cognitive changes. And propranolol can lead to orthostatic hypotension, bradycardia, and worsening of depression.

Hence the treatment here is individualized. Like many movement disorders, we end up using a series of trials to find what is the best treatment in each patient with TD. Because of safety issues and cost with tetrabenazine, valbenazine, and

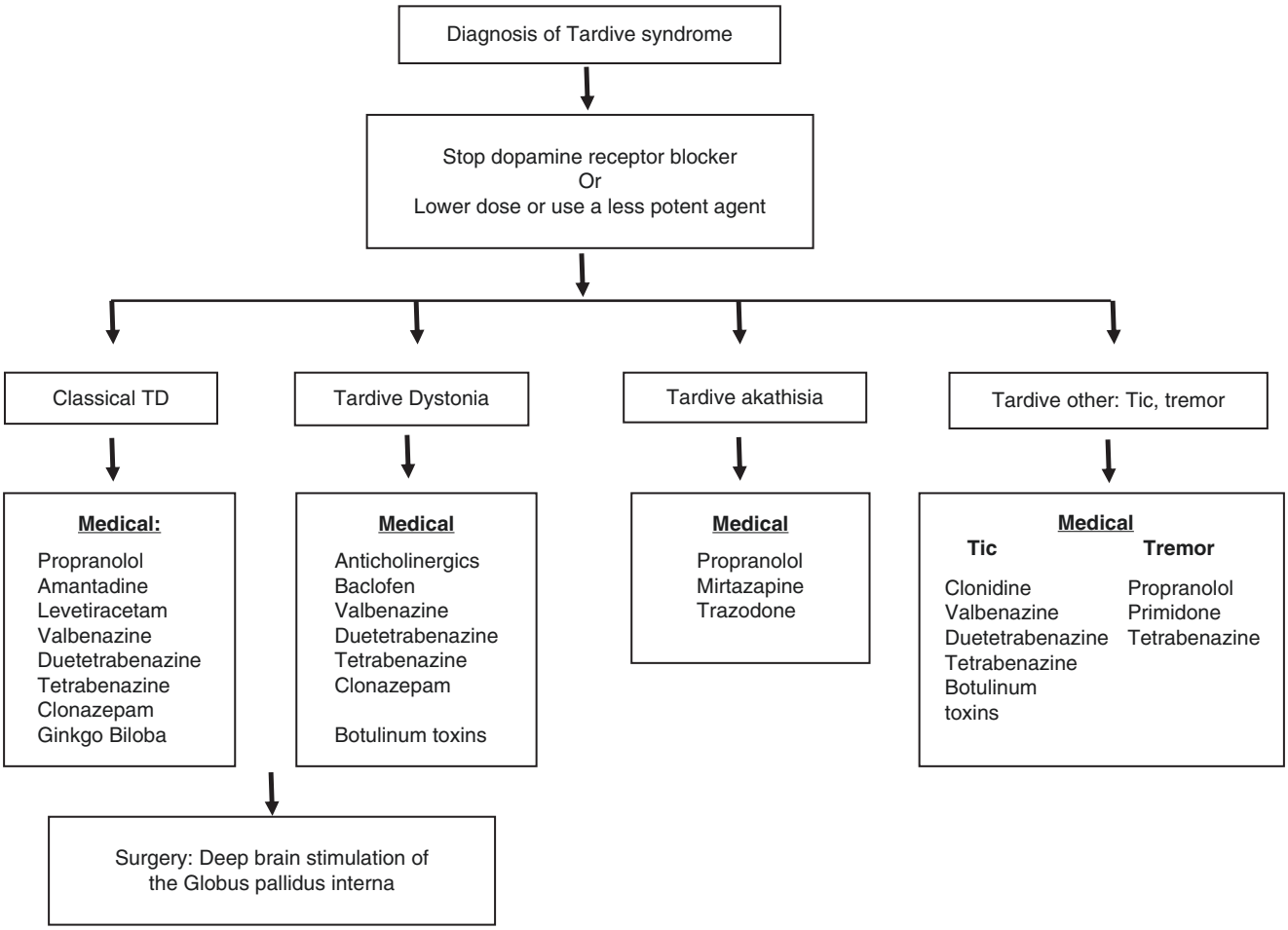

Fig. 64.1 Treatment algorithm

deutetrabenazine, despite possibly being the most effective treatments for TD, I may not consider them first. Depending on medical and psychiatric comorbidities, my order of use often is propranolol, amantadine, levetiracetam, VMAT2 inhibitors (valbenazine, deutetrabenazine, tetrabenazine), and clonazepam. Ginkgo biloba can be added at any time (Table 64.1, Fig. 64.1).

In patients with tardive dystonia, in contrast to classic TD, anticholinergics may be helpful, and either trihexyphenidyl or benztropine may be an option. For adults one must be careful about anticholinergic adverse effects such as confusion, constipation, blurred vision, and difficulty urinating including retention. VMAT2 inhibitors, baclofen, and clonazepam are other possibilities for tardive dystonia. Local injection of botulinum toxin may be very helpful and is a reasonable first choice particularly for tardive blepharospasm and oromandibular, lingual, and cervical dystonia. The doses and approaches for tardive dystonia are the same as with primary dystonia (see the sections on dystonia for details). This approach is less effective for chorea or stereotypies and for more widespread symptoms.

For other types of movements, there are additional choices (Table 64.1, Fig. 64.1), for example, akathisia is best treated with propranolol, mirtazapine, or trazodone. Tardive tics can be treated with clonidine, VMAT2 inhibitors, or botulinum toxin. In cases where the movements are so severe or possibly life-threatening, restating a neuroleptic may be considered, but this should be a temporary solution until other options are considered such as deep brain stimulation (DBS). In patients with severe dystonia or dyskinesia that is disabling and unresponsive to medications or botulinum toxin, DBS of the globus pallidus interna can be very effective. Properly placed leads can result in a >80% reduction in the movement disorder, but the time required for improvement varies among individuals and the distribution and type of tardive syndrome. Some patients respond quickly, in weeks, while others respond in a manner similar to DBS for primary dystonia, requiring months. The anatomical distribution also influences the rate of response; for example, facial dystonia, particularly blepharospasm, can respond rapidly, within weeks, while cervical and truncal dystonia may improve gradually over months to years after more intensive pro-

gramming. The surgery can be done in the standard fashion using cellular recording in an awake patient, but those with tardive cervical dystonia may have difficulty with stabilization in the stereotactic frame. More recently MRI-guided DBS procedures with the patient under general anesthesia are possible and better for these patients. Programming settings are individual, but generally the voltage is 3–4 volts, pulse width is 90–210 μs, and the frequency is between 60 and 185 hertz. Key concerns from the standpoint of the procedure include active depression preop, potentially worsening post-op, and the post-op complications of infection and hemorrhage which occur in small numbers but can cause significant morbidity.

Some key issues to consider for treating this particular patient included her age, the history of hypertension and use of antihypertensive agents, blood pressure and heart rate, and her history of depression and current level of depression. The depression was controlled. Blood pressure was still slightly elevated, and heart rate was in the 80s. Based on these findings and the presence of akathisia in addition to the classical TD, she was started on propranolol 10 mg PO daily titrating up by 10 mg every 4 days to 20 mg PO bid. She was examined 3 months later and was 90% improved. She was occasionally biting her tongue. The mouth movements occurred mostly when she was nervous, and that was true for the akathisia as well. The propranolol was increased to 60 mg per day and then switched to the extended-release formulation at the same dose. Follow-up 10 months later demonstrated continued improvement with excellent control. At this point there was no need to attempt any other medications. She tolerated the propranolol well without bradycardia, a drop in BP, or recurrence of depression.

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Treatment of Tardive Dystonia

65

Paul Greene

Case Report

A 76-year-old woman developed a movement disorder at age 51 after taking metoclopramide for several years for nausea. The movement disorder persisted after stopping metoclopramide. She had no prior exposure to dopamine receptor blocking agents (DRBAs) but developed depression with psychotic features in her early 60s and was treated with perphenazine and risperidone, and her movement disorder worsened. The DRBAs were eventually stopped, with unclear effect on her symptoms. In her mid-60s, she was treated with trihexyphenidyl, and her movement disorder changed. At the initial movement disorder evaluation at age 66, she had generalized chorea, forgetfulness, and restlessness, and there was concern about Huntington's disease (her mother died at age 22 of unknown cause, and a maternal aunt had a "nervous condition"). However, when trihexyphenidyl was stopped, the chorea disappeared. Her examination off trihexyphenidyl showed mild restless movements, marching in place with a sensation of restlessness, and mild oral-lingual dyskinesias that stopped when she put her finger on her lips. She had painful jerky retrocollis, some jerky inturning of her arms, and mild jerky truncal extension. When she stood or walked, the truncal extension worsened markedly and made it difficult to walk.

Lower doses of trihexyphenidyl and procyclidine produced marked chorea with persistent dystonia. Botulinum toxin (BTX) for retrocollis reduced her pain but did not significantly improve her retrocollis. Baclofen, levetiracetam, valproic acid, and quetiapine did not help. Addition of alpha-methyl-paratyrosine to quetiapine produced modest reduction in her truncal arching, but she still had trouble walking. Despite her history of depression, we finally started tetrabenazine (TBZ) with marked improvement in her signs and symptoms, but she developed parkinsonism and had several falls. Eventually we reduced TBZ to a dose where she had acceptable levels of both dystonia and parkinsonism without imbalance.

Discussion

Movement disorder neurologists make a distinction between tardive dyskinesia (TD) and TDyst, even though many patients have a combination of the two. Pure TD consists of repetitive movements that can involve almost any part of the body (face, tongue, jaw, trunk, or limbs) and, when mild, may not require treatment. TDyst consists of sustained muscle contractions causing abnormal postures and may also involve almost any voluntary muscle. TDyst often has a jerky almost myoclonic quality and frequently causes neck and/or trunk extension, but TDyst can be indistinguishable from idiopathic dystonia. Mild TDyst is more likely to require treatment than mild TD. The treatment options for TDyst consist primarily of medications, BTX injections, and deep brain stimulation (DBS). A few other modalities have been used in small numbers of patients with unclear results. It is not known if treatment outcomes are different for patients with TDyst who must continue taking DRBAs versus patients who can stop them. It is likely, although not proven, that patients free of DRBAs are more likely to experience a spontaneous remission, so DRBAs should be stopped when possible. In terms of treatment, we believe that the treatments described below apply whether dystonia is the predominant tardive symptom or whether it is only one troublesome feature among other tardive symptoms.

Botulinum toxin is useful for treating focal symptoms (such as blepharospasm, cervical dystonia, jaw opening or closing dystonia, etc.), and painful dystonic spasms in cases where a small number of muscles are especially troublesome. In these cases, especially if there is pain, it is reasonable to start treatment with BTX injections. BTX takes effect more quickly and has fewer side effects than most oral

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medications for TDyst. The approaches and doses for treating these focal TDyst are identical to the treatment of idiopathic dystonia involving the same areas.

If BTX injections are not effective, then oral medication trials are the next choice. Medications for idiopathic dystonia and other tardive syndromes are also the treatments for TDyst.

As with idiopathic dystonia, the medications most likely to be effective for TDyst are anticholinergics, baclofen, and clonazepam. Although less likely to produce significant benefit than medicines that interfere with the action of dopamine, they have fewer serious side effects and should be used first in most cases. If there is urgency in treating symptoms, it makes sense to use TBZ first (see below). Anticholinergics are best tolerated if the dose is increased gradually from a low dose (equivalent to 2.5 mg or 5 mg of trihexyphenidyl) on a TID or QID schedule with a plateau every several weeks to allow the brain effects to reach steady state. The common side effects are dry mouth, constipation, urinary retention, blurred vision, and short-term memory loss. If tardive dyskinesia (TD) coexists with TDyst, it may worsen. Worsening of psychosis is a risk in patients with endogenous psychosis, but many such patients will tolerate anticholinergics. Dry mouth, urinary retention, and constipation can be controlled by balancing the peripheral anticholinergic effect with pyridostigmine. Pyridostigmine does not help blurred vision, but this can be treated with pilocarpine eye drops. Significant short-term memory loss requires dose reduction or discontinuation. The major side effects of baclofen are sedation, insomnia, personality change, dry mouth, and urinary retention or frequency. More serious is the risk of seizures if the dose is reduced rapidly. As with anticholinergics, it is best to increase the dose gradually over weeks to minimize the risk of potential side effects. Clonazepam is less likely to be effective than baclofen or anticholinergics. The major side effects are sedation, irritability, and drooling. If clonazepam is started at bedtime, most patients develop tolerance to sedation.

Dopamine-interfering medications generally produce the most benefit in TDyst. Currently, non-DRBA medications that reduce the action of dopamine consist of dopamine depletors (reserpine, TBZ, deutetrabenazine and valbenazine), the aromatic-amino-acid decarboxylase inhibitor alpha methyldopa, and the competitive tyrosine hydroxylase inhibitor alpha-methyl-para-tyrosine (metyrosine). TBZ, deutetrabenazine and valbenazine are primarily dopamine depletors, but also weak DRBA, and can cause acute dystonic or akathitic reactions, and there is one report of TBZ causing a tardive syndrome. Deutetrabenazine and valbenazine are relatively new and side effects at effective doses are not well known. TBZ and reserpine are effective medications for TDyst. They have similar side effects, except that reserpine is more likely to cause orthostasis and less likely to cause acute reactions. Despite that, reserpine has two major problems: it is becoming difficult to obtain, and the brain half-life is so long that side effects such as depression and parkinsonism may appear as much as 4 weeks after treatment with a steady dose. TBZ is well tolerated in low doses (often sufficient to treat TD but not necessarily TDyst) but can have a variety of significant side effects at higher doses. Sensitivity to TBZ varies dramatically from person to person, but 25–50 mg per day is the minimum dose required to treat TDyst in most patients. Common side effects are sedation, insomnia, parkinsonism, depression, and apathy. Acute dystonic reactions and acute akathisia are uncommon in patients with TDyst. Depression is a major problem with TBZ, since many patients with TDyst may have primary depression. TBZ depletes serotonin and cannot only cause depression but also interferes with the action of antidepressants that increase levels of serotonin. Depression induced by TBZ usually requires discontinuation or dose reduction (treatment with MAO inhibitors can be considered as a last resort). Although most side effects of TBZ resolve quickly when the medication is stopped, TBZ-induced depression may last longer in patients with endogenous depression, and suicidal thoughts or attempts are possible. Parkinsonism induced by TBZ can be reduced by anticholinergics if tolerated and occasionally by dopaminergic agents (dopamine agonists and even levodopa) without worsening the TDyst.

As with other medications, the strategy for using TBZ is to start with a small dose (e.g., 12.5 mg daily) and increase gradually on a TID or QID schedule in order to manage side effects and achieve the lowest possible effective dose. Prolonged QT interval can occur with TBZ, especially if it is used in combination with other drugs that also prolong the QT interval. Metyrosine in moderate doses (up to 1000–2000 mg QHS) may produce modest benefit, but the benefit usually is transient. If metyrosine is combined with any other dopamine-interfering medication, the effects are enhanced and are persistent. Metyrosine has become hard to obtain, has a modest effect, and is rarely used today. Alpha methyldopa has rarely been used to treat tardive syndromes and is rarely used today.

Medications that have shown benefit for TD in controlled studies include amantadine, naloxone, levetiracetam, propranolol, ginkgo biloba, branched-chain amino acids, dopamine agonists, zonisamide, melatonin, vitamin E (with equivocal results), and clonidine. It is reasonable to try these if dopamine-interfering drugs are ineffective or not tolerated. There are many other medications reported to help TD in uncontrolled studies, including valproic acid, steroids, lecithin, L-dopa, buspirone, insulin, zolpidem, and others. It is not known how often any of these help tardive syndromes, including TDyst, but they can be tried if other medications are ineffective and if DBS is not an option. There have been several observations that tardive symptoms may disappear

during periods of mania, but no one has yet been able to turn this into a usable treatment.

DRBA may improve symptoms of TDyst, but many cases have been observed where such treatment causes only temporary improvement, after which tardive symptoms return and may be even worse than before treatment. For that reason, it is prudent to avoid using these agents. One possible exception is clozapine, which rarely causes tardive syndromes and can treat TDyst in some patients. In addition to side effects such as sedation, orthostasis, myoclonus, and seizures, patients require frequent CBCs due to the risk of agranulocytosis and are reluctant to take clozapine. The newly approved DRBA pimavanserin does not worsen Parkinson symptoms in doses that are adequate to treat psychosis and might be useful in treating TDyst, but that has not been documented.

Deep brain stimulation of the globus pallidus has been used with success in treating TDyst. Although DBS can produce dramatic improvement, some patients have no response. There have been suggestions that tonic dystonia may not improve as much as kinetic or jerky dystonia, but it is currently impossible to predict which patients will respond. Although there is no data, probably the risks of DBS in TDyst are similar to the risks of DBS in patients of similar age with idiopathic dystonia, the major one being intracerebral hemorrhage.

As with idiopathic dystonia, physical therapy has been used to treat TDyst with unclear results. The side effects of oral baclofen may be reduced or eliminated by using intrathecal baclofen, but there are only a few reports of intrathecal baclofen for TDyst, and these have produced equivocal results. There are several case reports and small series suggesting that ECT can help TDyst as well as other tardive syndromes. There are a small number of reports of STN DBS for TDyst. None of these treatments are widely used, but they could be considered as last resorts.

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Treatment of Drug-Induced Parkinsonism

66

Pierre R. Burkhard

Case

This was a 71-year-old man who was in good health, except for irritable bowel syndrome. In the last 1–2 months, he started to complain of becoming progressively slower while walking or performing activities of daily living. He also developed fatigue, pain in the cervical region and shoulders, and a feeling of being stiff. In addition, he noticed intermittent tremor at rest of both upper limbs while watching a sports event on television. His handwriting has become smaller, and his wife reported that her husband's voice changed, making him more difficult to understand. When he reported these changes, his general practitioner told him that he may have Parkinson's disease (PD) and therapy was initiated with levodopa-benserazide 100/25 mg t.i.d. After a month of taking this medication, not only did he not improve but he felt his condition was deteriorating further, which led his physician to increase levodopa-benserazide dosage to 200/50 mg four times daily. As the result of no benefit, he was sent to our institution for a second opinion.

When we first saw him, he denied taking any medication except for levodopa-benserazide. On examination, he exhibited a severe, essentially akinetic-rigid, rather symmetrical parkinsonian syndrome in addition to a mild and intermittent resting tremor of all four limbs more noticeable in the upper extremities. Posture was stooped and gait was short-stepped, but there was no freezing. The MDS-UPDRS part 3 score was 53. There was no cognitive decline and no feature suggestive of an atypical or secondary form of parkinsonism. In view of the rapid progression over a few months, the symmetrical aspect of parkinsonism, and the absence of levodopa response, the diagnosis of PD was challenged. An ^{123}I-ioflupane SPECT scan was performed and demonstrated no striatal uptake deficit, and a brain MRI proved normal for his age.

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At his third visit, when asked again about any other medication or drug or toxin he may have been exposed to in the recent past, he eventually recognized that he was chronically taking Deanxit™ 1 tablet daily for 9 years for his irritable bowel condition and, since about the last 3 months, he had increased his daily dosage to 2 tablets. Deanxit™ is a medication available in Switzerland, France, and other countries worldwide for decades for "mild to moderate manifestations of depression and anxiety," yet it has been recently banned in North America, Japan, Australia, and the UK. It contains a tricyclic antidepressant, melitracen chlorhydrate (10 mg per tablet), and a conventional neuroleptic of the thioxanthene family, flupentixol dichlorhydrate (0.5 mg per tablet). A tentative diagnosis of drug-induced parkinsonism (DIP) was therefore proposed, and this medication was discontinued, as was levodopa. Over the next 3 months, the patient's condition improved gradually, yet it took about 6 months for parkinsonism to completely resolve.

Discussion

This case illustrates a typical situation in clinical neurology, in general, and in movement disorders, in particular, where PD has been misdiagnosed for a common cause of secondary reversible parkinsonism, i.e., neuroleptic-induced parkinsonism. This is a condition that was recognized soon after the use of the first-generation neuroleptics as one of the most frequent extrapyramidal side effects. Indeed, in 1961, Ayd published a large survey of 3775 patients treated with the then so-called phenothiazine tranquilizers and demonstrated that, among the nearly 40% of cases exhibiting "extrapyramidal reactions" in the course of their therapy, DIP was the second most frequent side effect only after akathisia. If the percentage included mild or incomplete DIP such as mild akinesia, the percentage may have been much higher. It was also demonstrated that DIP is almost twice as frequent in women compared to men, the reverse of what is seen in PD where the

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male-to-female ratio is about 2:1 to 3:2. On the other hand, age distribution overlaps between DIP and PD, yet patients with DIP may be slightly older than those with PD. More recently, the prevalence of DIP has been variably estimated from one study to another, ranging from 10% to 60% in the psychiatric population, yet these figures may be decreasing with the wider use of atypical antipsychotics. In movement disorders clinics where parkinsonism is by far the most frequent complaint compared to hyperkinetic disorders, the prevalence of DIP has been reported to range from about 1% to 8%, perhaps higher in some centers, making it the second most frequent cause of parkinsonism after PD and the commonest of secondary parkinsonism. In general, epidemiological estimates of DIP are highly disparate as studies may suffer from many biases, notably the diagnostic criteria applied to define parkinsonism. Altogether, there is a consensus that DIP is largely under-recognized and likely overlooked by the medical community. Therefore, DIP should be well known from neurologists and general practitioners and always be considered in the differential diagnosis of newly developed parkinsonism cases, more so as it is reversible in most cases.

DIP typically occurs within the first 3 months after neuroleptics have been initiated or may occur much later, in particular, when one neuroleptic is switched for another one or when doses are increased, as in our case. It develops typically over a relatively short period of time, sometimes even acutely, and, at variance with the slow course of PD, may become quite severe within a few months. It manifests most commonly as an akinetic-rigid syndrome, often but not always symmetrical, resting tremor being less frequent than in PD, yet this notion has been challenged in some studies suggesting that postural, rather than resting tremor may be more consistent with DIP. However, it should be emphasized that DIP may sometimes fully mimic PD with an asymmetrical presentation and a typical tremor at rest. Akinesia may be particularly prominent, perhaps favored by the underlying psychiatric condition, whereas dysarthria, dysphagia, gait impairment, and other axial symptoms may be less common in DIP than in PD. Interestingly, parkinsonism and TD or other neuroleptic-related extrapyramidal symptoms like rabbit syndrome, akathisia, or oculogyric crisis may coexist in some patients, and this specific association is not seen in PD. Beyond movement disorders, PD is characterized by the early or premotor development of a variety of non-motor symptoms, including hyposmia, constipation and other features of autonomic dysfunction, and sleep disturbances. These symptoms are far less common in DIP, and their absence may be more suggestive of DIP than PD. Another feature of DIP that is nearly incompatible with a diagnosis of PD is that it poorly responds to levodopa or other dopaminergic agents, even at high doses, yet this is not unique to DIP and can also be seen in atypical parkinsonisms like MSA or PSP. There are exceptions to this rule as, for example, it has been reported that valproic acid-related parkinsonism may be levodopa-responsive. Finally, DIP is expected to regress after the offending agent has been discontinued, but it may take several months for parkinsonism to completely disappear.

To help in differentiating between DIP and PD in unclear situations, a number of ancillary tests might be useful, including olfactory testing, transcranial sonography, brain MRI, MIBG cardiac scintigraphy, and ^{123}I-ioflupane SPECT scan. The latter, which assesses specifically the integrity of the dopaminergic nigrostriatal pathway, is of particular interest as it is normal in pure DIP and abnormal in degenerative parkinsonism even very early in the disease course. In other words, a normal ^{123}I-ioflupane SPECT allows PD to be virtually ruled out, and, in addition to other suggestive features as reported above, is consistent with DIP and carries a favorable prognosis after discontinuation of the offending drug. However, because of its relatively high cost, ^{123}I-ioflupane SPECT should not be performed in all cases of suspected DIP but should be considered only in problematic cases, for example, when patients do not recover after drug withdrawal. In fact, improvement after drug discontinuation is the ultimate criterion for DIP, and full recovery is expected to occur in 70–90% of apparent DIP cases, although the recovery process may take up to 18 months. This means that about a quarter of them does not improve or only partially improves and some cases even worsen despite discontinuing the inciting agent. The current hypothesis is that these patients have preclinical PD or another degenerative form of parkinsonism that has been unmasked by the neuroleptic therapy. This is when ^{123}I-iofupane SPECT is of particular interest as this test may clearly demonstrate nigrostriatal pathway degeneration, thus modifying the prognosis and therapeutic strategy. It has also been proposed that some DIP-prone medications used chronically may have a direct toxic effect upon nigrostriatal neurons (referred to as the "double-hit" hypothesis) or that individuals with DIP may be asymptomatic carriers of PD-causing genes or may have genetic variants that increase their susceptibility to PD and that is ultimately triggered by the exposure to neuroleptics. Finally, rare DIP cases were examined at autopsy, and some exhibited neuropathological findings consistent with preclinical PD despite full recovery after neuroleptic withdrawal.

The clinical course can separate "pure" DIP from atypical DIP. In pure DIP, patients develop a progressive akinetic-rigid syndrome within months after exposure to a known offending agent, have a normal dopaminergic SPECT scan, and experience a complete resolution after causative medication withdrawal. In atypical DIP, patients may exhibit asymmetrical parkinsonism associated with suggestive non-motor symptoms, have an abnormal dopaminergic SPECT scan, and show incomplete or minimal recovery, all features suggesting an underlying degenerative or toxic process. Table 66.1 proposes diagnostic criteria for pure DIP, and

Table 66.2 highlights some characteristics of DIP that may distinguish it from PD.

Although DIP was initially reported after the use of typical neuroleptics in the 1950s, it is now clear that many other medications are also offending agents. Nearly all share with neuroleptics their capacity to interfere, directly or indirectly, with the dopaminergic nigrostriatal system, more specifically to alter D2 receptor stimulation in the striatum, yet this mechanism has not been established for all non-neuroleptic drugs, i.e., antiepileptics. The most commonly incriminated drugs, besides central (neuroleptics) and peripheral dopamine receptor antagonists (i.e., antiemetics), include calcium channel blockers, antidepressants, and antiepileptics. For further information, Table 66.3 lists most DIP-causing medications stratified according to their relative risk. It is important to mention that all classes of neuroleptics have been implicated in DIP including atypical agents, such as quetiapine or clozapine especially at high doses, although the risk related to the latter agents appears to be lower. It is also noteworthy to underline the issue of "hidden" antidopaminergic agents, which are sometimes prescribed for ill-defined psychiatric conditions believed to be anxiety-related, like in our case, or for indications outside psychiatry, like antiemetics, gastrointestinal promotility agents, anti-vertigo, or antihypertension drugs. Less commonly, and seemingly unlikely at first glance, some medications should not be forgotten when DIP is suspected. For example, in the setting of cancer, acute parkinsonism has been reported after bone marrow transplantation or chemotherapy containing, alone or in variable association, cytosine arabinoside, cyclophosphamide, and possible others. Immunosuppressants like cyclosporine and tacrolimus have also been implicated, as has been the case occasionally for H1 antihistamine agents or antibiotics like rifampicin, antivirals like acyclovir, and antifungals like amphotericin B. The question as to whether the DIP phenotype may vary from one offending agent to another has not been examined in detail, yet it may be possible that drugs like amiodarone, lithium, or calcium channel blockers may induce more tremor than typical neuroleptics.

Table 66.1 Proposed diagnostic criteria for "pure" DIP

Rapid (weeks to months) development of a rather symmetrical akinetic-rigid parkinsonian syndrome following initiation of a pharmacological agent known to induce parkinsonism
Normal ^{123}I-ioflupane SPECT scan or other presynaptic dopamine PET/SPECT scans
No or minimal improvement after therapeutic dose of levodopa or dopamine agonists
Complete resolution after withdrawal of the offending agent
No other cause of degenerative or secondary parkinsonism

Table 66.2 Features allowing to distinguish between DIP and PD

Distinguishing features	Drug-induced parkinsonism	Parkinson's disease
Age	Typically in the elderly	About sixth decade
Gender	More common in females	More common in males
Progression	Subacute (within weeks to a few months), sometimes acute	Slow (months to years)
Recently initiated treatment with neuroleptics or other DIP-inducing medications	Yes	No
Akinetic-rigid syndrome	Usually symmetrical	Asymmetrical
Tremor	Occasional, possibly more postural	Frequent, at rest
Response to levodopa	Poor or absent	Excellent
Outcome following causative drug withdrawal	Full recovery	No improvement or worsening
PD-related non-motor symptoms	Usually absent	Usually present
Presynaptic dopamine PET/SPECT scan	Normal	Abnormal
Concomitant neuroleptic-related movement disorders (TD, akathisia)	Possible	No

Besides medications, a number of toxic agents can produce acute or subacute parkinsonism, sometimes in isolation, such as accidental exposure to MPTP and organophosphate pesticides, or sometimes in the context of a more complex encephalopathy, like manganese, methanol, cyanide, carbon monoxide, or carbon disulfide poisoning. Interestingly, parkinsonism induced by organophosphate pesticides, like parathion and malathion, may be reversible and levodopa-responsive in some cases. The details of such intoxications are beyond the scope of the present chapter on DIP.

Treatment of DIP is difficult, and prevention should prevail by avoiding prescribing antipsychotics in nonpsychotic conditions, such as insomnia, mild anxiety, dyspepsia, vague dizziness, or stress-related or functional manifestations. It must also be underlined that DIP is often resistant to antiparkinsonian medications, including levodopa, dopamine agonists, or anticholinergics, yet it has been proposed that amantadine might be occasionally useful. Reducing dosage of the inciting drug might be of some help, but the mainstay of management is to discontinue the incriminated agent which is, in most cases, the only viable alternative, even by taking the risk of psychiatric decompensation. If this is the case, a global strategy is to try substituting the offending agent with a related compound that has a better side effect profile. Switching from a typical to an atypical antipsychotic, for example, is usually a valid option, yet DIP has also been reported in association with the latter. For nausea, metoclopramide may be replaced by domperidone or ondansetron.

Table 66.3 Medications that have been demonstrated to induced parkinsonism

Relative risk of DIP	Pharmacological class according to mechanism of action	Medications	Indications
High	Central dopamine receptors antagonists (typical and atypical neuroleptics)	Virtually all	Antipsychotics
	Dopamine depleters	Tetrabenazine Reserpine	Antichoreic Antihypertensive
	Dopamine synthesis blockers	Alpha-methyldopa	Antihypertensive
Intermediate	Peripheral dopamine receptor antagonists	Metoclopramide Domperidone Levosulpiride Clebopride Prochlorperazine	Antiemetics and gastric prokinetics
	Calcium channel blockers (P- and L-channel)	Flunarizine Cinnarizine Amlodipine Verapamil Diltiazem	Anti-vertigo Migraine Antihypertensive Antiarhythmics
	GABA enhancement Voltage-dependent calcium channel blockade	Valproate Phenytoin Levetiracetam	Antiepileptics
Low	Selective serotonin reuptake inhibitors	Fluoxetine Fluvoxamine Sertraline Citalopram/escitalopram Paroxetine	Antidepressants
	Tricyclics	Clomipramine Amitriptyline Desulepin Phenelzine	
	MAO inhibitors	Moclobemide	
	Others	Lithium Venlafaxine Mirtazapine	
	Miscellaneous	Amiodarone Procaine	Antiarhythmics
		Cyclosporine Tacrolimus	Immunosuppressants
		Levothyroxine Medroxyprogesterone Epinephrine	Hormones
		Lovastatin	Statins
		Cotrimoxazole Rifampicin	Antibiotics
		Aciclovir Vidarabine Anti-HIV agents	Antivirals
		Amphotericin B	Antifungals
		Alimemazine Aceprometazine Hydroxyzine	H1 antihistamines
		Cyclophosphamide Cytosine arabinoside Possibly others	Chemotherapeutic agents
		Meprobamate Trimetazidine Anticholinesterase	Others

At-risk patients, such as aged patients with cerebrovascular conditions and those who have already presented with a previous episode of DIP, should be followed up carefully when exposed to another risky compound. Altogether, the best treatment for DIP is detection as early as possible followed by the immediate interruption of the causal medication, keeping in mind that improvement may take some time to occur.

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Treatment of Tardive Akathisia

67

John C. Morgan

Case

A 35-year-old man presented because of an irresistible urge to move his body in the setting of chronic haloperidol therapy for schizophrenia. Schizophrenia was diagnosed at age 23 when he heard persecutory voices and became hyperreligious in the setting of a premorbid "loner" personality. He had fairly good control of his schizophrenia over many years with haloperidol therapy and continued to live with family but developed constant orofacial and tongue movements and a constant irresistible urge to move his legs and rock back and forth while seated over the past year. He had no family history of restless legs syndrome or a similar movement disorder, and his urge to move his body had no circadian pattern.

He was slightly obese and had comorbid hyperlipidemia and elevated blood glucose consistent with metabolic syndrome. He had a history of smoking one pack per day for 15 years, rarely drank ethanol, and denied illicit drug use. He was able to work in a supervised job setting for the past 17 years and had performed well working 20 h per week.

Medications at the initial visit included haloperidol decanoate injection 50 mg given intramuscularly once monthly, benztropine 1 mg twice per day, atorvastatin 20 mg per day, and metformin 500 mg twice per day.

On physical examination his blood pressure was 142/78 and heart rate was 74. He had orobuccolingual dyskinesia with intermittent tongue protrusion, lip pursing, and some lateral jaw movements. His entire body was in a constant state of motion and when asked to remain completely still, he could suppress most of his movements, but some lip pursing and leg movement persisted. He described an irresistible urge to move in his trunk and all four limbs. He rocked back and forth with his trunk in the seat and stood at times to walk and pace around the room. While seated, he would open and close his hands, plantarflex and dorsiflex his feet, and abduct/adduct his legs at the hip. The movements were reduced with his attempts at suppression but could not be suppressed completely. The remainder of his neurological exam was normal.

Routine laboratories demonstrated a normal complete blood count and comprehensive metabolic panel except for a blood glucose of 138 mg/dL. Ferritin level was 105 ng/ml.

He was diagnosed with tardive dyskinesia and tardive akathisia by his psychiatrist.

Discussion

Akathisia was a term coined by Haskovec at the start of the 20th century to describe patients whose problems were thought to be "hysterical" in nature. It comes from the Greek and means "not to sit." Dysphoria and restlessness were noted shortly after the introduction of antipsychotics to treat schizophrenia and other psychotic disorders in the 1950s. Akathisia is associated with both subjective restlessness and objective motor movements, while pseudoakathisia is a condition where motor movements are evident but a subjective sense of restlessness is lacking. Acute akathisia occurs shortly after initiating DBA therapy or when the dose is increased, and this form of akathisia often responds nicely to discontinuing the DBA or reducing the dose. If this is not possible, then β-adrenergic blocking agents and benzodiazepines are commonly helpful.

Munetz and Cornes introduced the term tardive akathisia in 1983 and described it as "an akathisia-like syndrome characterized by late onset, treatment resistance, and potential irreversibility despite discontinuance of neuroleptics." TA classically will get worse when the dose of DBA is reduced and may improve with an increased dose of the agent, like tardive dyskinesia (TD). Commonly TA is associated with

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the simultaneous presence of TD in many patients, and therefore TA might be considered a subtype of TD by some authors.

TA has been a problem in the utilization of dopamine receptor blocking agents (DBA) for the past 60 years, and tardive syndromes (TS) are likely to become more prevalent than in the past given frequent use of second-generation antipsychotics for nonpsychotic disorders such as bipolar disorder, depression, sleep, and anxiety. While second-generation antipsychotics likely have somewhat lower risk of TS due to less D2-dopamine receptor blockade, their widespread use has led to considerably more TS over time. The definition of TA by many today includes delayed onset (>3 months of therapy), not related to a recent change in drugs or dose, and it is frequently associated with TS. While most cases of akathisia are associated with exposure to DBA, it can occur in the setting of therapy with other drugs such as SSRIs or in withdrawal states from opiates, benzodiazepines, and other drugs. The prevalence of TA ranges from 8% in some studies to 40% of chronically treated neuroleptic patients in other studies. In developmentally challenged individuals, the prevalence is 6–14% with chronic treatment. Older age and female gender likely predisposes to TA as in TD.

Pathophysiologically, TA may result from postsynaptic dopamine receptor blockade in the mesocortical dopamine pathways, noradrenergic mechanisms, or the descending spinal dopamine pathway. Given the overlap with TD, some authors have proposed that the pathophysiology of TA is similar to TD, especially the problem of supersensitive dopamine receptors in the nigrostriatal pathway over time. Others authors have proposed problems in GABAergic neurotransmission or increased noradrenergic activity. Acute akathisia may respond to opioids in some patients (less likely in TA) and so the influence of neuroleptics on opioid neurotransmission may be at play as well. There is also some evidence that CNS iron deficiency may play a role in TA as can occur in both primary and secondary restless legs syndrome (RLS), but this is controversial. Unlike RLS, however, akathisia lacks a circadian pattern, affecting patients throughout the day and the night.

The 2013 AAN Practice Parameter on tardive syndromes by Bhidayasiri et al. recommended clonazepam (for TD) and ginkgo biloba (for TS) treatment with Level B recommendations. I have found clonazepam to be useful for both TD and TA in practice, but ginkgo biloba is rarely used for TS in the United States. Treatment of TS with amantadine or tetrabenazine received a Level C recommendation. It is common practice to try to remove the offending DBA first in the setting of TS, but the data supporting this is insufficient (Level U). Most of the data in this practice parameter is derived from trials and case series focusing on treatment of TD with little, if any data focused on TA.

Most clinicians would recommend first trying to remove the offending agent (if possible), reduce the dose, or switch to a less potent DBA. In many patients (especially someone with schizophrenia or other psychosis), it may be impossible to stop the offending agent. In other cases, such as adjunctive treatment with neuroleptics for depression or chronic use of metoclopramide for gastroparesis, other treatment options exist, and there should be a significant effort to discontinue the DBA. It is wise to remove anticholinergic drugs (benztropine, trihexyphenidyl) in patients with TD given these medications may classically worsen the movement disorder. These drugs can be somewhat helpful in tardive dystonia, however.

There have only been small blinded trials and open-label studies that examined the therapy of TA with variable amounts of success. The largest open-label treatment series was published by Burke et al. (1989a), and these authors found that the dopamine-depleting agents reserpine and tetrabenazine were most effective in their attempts to treat TA in 52 patients. Sachdev studied numerous placebo-controlled therapies in a schizophrenic patient with TA treated chronically with neuroleptics including selective and nonselective β-adrenergic blocking agents, benztropine, bromocriptine, physostigmine, clonidine, and metoclopramide. From his work in a limited number of patients, some with TA may benefit from anticholinergics or nonselective β-adrenergic blocking agents. Clonidine was also shown to be helpful for some patients with TA in case reports by other authors.

Dopamine-depleting agents such as tetrabenazine, reserpine, deutetrabenazine, and valbenazine may be useful in treating TA, but some patients may derive little, if any, benefit and otherwise may actually develop acute akathisia. Valbenazine and deutetrabenazine are currently in development for the treatment of TD with FDA approval of valbenazine for TD just occurring in April 2017. A few patients in the Phase III trial of valbenazine for the treatment of TD reported worsening or emergence of akathisia, but it remains to be seen if this is relevant in practice. Waln and Jankovic recently demonstrated significant improvement in several patients with TA using zolpidem despite failing other therapies (including tetrabenazine). There is very little good evidence about medications that definitively work in patients with TA, but clonazepam, clonidine, dopamine-depleting agents, propranolol, mirtazapine, trazodone, and zolpidem may be worthwhile to try (Table 67.1).

There are case reports of ropinirole and pregabalin amelioration in TA related to aripiprazole therapy. Also, another case report demonstrated that the monoamine oxidase-A inhibitor moclobemide improved TA. Trazodone dosed at 100 mg twice per day was shown to help one patient suffering with TA who was not responsive to tetrabenazine, propranolol, clonazepam, and other agents. Mirtazapine dosed at 15 mg per day may also be useful in acute akathisia or TA and is worth considering given that in one placebo-controlled trial, it was shown to be better tolerated in acute akathisia versus 80 mg per day of propranolol. Another case report

Table 67.1 Drug dosing in tardive akathisia

Tetrabenazine	12.5–25 mg	BID to TID
Reserpine	0.25–5 mg	Daily
Propranolol	Up to 80 mg	TID
Clonazepam	Up to 2 mg	BID
Dopamine agonists[a]	Variable	BID to TID
Pregabalin	Up to 200 mg	TID
Clonidine	Up to 0.3 mg divided	BID
Zolpidem	5–10 mg	BID
Mirtazapine	15–30 mg	QHS
Trazodone	Up to 200 mg	QHS or BID

BID twice per day, *TID* three times per day
[a]Care should be taken in prescribing dopamine agonists in the setting of psychosis given these drugs may worsen these conditions

found that the anticholinergic drug procyclidine combined with the benzodiazepine was effective. Others have not found dopamine agonists effective in TA. Electroconvulsive therapy was also reported to improve TA in one case report.

Side effects are a significant concern with many of the drugs used to treat TA, especially in the elderly. Propranolol can cause symptomatic bradycardia and orthostatic hypotension, erectile dysfunction, as well as insomnia and has the potential to worsen depression. Tetrabenazine and other dopamine-depleting agents can potentially worsen depression, cause orthostatic hypotension and sedation, or cause parkinsonism, and they are currently very costly. Amantadine can cause anticholinergic side effects including cognitive impairment, constipation, and urinary retention. It can also cause lower extremity edema, livedo reticularis, and very rarely corneal edema. Clonazepam can be associated with oversedation, increased risk of falls in the elderly, and cognitive changes. Clonidine can cause problems with hypotension. Zolpidem can be sedating and lead to unusual behaviors during sleep in some.

In this patient's case, the patient was taken off benztropine given he had TD concurrently with TA, and haloperidol injections were also discontinued. He was started on oral aripiprazole with little improvement and perhaps some worsening in his TD and TA. At that point propranolol was added at 20 mg bid and titrated to 60 mg bid with some improvement in TA symptoms over baseline. Further increase in propranolol to 80 mg bid provided a little more improvement, but he began to feel fatigued. At this point tetrabenazine 12.5 mg bid was added, and the patient experienced nice improvement in his TD and TA. Further increase to 25 mg bid resulted in marked improvement in both TS. The patient complained of some mild sedation on propranolol 60 mg bid and tetrabenazine 25 mg bid but was pleased with his overall control of symptoms.

Treatment of TA requires an individualized approach. Certain patients can come off of neuroleptics given they do not have significant psychosis. In other cases, a clinician should try and either reduce the dose of the offending DBA or switching to a less potent DBA. If this is not possible, then adding on additional drugs is necessary. The unfortunate truth about TA and other TS is that they are often very difficult to treat, and the majority of patients may experience less than optimal benefits with current therapies. In the series by Burke et al., only 1/3 of patients had complete improvement of TA with treatment. Experience in a university-based movement disorders clinic also illustrates that most patients with TA, TD, and other TS continue to suffer despite best efforts to treat these conditions.

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Treatment of Acute Dystonic Reactions

68

Daniel Tarsy

Case

A 27-year-old man presented to an emergency room complaining of a swelling sensation in his tongue and throat present for about 2 days. This was preceded by a flu-like syndrome several days earlier. Neurological examination was normal. A neurology consultant who saw the patient noted mild intermittent retrocollis with extensor posturing of his head and neck. On closer questioning the patient recalled that he had also been experiencing nausea and had vomited once 3 days before onset of neurological symptoms for which his PCP had prescribed prochlorperazine 10 mg bid; two doses were taken; the last was 2 days before coming to the emergency room. An ADR to a phenothiazine was suspected, and he was given diphenhydramine 50 mg by injection. His abnormal tongue and throat sensations and retrocollis resolved immediately. He was discharged home and advised to take diphenhydramine 50 mg orally every 4 h as needed in case of recurrence of his neurological symptoms.

Discussion

Acute dystonic reactions are extrapyramidal reactions that occur in about 2% of patients after receiving a DRB, quite often after their very first dose. They attracted a good deal of attention and research interest shortly after the introduction of APDs into clinical practice in the early 1960s. The most common drugs causing ADRs are APDs, but they may also occur following initiation of certain antiemetics which block dopamine receptors such as metoclopramide and prochlorperazine, occasionally after serotonin reuptake antidepressants, after certain calcium channel blockers with DRB properties which are not available in the United States such as cinnarizine and flunarizine and have very rarely been reported following miscellaneous drugs such as diphenhydramine, chloroquine, ethosuximide, and domperidone. They are more common in children and young adult males in contrast to other drug-induced extrapyramidal reactions such as drug-induced parkinsonism and tardive dyskinesia which are more common in older individuals. ADRs vary in presentation and may include intermittent or more sustained muscle spasms and abnormal postures of the eyes, face, neck, and throat. Oculogyric crises, blepharospasm, trismus, oromandibular dystonia, facial grimacing, protrusion or twisting of the tongue, distortions of the lips, or glossopharyngeal contractions may occur, and in severe cases dysarthria, dysphagia, jaw dislocation, and respiratory stridor may result. Neck muscles are very commonly affected producing spasmodic torticollis, most commonly of the retrocollis type. In some cases subtle forms of orofacial dystonia may occur without readily apparent muscle spasm and cause subjective cramping sensations in the jaw, tongue, or throat causing difficulty in chewing, swallowing, or speaking. The trunk is more severely affected in children causing opisthotonos, scoliosis, or lordosis. Torsional movements of the extremities with hyperpronation and adduction postures are much less common.

Acute dystonic reactions may be painful and are commonly very frightening, and these features, along with their acute onset, are the reason that the majority of such patients are seen and treated in an emergency room setting. If unfamiliar with the signs of an acute dystonic reaction, particularly if there is axial hypertonia, it may be confused with seizures, tetanus, rabies, encephalitis, meningitis, or subarachnoid hemorrhage. And, because dystonic signs sometimes remit and exacerbate or appear to respond to reassurance and suggestion, they can be mistaken for hysterical reactions.

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Acute dystonic reactions are the earliest of the extrapyramidal side effects to appear and typically begin within hours of a single dose of a DBR. Sometimes there may be a delay of 12–36 h between drug administration and the appearance of dystonia which temporarily obscures the diagnosis. If untreated, ADRs typically wane and eventually remit spontaneously but may fluctuate in severity over several hours or days after a single dose. They will usually reappear in the future if other APDs of equal potency are introduced. Long-acting parenteral phenothiazines given once monthly, such as fluphenazine decanoate, may produce acute dyskinesias in a cyclical pattern within 72 h of each administration and in this setting are sometimes confused with tardive dyskinesia. Persistent dyskinesia or dystonia has not been reported following acute and brief exposure to ordinary doses of antipsychotic drugs. There are very rare reports of persistent dystonia or dyskinesia following relatively brief exposure to ADRs, but these have not occurred after single doses. Acute dystonic reactions might also be expected to occur following the use of presynaptic dopamine-depleting drugs such as reserpine or tetrabenazine. There have been no documented cases of ADRs following the use of reserpine, but they have been reported after the use of tetrabenazine which also has dopamine receptor-blocking properties. Following routine clinical use of APDs, the overall incidence of ADRs is estimated at 2–10% although there is considerable variation depending on the potency and dose of DRB used.

The pathophysiology of ADRs is uncertain. Although these reactions were at one time regarded as idiosyncratic, their incidence appears to be especially common after treatment with high-potency DRBs with relatively low anticholinergic potency and to be somewhat dose dependent. In one clinical study, patients with ADRs had higher erythrocyte phenothiazine concentrations than patients without dyskinesia. Although impaired synaptic dopamine neurotransmission is a reasonable mechanism, several clinical observations have raised doubts about this explanation. The fact that reserpine, despite its ability to produce acute and rapid presynaptic dopamine depletion, does not produce ADRs suggests that acute inhibition of DA transmission is insufficient for their production. Although tetrabenazine, also a depletor of presynaptic dopamine, may produce ADRs, this may be due to its additional property as a DRB. The clinical similarity between APD-induced ADRs, dystonia produced by levodopa in patients with Parkinson's disease, and the dystonias associated with tardive dyskinesia has suggested the alternative possibility that activation rather than blockade of DA mechanisms may be responsible.

Acute dystonic reactions following administration of DRBs have been described in baboons and marmoset monkeys. Similar to humans, baboons show individual susceptibility as only a small minority of animals develop acute dystonia following haloperidol treatment. Catecholamine depletion, produced by pretreatment with reserpine or reserpine plus α-methyltyrosine, greatly reduces or abolishes haloperidol-induced dystonia consistent with the dependency of ADRs on presynaptic catecholaminergic mechanisms. In Cebus monkeys, a monoamine oxidase inhibitor reduced haloperidol-induced ADRs, consistent with the traditional view that acute dystonia is due to dopamine inhibition rather than facilitation.

The synthesis and release of dopamine in the nigrostriatal system increases immediately in response to blockade of dopamine receptors. This presumably compensatory increase in dopamine synthesis and metabolic turnover is a complex function mediated by long loop as well as local striatonigral feedback connections and effects on dopamine autoreceptors. It has been suggested that activation of nigrostriatal dopamine turnover produced by dopamine receptor blockade may account for ADRs. Similar to ADRs, the activation of dopamine turnover following dopamine receptor blockade is a relatively transient phenomenon that declines with repeated drug exposure. This may correspond to the clinical observation that patients who experience ADRs sometimes develop "tolerance" to this effect following repeated DRB exposure even in the absence of anticholinergic treatment. One study of prophylactic anticholinergic drugs showed that the incidence of ADRs diminishes greatly after 1 week of DRB treatment. In man, ADRs often occur after a delay of 24–36 h after a single dose although they appear more acutely in non-human primates. In one human study, ADRs occurred 23–56 h after a single dose of butaperazine, at a time when plasma and red cell butaperazine concentrations were falling. However, if ADRs are due to accelerated dopamine turnover, their appearance in the presence of a DRB seems difficult to explain. However, in animal studies striatonigral DA turnover peaks earlier than the appearance of acute dyskinesia in humans so that delayed onset of ADRs may be due to a combination of falling striatal DRB concentrations coupled with a continued increase in synaptic dopamine availability. Moreover, since a single dose of APD can produce dopamine supersensitivity that persists for 24–48 h after drug administration, enhanced DA release acting on incompletely blocked and increasingly sensitive dopamine receptors may be responsible for ADRs.

The fact that anticholinergic drugs dramatically abort ADRs appears to be evidence for acute dopamine receptor blockade with restoration of dopamine-acetylcholine balance by cholinergic blockade. That apomorphine, a potent direct DA receptor agonist, also reverses ADRs provides additional evidence that acute dyskinesia results from acute dopamine deficiency. However, in view of the hypothesis of dopamine activation discussed above, the ability of anticholinergic drugs and apomorphine to inhibit DA turnover may

be more relevant mechanisms. Anticholinergic drugs block the increase in DA turnover produced by DRBs, while apomorphine reduces nigrostriatal DA turnover and suppresses nigrostriatal firing rates by activation of presynaptic autoregulatory DA receptors.

As previously mentioned, ADRs are far more common in children and young male adults than in older individuals. In addition, paralleling idiopathic torsion dystonia, children frequently show more severe trunk and extremity dystonia, while adults usually show more restricted involvement of the neck, face, tongue, or arms. If ADRs are due to activation of dopamine mechanisms, then it is possible that children and young adults may respond to DRBs with brisker activation of nigrostriatal DA turnover due to their larger numbers of nigrostriatal neurons and higher concentrations of striatal dopamine concentration.

Acute dystonic reactions following treatment with DRBs are easily recognized and readily reversed in both humans and experimental animals. However, it is important to be aware of minor but uncomfortable dystonic manifestations that often escape diagnosis. The frequent delay of several hours between administration of a single dose of APD and the appearance of dyskinesia is a common cause of misdiagnosis. Successful reversal of ADRs, often in an emergency room setting, is a very dramatic phenomenon. Intravenous or intramuscular benzotropine (2 mg intramuscularly) is highly effective for severe ADRs, while oral anticholinergics may suffice for milder forms. If the DRB is discontinued, repeated administration of oral benzotropine may remain necessary for a period of 24–48 h due to the briefer action of anticholinergic drugs. The antihistaminic agent diphenhydramine (50 mg intramuscularly) is similarly effective, presumably because of its anticholinergic properties, and may be given either parenterally or by mouth. Intravenous diazepam has also been recommended if an anticholinergic agent is not readily available but is a second-line agent and should be used with caution because of the potential risk of respiratory depression.

The value of prophylactic anticholinergic drugs for prevention of extrapyramidal reactions is in general uncertain and controversial. For example, some studies have shown no reduction in the incidence of extrapyramidal syndromes, such as drug-induced parkinsonism, although the severity of symptoms may be reduced. However, in the case of ADRs, their incidence is clearly reduced by prophylactic treatment. Given the very uncomfortable and distressing nature of ADRs, those young individuals in whom ADRs have previously occurred and in whom anticholinergic toxicity is not an issue should be treated with prophylactic anticholinergic treatment for the first 30 days of ADR treatment to prevent recurrences.

In the case described above, several features of ADRs are present. Firstly, the ADR appeared in a young man, with retrocollis as the main neurologic finding. Secondly, the history of treatment with a DRB became evident only after close questioning by a neurology consultant. Thirdly, there was a delay of several days between exposure to the DRB and appearance of the ADR. Fourth, treatment with diphenhydramine, an anticholinergic drug, produced immediate relief of symptoms. And finally, because of the possibility of recurrence of symptoms over the next few days, he was supplied with oral diphenhydramine to use at home if symptoms returned.

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Treatment of Neuroleptic Malignant Syndrome

69

Robert Rodnitzky

Case

A 60-year-old man was admitted to the emergency department with a 4-day history of increasing somnolence and left hemiparesis. Computerized tomography of the head revealed a large right-sided frontoparietal subacute subdural hematoma with a 3 mm midline shift. He was taken to the operating room, and the subdural collection of blood was removed. Postoperative CT scan revealed that the midline shift was markedly improved. Upon returning to the intensive care unit for postoperative care, he was noted to be confused, combative, and noncooperative. A bedside electroencephalogram revealed no evidence of seizure activity. A complete blood count was normal as were serum electrolytes, BUN, and creatinine. A diagnosis of postoperative delirium was made, and he was treated with 5 mg of haloperidol intravenously with moderate benefit. This dosage was repeated on three occasions over the next 36 h due to recrudescence of the delirium. At 42 h postoperatively, he developed a fever of 40.1C. There was no evidence of wound infection, and a chest X-ray and urinalysis were normal. The white blood cell count was 12,400 without a left shift. He had developed moderate axial rigidity. His pulse was 119 and his blood pressure was labile, as high as 164/102 and as low as 104/64. Haloperidol was noted to be less beneficial for his confusion, and he seemed to be more somnolent. Because of suspicion of neuroleptic malignant syndrome, a serum creatine kinase [CK] was obtained and was found to be elevated at 5800 U/L. Based on the findings of an elevated CK level, labile autonomic parameters, rigidity, and worsening somnolence and confusion, a diagnosis of neuroleptic malignant syndrome was made. Haloperidol was discontinued. Liver function tests were obtained and were normal. He received 95 mg (1 mg/kg) of dantrolene intravenously repeated at 8-h intervals. Bromocriptine therapy was considered but was not administered due to concern for lowering his already low blood pressure. His urine was alkalinized. Over the next 3 days, the CK gradually came down to 2000 U/L, and the blood pressure stabilized at normal levels. Liver function tests were monitored while on dantrolene and remained normal. By day 6, body temperature had returned to normal and CK normalized. Dantrolene was discontinued and replaced with amantadine 100 mg twice daily. By day 9 he returned to an apparently normal clinical state. Amantadine was continued for an additional 5 days and then discontinued.

Discussion

Neuroleptic malignant syndrome (NMS) was first described in the 1960s shortly after the clinical introduction of neuroleptic drugs for the treatment of schizophrenia. It has since become apparent that the dopamine receptor-blocking action of neuroleptic agents is critical to the etiopathogenesis of this syndrome. All of the newer atypical antipsychotic agents have been reported to cause NMS as well. Aside from neuroleptic drugs, other dopamine receptor-blocking agents (DRBA) including the antiemetics metoclopramide and prochlorperazine as well as the dopamine-depleting agent tetrabenazine can result in NMS as well. Antidepressants including tricyclic agents, selective serotonin reuptake inhibitors, and lithium, either alone or in combination, have occasionally been reported to cause a syndrome resembling NMS, but the clinical description in these published cases is often difficult to distinguish from serotonin syndrome. Neuroleptic malignant syndrome typically appears shortly after the institution of a DRBA or after an increase in dosage. The onset of symptoms can be as long as 1 month after the inciting pharmacologic event, but 16% of cases appear within the first 24 h and 30% in 2 days. Risk factors for development of NMS include male gender, young age, dehydration, and agitation.

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Attempts have been made to establish definitive criteria for the diagnosis of NMS, but none have been widely accepted, in part because it has become apparent that all of the usual clinical components of the syndrome may not be present, especially when the causative drug is an atypical antipsychotic agent. There are, however, several clinical manifestations which in combination are considered to be the classical manifestation of the syndrome and are highly suggestive of the diagnosis given the proper preceding exposure to a DRBA. The classical clinical features of NMS are elevated body temperature, muscle rigidity, change in mental status, and autonomic lability. Body temperature typically rises above 38C. Other movement disorders such as tremor or dystonia can appear alone or along with rigidity. Autonomic lability often results in tachycardia and prominent blood pressure swings. Other features such as leukocytosis, usually without a left shift, and urinary incontinence are fairly frequent. Creatine kinase levels are usually elevated to at least 1000 U/L and up to 20,000 U/L in some patients. While all of the atypical antipsychotic agents currently in use can cause NMS, as mentioned above, the clinical syndrome resulting from their use is often less severe and/or devoid of one or more of the cardinal clinical features such as hyperthermia. In the sample case described above, most of the clinical and laboratory criteria were met, with a fever of 40.1 °C, rigidity, leukocytosis, elevated CK, and worsening alteration in level of consciousness, all beginning within 2 days of the onset of DRBA therapy.

A syndrome almost identical to NMS can occur in Parkinson's disease (PD) patients who have experienced a rapid reduction or abrupt cessation of dopaminergic therapy. When a NMS-like syndrome occurs under these circumstances, it has been referred to as the Parkinson-hyperpyrexia syndrome (PHS). Most commonly this results from discontinuance of levodopa but has also been reported after discontinuance of amantadine or a dopamine agonist. Similarly, interference with levodopa absorption by enteral feeding postoperatively and reduction in levodopa dosage after initiation of deep brain stimulation have both been reported to cause PHS. Accordingly, if a reduction or cessation in dopaminergic therapy is planned for any reason in a Parkinson's disease patient, I always try, if clinically feasible, to accomplish the reduction gradually to reduce the risk of PHS.

The first principal therapy in treating NMS is to discontinue the presumed causative drug. You should also discontinue exacerbating drugs such as the anticholinergic agents trihexyphenidyl, commonly used in PD patients, or benztropine, often co-administered with neuroleptics in psychiatric patients. This class of drugs can exacerbate hyperthermia by reducing heat dissipation, thereby worsening the symptoms of NMS. In patients with significant medical sequelae such as cardiac arrhythmias, renal failure, respiratory depression, or severe intractable hyperthermia, I recommend admission to the ICU where these severe complications can be expeditiously treated. Regarding body temperature, it is important to remember that aspirin or other antipyretics do not improve the hyperthermia of NMS. To treat hyperthermia, I stress rehydration, as dehydration is common in these patients. Attention to rehydration and alkalinization of the urine is important in combating renal dysfunction due to myoglobinuria. Reducing muscle contraction with dantrolene, as described below, and extracorporeal cooling techniques is also useful. However, if core temperature cannot be lowered below 41 degrees C with these measures, the patient should be intubated, ventilated artificially in the ICU, and pharmacologically paralyzed.

The pharmacologic treatment of NMS is largely based on the accumulated experience of clinicians with this syndrome rather than on controlled studies. Reported meta-analyses of case reports have provided conflicting results as to whether medical therapy does or does not promote recovery and reduce mortality. The largest of these reports, analyzing 734 cases from the literature, concluded that supportive care alone was associated with a 21% mortality rate compared to 6–9% among patients who had received medical therapy. On the other hand, a smaller literature review of 52 cases concluded that there was no difference in outcome between supportive care and drug therapy. It is fair to say, however, that most clinicians today opt for drug therapy in addition to rigorous supportive care. The most commonly used drug therapies are bromocriptine and dantrolene. As to which to try first, I opt for dantrolene if the patient has very significant hyperthermia, a very significant elevation of CK, or significant rhabdomyolysis. This agent improves these signs by relaxing the excessive muscular contraction seen in NMS. The starting dose is 1–2 mg per kilogram intravenously with up to 10 mg per kilogram per day, administered on a 6-h schedule. Most patients will require dosages in the lower part of this range. In patients in whom movement disorder and mental status changes are the most prominent symptoms, I try bromocriptine first, given orally or enteraly at a dosage of 2.5 mg every 6–8 h. Many patients will require both of these agents. Bromocriptine should not be given in patients with autonomic instability resulting in hypotension since blood pressure may be further lowered by this agent. Other dopaminergic agents have been used, most commonly amantadine but also levodopa, apomorphine, and rotigotine; the latter has the advantage of transcutaneous administration. Although there are scattered reports referring to the use of these alternative therapies for NMS, among them, I have only used amantadine as adjunctive treatment in a dosage of 100 mg twice daily. Dantrolene and bromocriptine, if effective, should be continued for 10 days after the symptoms resolve and should be tapered off to

avoid rebound worsening or recurrence. Regarding patients with Parkinson's disease and Parkinson-hyperpyrexia syndrome, the causative anti-Parkinson's medication which had been reduced or discontinued should be replaced.

Should medical therapy not be effective for the NMS, electroconvulsive therapy should be considered. The use of succinylcholine should be avoided in patients with NMS receiving electroconvulsive therapy due to an increased risk of serious cardiac arrhythmias.

Even with modern intensive therapy, the mortality of NMS in a recent review of over 1300 cases was 5.6%. Older age, acute kidney injury, sepsis, and especially respiratory failure are the most significant predictors of mortality. Fortunately, most patients can be expected to improve within 1–2 weeks. As noted above, apparently successful medical treatment should be continued for 10–14 days after recovery. Once treatment for NMS is completed, consideration of rechallenge with an antipsychotic drug is important since many psychiatric patients require dopamine-blocking agents to adequately control their psychosis. I recommend waiting until 2 weeks have passed during which the patient is symptom-free and then introducing therapy with the lowest potency atypical agent that is feasible, at a low dosage, being careful to monitor for the recurrent appearance of fever, elevated CK, or other NMS symptoms. For psychiatric patients who cannot go 2 weeks without antipsychotic agents, electroconvulsive therapy is an option during this time.

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Treatment of Serotonin Syndrome

70

Stewart A. Factor

Case

A 25-year-old man was seen in hospital consultation because of 1–2 days of increased anxiety, associated confusion, and a movement disorder. He had a medical history of depression and anxiety and had been admitted with a traumatic back injury after falling 5 feet from a ladder. He had been treated with mirtazapine 30 mg/night and fluoxetine 20 mg/day for the psychiatric issues. Upon admission he had an MRI of the lumbar spine which demonstrated a compression fraction at L5. He was treated with intravenous fentanyl 100 mcg/hr. Within 8 h he developed increased anxiety and confusion. On examination he was febrile at 102° F and was diaphoretic. He was awake but kept his eyes closed and was lethargic and disoriented to place and time. Key findings included motor impersistence with tongue protrusion, tongue tremor, and multifocal myoclonus involving the neck, face, and extremities. It increased when the patient held his arms in front of him and further with finger to nose; he had asterixis (negative myoclonus) and a fine postural tremor. He had normal muscle tone and no bradykinesia. He had no ataxia. Reflexes were brisk with patella and ankle clonus but downgoing toes. He could not walk. Abnormal labs included white blood count of 12.7×10^3/mcL (normal 4.2–9.1) and creatine kinase of 445 units/L (normal 49–397). Computerized tomography brain scan was normal.

He was treated with removal of the fentanyl and mirtazapine, IV fluids, acetaminophen, and clonazepam 0.5 mg q 8h PRN anxiety. He only received one dose over 2 days, but the syndrome resolved by then including the fever, confusion, and movement disorder. No other treatment was necessary, and he recovered fully.

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Discussion

Historically, serotonin syndrome was reported to occur with the combination of therapeutic doses of tricyclics or SSRIs (>SNRIs) and nonselective monoamine oxidase inhibitors (MAOI). However, other drugs such as fentanyl, tramadol, methylphenidate, methylene blue, ondansetron, valproate, linezolid, dextromethorphan, meperidine, cyclobenzaprine, and ecstasy have also been reported to cause serotonin syndrome when used with SSRIs or SNRIs as seen in the case report. In fact the most common combination in the literature is paroxetine and tramadol. It is also possible that high doses of a single serotonergic drug can cause serotonin syndrome. The occurrence relates to excessive stimulation of the 5HT1 and 5HT2 receptors and secondary inhibition of DA neurons in the SNc.

The serotonin syndrome generally develops over hours to days after initiation of the second drug or an increase in the dose. The clinical features are in several realms including motor, mental, and autonomic. The most prominent motor signs are myoclonus and hyperreflexia (clonus) but also include tremor, dystonia, rigidity, as well as extensor plantar reflexes. The mental features are confusion, agitation, disorientation, and restlessness. Autonomic instability includes fever, nausea, diarrhea, flushing, diaphoresis, rigors, tachycardia, tachypnea, BP change, and pupillary dilatation. In severe cases high fever, seizures, oculogyric crisis, and opisthotonus are seen. Laboratory changes include elevated creatine kinase, leukocytosis, metabolic acidosis, and possible rhabdomyolysis. Reported mortality rates range from 2.4% to 12% with death occurring because of DIC, myoglobinuria with renal failure, and cardiac arrhythmias.

The serotonin syndrome may appear to be clinically similar, if not identical, to neuroleptic malignant syndrome. Diagnosis will depend on the drug combination that triggered the event. The differential can be particularly complicated when the patient is treated with antidepressants and an atypical antipsychotic, especially one with serotonergic

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properties. Some in the literature have labeled such cases neuroleptic malignant syndrome and others serotonin syndrome. Since there are no diagnostic markers for either disorder, the therapeutic approach should be the same. Other disorders in the differential include anticholinergic toxicity, acute dystonic reaction, acute encephalitis or meningitis, catatonia, heat stroke, sympathomimetic intoxication, cocaine, methamphetamine, and PCP intoxication.

Two sets of diagnostic criteria have been developed for the serotonin syndrome. The Sternbach criteria published in 1991 include (1) a recent increase or addition of known serotonergic agent to an established regimen and (2) at least three of the following: mental status change, agitation, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, fever, and (3) other etiologies ruled out.

The Hunter Criteria, published in 2003, include clonus as a prime feature. They include any of the following findings: spontaneous clonus, inducible clonus with agitation and or diaphoresis, ocular clonus plus agitation or diaphoresis, tremor plus hyperreflexia, and hypertonia plus hyperpyrexia plus ocular clonus or inducible clonus.

The key to the treatment of serotonin syndrome is recognition. Once recognized, the principal treatment step involves withdrawal of the causative agent(s), and generally the syndrome will resolve over hours to days, as seen in this case. Patients should be closely observed until resolution and supportive measures that may be required include antipyretics and intravenous fluids. On rare occasions patients will require treatment for myoclonus with clonazepam at doses up to 0.5 mg TID or lorazepam 0.5 TID, but these can worsen mental status changes. As with most drug-induced movement disorders, there is a propensity for physicians to try anticholinergics, but they have limited use in this scenario and can add to mental status dysfunction as well. Antiserotonergic medications such as cyproheptadine (4–20 mg per day), methysergide (4–8 mg daily), or propranolol (up to 120 mg per day) may be helpful but should only be used short term. I have not seen the need to use these drugs in the cases I have seen. In severe cases treatment of seizures, arrhythmias, coagulopathy, and rigidity may be necessary. To prevent a recurrence, high dosages or combinations of serotonergic medications should be avoided.

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Part X

Other

Treatment of Paroxysmal Kinesigenic Dyskinesias

71

Nikola Kresojević, Roberto Erro, and Kailash Bhatia

Case 1: Isolated Paroxysmal Kinesigenic Dyskinesia (PKD) and *Proline–Rich Transmembrane Protein 2* (*PRRT2*) Mutation

This patient, a 31-year-old man, was referred to us because of episodes of abnormal posturing of arms and dystonic movements of fingers and toes, sometimes spreading to the trunk. Attacks were triggered by sudden movements after periods of rest, for example, exiting the car or getting out of bed. The first episode appeared around the age of 10. On average, it would last 30 s with a frequency of 50 attacks per day. He noticed that attacks had become rarer during his 20s and currently occur only twice a week. He learned he could prevent the episodes by avoiding sudden movements. Otherwise, he has been in good health, and there was no family history of relevance. Previous investigations were inconclusive including brain MRI, EEG and CSF analysis including glucose and lactate levels, all of which were normal. A trial with levodopa in childhood was ineffective. When we saw him, he was found to be positive for a *PRRT2* mutation, but his condition did not require treatment since the rare episodes of PKD did not affect his quality of life.

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Case 2: *PRRT2*, PKD and Infantile Convulsions Choreoathetosis (ICCA) Syndrome

This is a male patient who was seen by us at the age of 17. His first symptoms were three isolated seizures occurring between the ages of 6 and 18 months. Since then, there was no recurrence of seizures, and he had been doing well until the age of 14. At that time he started experiencing repetitive sudden episodes of cramping and twisting of his feet, spreading to his trunk and arms. Sometimes his jaw would also clench interfering with articulation. The involuntary movements were not suppressible, were variable in severity, but not as much in phenomenology, and were brought on by sudden movements and startle. Attack duration was always less than 40 s, and the frequency was as many as 100 times daily. His consciousness was always preserved during the attacks. His family history was positive for migraine (mother and brother) and infantile seizures (mother), while all investigations turned out to be normal. He screened positive for a *PRRT2* mutation and was successfully treated with carbamazepine (CBZ), 100 mg twice daily.

Case 3: *PRRT2*, PKD and Migraine

This last patient is a 24-year-old woman who was referred to us for episodes of dystonia of her feet, usually triggered by initiation of voluntary movements. The episodes started at age 6. Furthermore, she has had migraine without aura since age 15. Since she was prescribed prophylactic therapy with propranolol, her migraine attacks occurred less frequently, down to about once every 2 months. She felt that severity and frequency of headache and PKD were not related. Brain imaging, EEG and CSF analyses were all normal. Her family

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history was positive for migraine (mother, aunt and cousin). She screened positive for a *PRRT2* mutation and consequently was placed on CBZ, 50 mg twice daily, with a dramatic benefit on PKD, but not obvious change in her migraines.

Discussion

The three cases reported above illustrate the phenotypic spectrum of *PRRT2* mutations in which paroxysmal dyskinesias, of the kinesigenic variant in almost all subjects, occur in isolation or in combination with other episodic disorders, namely, epilepsy and migraine.

PKD is the most common variant within the group of paroxysmal dyskinesias (PxD), a rubric of conditions characterized by brief attacks of chorea and/or dystonia and, usually, a normal interictal examination. The term kinesigenic implies that sudden voluntary movements trigger the attacks. According to an old classification, PKD could be further stratified into primary (i.e. where no causes could be found) and secondary (symptomatic) forms. However, the term primary is being increasingly dismissed based on the discovery that mutations in the gene encoding the *proline-rich transmembrane protein 2 (PRRT2)* are responsible for the majority of "primary" PKD cases. There are a number of secondary causes associated with PKD (Table 71.1). Owing to the aetiological heterogeneity underlying PKD, it is essential to reach a definitive diagnosis to tailor appropriate management.

Table 71.1 Different aetiologies associated with episodic movement disorders resembling paroxysmal kinesigenic dyskinesias

Immune-mediated disorders	Multiple sclerosis
	Acute disseminated encephalomyelitis
	Systemic lupus erythematosus
	VGKC complex protein antibody encephalitis
	Anti-Caspr2 syndrome
	Hashimoto encephalopathy
Vascular	Stroke
	Chronic cerebral hematoma
	Cortical vascular malformations
	Transient ischaemic attack
	Moyamoya
Metabolic causes	Hypo-/hyperglycaemia
	Hypocalcemia/hypoparathyroidism/ pseudohypoparathyroidism
	Thyrotoxicosis
	Wilson's disease
Trauma	Central and peripheral
Other	Focal epilepsy
	Basal ganglia calcifications
	Central pontine myelinolysis
	Encephalitis/postinfectious
	Meningovascular syphilis
	Progressive supranuclear palsy
	Neuroacanthocytosis
	Human immunodeficiency virus infection
	Brain lymphoma
	Hemiatrophy/cortical dysgenesis
	Hypoxic-ischemic encephalopathy

Legend: VGKC, voltage-gated potassium channel

PRRT2 mutations are inherited in an autosomal dominant fashion with reduced penetrance for PKD but nearly full penetrance if infantile convulsions are taken into account. Most *PRRT2* patients are of Far East Asian ancestry. Disease onset is in childhood, rarely adulthood. Both sexes are affected, but males are more commonly affected than females.

PKD is typically characterized by a combination of dystonia and chorea, sometimes with ballistic elements. Unilateral distribution is reported, but generalized attacks are more frequent, and in some patients the face is also affected. Attacks are very brief, usually lasting less than 60 s, while their frequency is as high as 100 times daily, with a tendency to decrease with advancing age. About half of the patients may experience a premonitory sensory aura (i.e. sensory symptoms in the initial site of attacks). Episodes are not painful, consciousness is always intact and between attacks patients are usually normal. Triggers for PKD are, by definition, sudden voluntary movements or changes in the pattern of ongoing movements such as arising from chair, transition from walking to running, etc. However, in addition to the kinesigenic precipitant that is present in virtually all patients, about 40% of the patients also have other triggers including intention to move, anxiety, startle with loud noises, coffee intake and sleep deprivation.

Besides PKD, *PRRT2* mutations are associated with other paroxysmal disorders including different forms of epileptic seizures, hemiplegic or other forms of migraine (HM), episodic ataxia (EA) and paroxysmal hypnogenic dyskinesia. These features should be addressed when investigating patients with suspected PKD, since these will render the presence of *PRRT2* mutations more likely. A certain degree of phenotypic and genetic overlap between the various paroxysmal dyskinesias (PxDs) has been reported. Hence, in selected cases, genetic screening of all three main genes responsible for PxDs might turn out to be useful. The identification of the underlying cause is crucial in terms of therapeutic implications. Recognition of *PRRT2* mutations is important with regard to prognosis (there is a natural remission of attacks in adulthood).

Treatment efficacy and overall outcome depend on the aetiology of PKD. Several antiepileptic drugs (AED) have been reported to be effective with treatment response being higher in patients with *PRRT2* mutations than in cases without them. It needs to be emphasized that for "symptomatic" PKD, treatment strategies should first target the underlying process when possible, while AED could be used empirically, off-label, if necessary.

Most *PRRT2* cases are successfully treated with low doses of CBZ (50–600 mg daily) which is considered drug of choice. With CBZ patients are usually event-free or have substantial improvement. Oxcarbazepine and CBZ seem to have similar effectiveness and tolerability in PKD. Other AED including phenytoin, valproate, lacosamide, phenobarbital, clonazepam, topiramate and lamotrigine are also effective. Rarely, calcium channel blockers (flunarizine) and L-DOPA have been also reported to be effective in genetically undetermined PKD and might be tried if AED are ineffective or may be used in cases without *PRRT2* mutations. Treatments should be individualized to minimize adverse reactions, especially in patients of Far East ancestry, who are more prone to manifest idiosyncrasy with CBZ. Sensitivity to drugs, childbearing potential, severity and frequency of attacks and concomitant symptoms are also important features to be kept in mind when choosing the most suitable drug for PKD.

When *PRRT2*-associated PKD is associated with other disorders, a multidisciplinary approach should be considered for management (including an epileptologist and/or a headache specialist). In patients with PKD combined with epilepsy, monotherapy with CBZ should be favoured. On the other hand, topiramate and valproate, which are commonly used for migraine prophylaxis, have been reported to also be effective for PKD and should be tried first when migraine is present. This may not be the case for patients with hemiplegic migraine (HM). CBZ, which is generally thought to be ineffective for migraine, has been reported to improve both dyskinetic and headache attacks, in some *PRRT2* cases with PKD and HM. Valproate, lamotrigine and flunarizine have been found to have a prophylactic role in HM, and should be therefore considered if CBZ is proven ineffective. In PKD cases combined with episodic ataxia (EA), acetazolamide should be considered alone or in addition to CBZ. There are inconsistent data on acetazolamide efficacy in sporadic cases with PKD phenotype, but in some complete resolution of symptoms occurred. One patient, a homozygote for *PRRT2* mutations, with a severe phenotype including PKD, EA, mental retardation and absences, was treated successfully with acetazolamide and lamotrigine which reduced all paroxysmal events. A few other homozygous or compound heterozygous cases with *PRRT2* mutations were reported with EA and PxD and partially responded to CBZ or other AED.

Various disorders may produce episodes of abnormal movement resembling PKD. Thus, the diagnostic workup should be primarily oriented according to the associated features that would render *PRRT2* mutations less likely. Red flags that should prompt clinicians to look for other causes include late age at onset, prolonged or painful attacks, increase in attack frequency with advancing age, abnormal neurological findings between attacks and abnormal brain MRI or CSF findings (glucose and lactate levels, pterin pathway metabolite abnormalities). Table 71.1 lists the conditions that have been associated with episodic movement disorders resembling PKD. Treatment strategies should be tailored accordingly. Whenever a specific treatment is not available or is ineffective, symptomatic therapy should be considered on empirical basis. Some of patients with "symptomatic" PKD might benefit from CBZ and other AED, as in *PRRT2* cases.

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Treatment of Paroxysmal Nonkinesigenic Dyskinesia

72

Zain Guduru and Kapil D. Sethi

Case

We saw a 7-year-old boy in the clinic who developed episodic abnormal involuntary movements at the age of 3 years. He was a product of full-term normal delivery, and his developmental milestones were normal. In between the episodes, he was completely normal.

These attacks occurred two to three times per week and were not brought on by sudden movement or startle or prolonged running. Most of the time, there was no apparent precipitating factor, but at times if he stayed up late at night, he was more likely to have an attack. In addition, sometimes drinking a lot of Coca Cola or Mountain Dew precipitated the attack. There was no aura, and he developed generalized involuntary jerking and sometimes writhing movements that also involved his face. He remained alert and in fact was able to walk around during some of the milder attacks. These attacks lasted for 20 min to 6 h. Going to sleep invariably abolished them. There was no pain during the attack, and he never experienced urinary incontinence.

There was no family history of similar attacks. There was no previous head injury or encephalitis. Complete laboratory workup including ionized calcium was normal. MRI and EEG were normal.

A diagnosis of primary PNKD was made, and he was successively tried on carbamazepine titrated to 100 mg tid, benztropine gradually titrated to 4 mg tid, and clonazepam up to 1 mg tid. None of the medications were consistently helpful, but clonazepam reduced the frequency of the attacks. Deep brain stimulation of the globus pallidus interna was considered, but we did not think that these attacks were severe and disruptive enough to warrant it. Parents were advised to maintain a regular sleep schedule and avoid caffeinated beverages. Over the next 2 years, the attacks decreased in frequency and severity and did not return.

Discussion

Paroxysmal nonkinesigenic dyskinesia (PNKD) is usually inherited as an autosomal dominant trait. The attacks occur more often in males but not as consistently as seen in paroxysmal kinesigenic dyskinesia (PKD). The age of onset can be in early childhood, as in our case, but attacks may not start until the early 20s (mean age of onset is 8 years). The frequency varies from three per day to two per year. The usual precipitating factors are fatigue, alcohol, caffeine, and emotional excitement. Sleep benefit was found in one-third of reported families, particularly in those with p.ALA7val mutation in the MR-1 gene. The abnormal movements seen include choreoathetosis, dystonia, ballism, or combinations of all the three. Eighty percent of genetically proven cases were found to have a combination of dystonia and chorea, and 12% had dystonia only. Movements usually begin on one side and tend to spread or even generalize. The usual duration is minutes to 3–4 h. PKD, on the other hand, is precipitated by sudden movement or startle; the attacks are much shorter (seconds to minutes in duration), and the frequency is far greater. However, some PNKD attacks may last only for seconds. During the attack the patient may be unable to communicate but continues to breathe normally, and consciousness is preserved. Attacks are preceded by an aura in 63% of patients which are characterized by abnormal sensation, tightness, weakness, or speech disturbance.

In sporadic cases, onset age tends to be even higher; many of the sporadic PNKD patients in fact have a psychogenic movement disorder. Secondary causes include multiple sclerosis (MS), vascular lesions involving basal ganglia, or thalamus. Less common etiologies include head trauma and

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endocrine disorders including hypoparathyroidism, thyrotoxicosis, basal ganglia calcification, and HIV. Secondary PNKD might have interictal neurologic symptoms reflecting the underlying disorder, as opposed to primary paroxysmal dyskinesias with normal neurologic examination between the paroxysms. PNKD has been reported in a patient with familial ataxia, and in one family PNKD was accompanied by myokymia. In one series 6 patients with HIV had paroxysmal dyskinesia, 2/6 patients had PKD, and 4/6 patients had PNKD. Some families also have exertional cramping, which may be a forme fruste of PNKD or may be paroxysmal exertion-induced dyskinesia. EEGs and brain imaging in the idiopathic cases were normal.

PNKD was first described by Mount and Reback in 1940 under the name "familial paroxysmal choreoathetosis." A linkage study on an Italian family with PNKD by Fink et al. in 1996 first mapped the disease allele to chromosome 2q35, but the disease-causing gene was not identified until 2004. Most of the families involved are of European descent. Recently, a second locus was identified at 2q31, and other genes are being discovered (SLC2A1 and PRRT2). p. ALA7val mutation in PNKD/MR-1 gene is common. The mechanism by which the gene mutations cause clinical manifestations is not clear, but some hypotheses have been proposed. PNKD/MR-1 gene has homology with hydroxyacylglutathione hydrolase (HAGH) gene, which functions in a pathway to detoxify methylglyoxal from coffee and alcoholic. This could explain the attacks provoked particularly by caffeine and alcohol. Genetic tests for these mutations are available but not require for routinely use.

Three different missense mutations (A7V, A9V, A33P) have been described; all of them reside in the N-terminal region that has been suggested to code for a mitochondrial targeting sequence, necessary for the correct subcellular localization of the protein into mitochondria. This suggests that mitochondria could have a role in the pathogenesis of PNKD.

Avoidance of the precipitating factors can be helpful. Unlike PKD, PNKD does not respond to anticonvulsants, and medical treatment is less rewarding. However, anticonvulsants should be tried in every case, and an occasional patient may respond to carbamazepine (200–400 mg/day). Other drugs that have been tried include clonazepam (0.25 mg BID), diazepam (2 mg, 2–3 times/day), haloperidol, alternate-day oxazepam, anticholinergics such as benztropine and trihexyphenidyl (up to 20 mg total daily dose), and levetiracetam (500 mg BID), however, without consistent success although clonazepam may benefit some. A case report showed that sublingual lorazepam (2–3 mg during episodes) was successfully used to treat two children with PNKD from a large kindred. Benzodiazepines appeared to be of benefit in one-third to three-fourths of patients with PNKD. Deep brain stimulation (DBS) is also being explored as a potential therapeutic option in the treatment of medically refractory PNKD. Loher et al. have assessed the effect of chronic stimulation of the ventral intermediate (Vim) thalamus for treatment of dystonic PNKD. Chronic stimulation through a stereotactically implanted monopolar electrode in the left Vim resulted in a decrease of the frequency, duration, and intensity of the dystonic paroxysmal movement disorder, and the benefit of stimulation was maintained over 4 years of follow-up. Long-term follow-up was reported after 9 years and showed mild loss of stimulation effect. The effect was regained when the target was changed to the GPi. Schutte et al. reported two PNKD patients who responded very well to GPi DBS with complete suppression of dyskinesia. Similar to PKD, secondary PNKD may also improve with treatment of the underlying etiology as seen in the case of PNKD secondary to celiac disease. The patient's neurologic symptoms resolved upon the institution of gluten-free diet. Another patient had a 7-year history of episodes resembling PNKD secondary to idiopathic hypoparathyroidism. This patient was refractory to valproate but responded to levetiracetam.

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Treatment of Psychogenic (Functional) Movement Disorders

73

Mark J. Edwards

Case

This 23-year-old lady presented to the movement disorder clinic with a 9-month history of right arm tremor, right-sided weakness, right shoulder pain and paraesthesia affecting the whole of the right side of the body, including the face. She described the onset of symptoms 9 months previously occurring suddenly just after she had finished donating blood (something she had done twice previously without incident). She described standing up, feeling weak and unsteady and then losing awareness, falling to the ground. Witnesses told her that she became pale and then fell to the ground. She was unarousable for 15 s and then came round feeling unwell, lightheaded and with shaking of the whole body. She was taken to the hospital, by which time the shaking had largely subsided but continued to affect the right arm. She described sensory disturbance down the right side of the body including the face, and when she was examined, she was told her right side was weak. The initial diagnosis communicated to her was that she had likely had a stroke. Urgent MRI imaging was normal, and she was referred for neurology review. Her recollection of this review is that she was told that her scan was normal and nothing could be found to explain her symptoms. She was told that her symptoms were likely to be stress-related and would resolve with rest. She was discharged from the hospital without any specific plans for follow-up.

Over the 9 months before she was seen in clinic, her symptoms had continued, and she developed shoulder pain and fatigue. Her mobility became increasingly limited by fatigue and weakness in the right leg. She reported difficulty with simple tasks due to her right arm tremor. She was unable to return to work as a supermarket cashier and became reliant on her mother and boyfriend for financial and domestic support. She reported low mood, reduced appetite and poor sleep.

On review in the movement disorder clinic, she reported previously being well. She had a diagnosis of benign joint hypermobility syndrome with "growing pains" in her legs as a teenager. She reported frequent fainting as a teen and commonly experienced tachycardia on standing for prolonged periods. She had a period of anxiety and depression aged 16–18 triggered by the death of her grandfather for which she was treated successfully with antidepressants. She reported working hard in the run up to developing symptoms, as she was saving for a deposit to buy an apartment. She worked full time as a supermarket cashier, frequently did overtime shifts and was also studying part-time for a vocational qualification in childcare.

She had normal cranial nerves. Limb examination revealed a "give-way" pattern of weakness on the right. She had a positive right Hoover's sign with 4/5 power of right hip extension when tested directly, increasing to 5/5 when triggered by left hip flexion. She had a right arm tremor that was present at rest, on posture and during action. The axis and frequency of the tremor were variable, and brief pauses were observed during history taking. When performing externally paced tapping movements with the left hand, the right-sided tremor paused for several seconds. When she performed ballistic movements of the left arm, there was a brief pause in the right-sided tremor. On sensory testing she reported return of normal sensation exactly in the midline in her face and body. She reported vibration from a tuning fork applied to the right side of the forehead to be less than the left.

I explained the diagnosis of a functional movement disorder to her. I specifically indicated that I believed her symptoms were real and were not imagined, put on or "all in the mind". I explained a functional movement disorder as a common cause of movement disorder which is genuine but different in mechanism from movement disorders caused by structural or degenerative disease. I explained how I made

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the diagnosis and showed how the way her tremor could stop with distraction and how, although she was unable to move her right leg strongly, I could get the muscles to turn on normally by triggering the movement "automatically". I explained how this made me confident that the "basic wiring" of the system was okay and that the problem lays in her ability to access the body normally.

I then discussed different ways of thinking about functional movement disorders and specifically the role of psychological factors. I acknowledged how discussion of psychological factors can often come across as suggesting symptoms are not real or made up. I explained that there were likely to be many routes to developing a functional movement disorder and that I viewed psychological factors as risk factors that can make an individual more likely to develop a functional movement disorder but that as with risk factors for any illness, for an individual person, a particular risk factor may or may not be relevant. In this context we had a broad discussion of the triggering event itself (a simple faint), her background of joint hypermobility causing pain and mild autonomic disturbance, her past history of anxiety and depression and her recent very busy schedule. I explained that functional movement disorders can improve significantly with treatment but that this can be slow and may not happen for everyone.

I explained that the best approach given her individual situation was to embark on a specialist physiotherapy-based programme specifically for people with functional movement disorders. She was seen twice a day over a period of 5 days by a specialist physiotherapist who provided education regarding the symptoms and their precipitants and explored physical techniques based on distraction and competing manoeuvres in order for her to gain control over her tremor and access more consistent power in her right leg. By the end of 5 days of treatment, her gait significantly normalised, and she could stop the tremor for several minutes at a time. Over the following 6 months, symptoms continued to improve, and she returned to work part-time.

Discussion

Functional movement disorders are common and are often disabling. Quality of life studies suggest that as a group, patients with functional movement disorders have impairment of quality of life similar to people with Parkinson's disease. Persistence of symptoms long term is quite common (at least 50% of patients), and the resulting disability represents a significant burden to patients, their families and society.

The key positive feature of most functional movement disorders is that there are periods of complete normalisation of the movement problem. This can be triggered during examination by distraction or simply by observing the patient during history taking. Patients may tell you about periods of time when their symptoms have transiently stopped. For most organic movement disorders, episodes of complete resolution do not occur, and certainly complete resolution of a movement disorder via distraction is not seen in organic movement disorders (except sometimes in people with tics). The transient normalisation of the movement via distraction is a very useful starting point for explaining how you have made the diagnosis, and also it provides a demonstration of the potential for reversibility. There are situations (e.g. with fixed dystonic postures) where distractibility is hard to demonstrate – in this situation one relies more on pattern recognition and the incongruity of the observed movement disorder with movement disorders known to be caused by neurological damage or degeneration.

This case exemplifies the crux of the problem in the interaction between healthcare and patients with functional movement disorders. The diagnosis of a functional movement disorder was made very quickly (and correctly) at the first neurological review. However, this diagnosis was not communicated in a way the patient could understand and left her feeling dismissed and not taken seriously. The explanation given was itself very inadequate – it failed entirely to appreciate the complexity of the aetiology of functional movement disorders. No treatment was offered and nor was any follow-up arranged. This left the patient without any plan or any knowledge about how to face the situation.

Communication of the diagnosis is key, and I outlined in the case description an approach. It is crucial to realise that this approach needs to be flexible in its content relating to the individual circumstances of the patient. However, key elements remain: (1) a clear statement of belief and acknowledgement of the reality of symptoms, (2) explaining *how* the diagnosis was made, trying where possible to use the positive physical signs as explanatory aids, (3) discussing why the problem may have happened but acknowledging complexity and individual differences. This third point is very important. While it is true that people with functional movement disorders have higher rates of traumatic life events, personality disorder and other psychiatric diagnoses than those without, many people with functional movement disorders do not have these problems. Therefore, if one bases an explanation for the diagnosis on these factors, "you have a functional disorder because you have had a traumatic episode in the past", then in many patients the explanation is meaningless. Even for those with, for example, a traumatic past event, it still rarely makes sense to patients (or anyone) that the only issue to focus on is the past event, disregarding all the current symptoms.

I would argue that the diagnostic explanation, triage into treatment and follow-up should be the responsibility of the neurologist. First, patients have neurological symptoms and are understandably expecting a diagnosis from a neurologist. It is therefore not really acceptable for the neurologist to

make a non-diagnosis, "you don't have a neurological problem", and then to refer the patient to psychiatry. Second, at least 15% of patients with functional movement disorders have other neurological problems. This co-occurrence of problems can be complex to disentangle, and a neurologist is best placed to do this. Psychiatrists may well have a valuable role to play in management of selected patients with FMD. However, this role is not in diagnosis but rather in exploring the psychological underpinnings present in some people and assisting with management. This requires an understanding of functional disorders from the psychiatrist and good team working between the neurologist psychiatrists and therapists involved in treatment.

Treatment needs to be individualised and cannot proceed without a shared understanding of the diagnosis. Patients are very different one from another, with different co-morbidities (both physical and psychiatric). The skill of treatment triage is therefore an important one. Unfortunately, despite a growing evidence base for treatment, services remain very limited, and access to rehabilitation may be blocked by a misunderstanding that all patients have to be treated within psychiatric services, which themselves lack expertise in treating this patient group. In my view there is good evidence now to support the benefit of specific services for functional movement disorders over generic services. In each patient I would consider a number of management routes. The simplest is diagnostic explanation, reassurance, referral to sources of education (e.g. www.neurosymptoms.org) and an offer of follow-up. Physiotherapy has a clear evidence base for effectiveness but requires specific expertise. There are now consensus guidelines for physiotherapy in functional movement disorders which can help guide service developments. Psychologically based treatment can be effective, but the evidence base is limited. In my experience it works best when it is used to treat specific aspects of symptoms (e.g. co-morbid anxiety disorder) in the context of a good diagnostic explanation. For a sub-group of patients, pain is a dominant symptom, and for these people referral into a chronic pain management programme that focuses on physical and psychological techniques to manage pain can be useful. For those with severe symptoms, inpatient multidisciplinary rehabilitation including psychiatric and neurological input as well as therapy input from psychology, physiotherapy and occupational therapy can be useful for some, and an evidence base for this treatment is developing. However, it remains difficult to predict which patients are most likely to benefit from this (expensive) intervention. Experimental treatment approaches include using transcranial magnetic stimulation and "therapeutic sedation", but their place in patient management remains uncertain.

In the long term, even with access to treatment, many patients remain with symptoms that are disabling. As with patients with other causes of chronic neurological symptoms, supportive care with an emphasis of self-management is key and can enable such people to maintain a degree of independence and quality of life despite ongoing symptoms.

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Treatment of Wilson Disease

74

Alan Freeman

Case

A 25-year-old right-handed woman was seen for a history of bilateral upper extremity tremor of 2 years duration. The tremor, worse on the right, interfered with her activities of daily living including writing and putting on makeup and was embarrassing. She was told that this was essential tremor and tried propranolol and primidone without success; alcohol seemed to help. Her father had a history of tremor. No other family history or consanguinity. Her examination was notable for a moderate to severe postural and action tremor of the upper extremities. This was most notable when making a "pair of wings" with the hands in front of the nose and the arms extended at the same level. A handwriting sample showed significant tremor.

Since she had a significant tremor that did not respond to medications used to treat essential tremor, and because of her age, I ordered a serum ceruloplasmin. The result was 20 mg/dl, which was low (normal 21–53). A 24-h urine specimen for copper was 643 mcg/dl with the upper limits of normal being 50. She was seen by ophthalmology who confirmed that she had Kayser-Fleischer rings, consistent with Wilson disease (Fig. 74.1). We discussed medications used to treat Wilson disease, and I decided to start her on trientine 500 mg in the morning, 250 mg in the afternoon, and 500 mg in the evening. I told her to avoid foods that are high in copper including shellfish, nuts, and chocolate. Her subsequent examinations showed significant improvement in the upper extremity tremor making her activities of daily living much easier and improving her quality of life. The Kayser-Fleischer rings also gradually disappeared. Early during treatment she became pregnant but did not change her dose of medication. She subsequently delivered a healthy baby boy. I had her evaluated by the gastroenterology service, and her initial abdominal CT scan showed early cirrhotic changes in the left hepatic lobe.

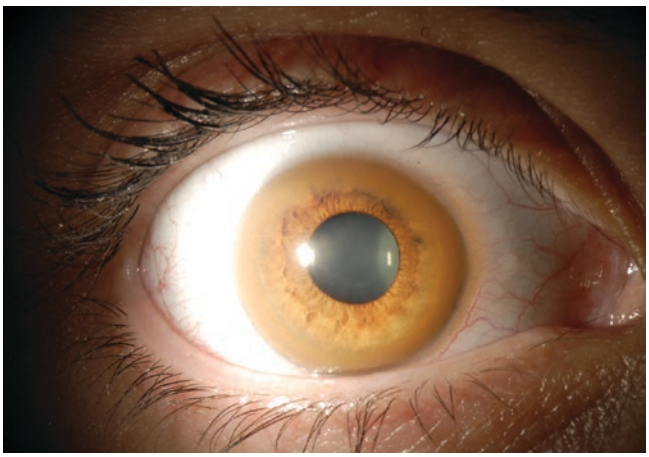

Fig. 74.1 Kayser-Fleischer ring when patient first seen

Discussion

Wilson disease is an autosomal recessive disorder primarily affecting the liver and basal ganglia. The responsible gene, discovered in 1993, is ATP7B on chromosome 13. More than 500 ATP7B mutations so far have been described in Wilson disease with the H1069Q mutation found frequently in patients of Eastern European descent.

The predominant clinical features are hepatic, neurologic, and psychiatric, although other systems are involved. Liver disease is the initial clinical manifestation of Wilson disease in about 40% of patients, particularly in patients under the age of 20, and includes acute hepatitis, chronic hepatitis, cirrhosis, and acute liver failure. Neurologic manifestations are the initial finding also in about 40% of the patients, typically over the age of 20. Symptoms of basal ganglia dysfunction are the hallmarks of Wilson disease. These include tremor (classically a proximal course high-amplitude tremor

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described as "wing beating"), dystonia, and parkinsonism as well as dysarthria and dysphagia. Psychiatric symptoms occur in 20–30% of patients including personality changes, depression, acute psychosis, or mild cognitive impairment. Ocular manifestations include the Kayser-Fleischer (KF) ring and sunflower cataracts. The KF ring is formed by deposition of copper in Descemet's membrane in the cornea which is gold, brown, or green in color and appears in the superior and then the inferior aspect of the cornea. It is best visualized with a slit-lamp examination by an ophthalmologist or neuro-ophthalmologist. The KF rings occur in 98% of patients with neurologic disease and in about 80% all cases. It may be seen in about 60% of presymptomatic individuals. It is not pathognomonic for Wilson disease and has been described in other conditions causing hepatic dysfunction including primary biliary cirrhosis and autoimmune hepatitis. Sunflower cataracts are seen in the anterior lens and have a sunflower- or sunburst-like appearance. They do not interfere with vision. Other systemic manifestations include Coombs negative hemolytic anemia, arthritis and osteoporosis, renal tubular acidosis, and myocardial involvement including cardiomyopathy, congestive heart failure, and electrocardiographic abnormalities.

The diagnosis of Wilson disease requires a high index of suspicion as well as evaluating family members of probands (Table 74.1). A serum ceruloplasmin should be checked in all patients, but this may be borderline normal in 5–15% of patients. Ceruloplasmin is an acute phase reactant and may be falsely elevated during infections or other inflammatory processes as well as during pregnancy or with the use of birth control pills. Ceruloplasmin may be low with malabsorption syndromes or with end-stage liver disease of any etiology as well as in heterozygotes for the Wilson's disease gene. Serum free copper (non-ceruloplasmin bound) is elevated in most untreated patients although it can be elevated in acute liver failure of any etiology. Urinary 24-h copper excretion typically is greater than 100 μg and is considered diagnostic in symptomatic Wilson disease patients. It is not pathognomonic for Wilson disease as this can be elevated in other liver diseases such as autoimmune hepatitis and obstructive liver diseases. As noted above, all patients with suspicion of Wilson disease should be checked for KF rings. Liver biopsy is a sensitive test for Wilson disease as copper content is typically greater than 250 μg/g dry weight. A copper content of less than 50 μg/g is helpful in eliminating the diagnosis in untreated patients. Other liver diseases, such as primary biliary cirrhosis, which also have elevated liver copper can be distinguished clinically. Since there is risk with a liver biopsy, this is not used as a screening procedure. Genetic testing is of limited use due to the greater than 500 ATP7B mutations. However, if a mutation has been found, then first-degree relatives of the patient with Wilson disease should be screened (as well as checking a serum ceruloplasmin level, 24-h urine for copper, and slit-lamp examination for KF rings). Brain MRI findings show hyperintensity on T2 imaging in the basal ganglia, tectal plate, and central pons. The "face of the giant panda" can be seen in the midbrain, although it is rare. Involvement of the pons can give the "face of the cub."

Treatment is lifelong for Wilson disease patients. They should avoid foods with high copper content such as chocolate, nuts, shellfish, and liver. Copper containers should be avoided for cooking. Medications for treatment include copper chelators as well as inhibitors of intestinal copper absorption (Table 74.2). The copper chelator penicillamine has been the preferred treatment for Wilson disease. It is best absorbed on an empty stomach. The initial dose is 250–500 mg/day with a maximum dose typically 1000–1500 mg/day. It may take several months before improvement in symptoms is noted. Treatment is monitored by measuring 24-h urine copper, and with chronic treatment urinary copper excretion is 200–500 μg/day. Unfortunately penicillamine has many side effects including neutropenia, thrombocytopenia, nephrotoxicity, and degenerative changes in the skin. Worsening of neurologic symptoms can occur in 10–50% of the patients during the initial treatment phase, and thus alternative chelators may be considered. Trientine, like penicillamine, promotes copper excretion. Neurologic worsening after treatment with trientine occurs but is less common than with penicillamine. Trientine has side effects such as gastritis and aplastic anemia. Trientine should also be given on an empty stomach. It also chelates iron, and therefore adminis-

Table 74.1 Evaluation for Wilson disease

Serum ceruloplasmin	Reduced
24-h urine copper	Increased
Liver biopsy	Increased copper
Genetic testing	ATP7B mutation

Table 74.2 Treatment for Wilson disease

Drug	Typical dose	Mechanism	Side effects
Penicillamine	1000–1500 mg/d	Copper chelator	Bone marrow suppression Proteinuria Autoimmunity
Trientine	750–1500 mg/d	Copper chelator	Sideroblastic anemia
Zinc	150 mg/d	Interferes with copper uptake from GI tract	Gastritis
Tetrathiomolybdate	Not FDA approved	Less likely to cause neurologic deterioration	

tration with iron should be avoided as the complex with iron is toxic. A typical adult dose is 750–1500 mg/day in two or three divided doses. Treatment monitoring is the same as for penicillamine. Zinc can be also used for treatment and works by inhibiting copper absorption from the gastrointestinal mucosa. It is typically used as maintenance treatment but can be used initially in patients who are asymptomatic or presymptomatic. The typical dose is 150 mg/day administered in three divided doses. Side effects are fewer, with gastric irritation being the main one. Neurologic deterioration is uncommon with zinc. Tetrathiomolybdate is an experimental medication that has been used for many years. It works by interfering with intestinal uptake of copper as well as binding copper from plasma. Potential side effects include bone marrow depression and hepatotoxicity although it is less likely to cause neurologic deterioration when it is initiated.

Patients with liver failure should be offered liver transplantation. Since the transplanted liver does not have ATP7B defect, copper metabolism normalizes after transplantation and continued chelation is no longer necessary. The data is controversial in patients who have stable liver function with predominantly neurologic manifestations. It is thought that these patients may not be good candidates for liver transplantation as outcomes are not always beneficial.

It is recommended that pregnant women continue treatment as did my patient as interruption of treatment can result in acute liver failure.

Patients should be monitored at least twice a year to confirm improvement as well as compliance with therapy. They should have lab tests including liver function studies, serum copper and ceruloplasmin, CBC, and a 24-h urine for copper. Typical 24-h urine copper excretion while being treated with copper chelators is 200–500 μg/day. Levels below this may indicate overtreatment or excessive copper removal. During follow-up ophthalmologic examinations, KF rings should disappear with proper treatment (Fig. 74.2).

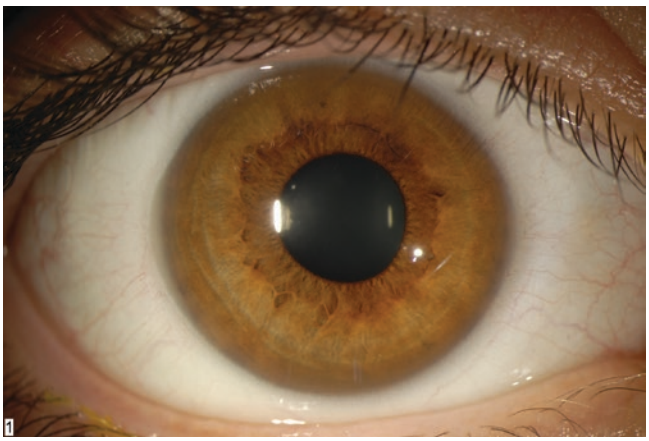

Fig. 74.2 Disappearance of Kayser-Fleisher ring after treatment

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Treatment of Hemifacial Spasm

75

Carlos Singer

Case

The patient is a 36-year-old man, working at high managerial and customer relation levels, who started noticing bothersome contractions of the left lower eyelid. His past medical history included an inguinal hernia, obstructive sleep apnea under control with oral appliance (no obesity), right rotator cuff tear, and dyslipidemia. His only medication was atorvastatin. He had no history of Bell's palsy.

Exam disclosed synchronous brief contractions of the left lower eyelid that would come in flurries in a spontaneous fashion and that would not cause palpebral fissure closure. The rest of his neurological examination was unremarkable.

It was initially thought this abnormal movement represented either eyelid myokymia or early hemifacial spasm. Injections with botulinum toxin were initiated with success. Over the ensuing months, eyelid contractions were associated with partial palpebral fissure closure and a few months later with left mid-cheek contraction.

MRI of the brain including MRA revealed a tortuous and ectatic left distal vertebral artery that impinged and posteriorly displaced the root entry zone of the left cranial nerves 7/8 complex and mild mass effect on the left hypoglossal and left abducens nerves. Neurovascular surgery consultations were obtained, but the patient preferred to continue receiving botulinum toxin injections every 4–6 months, which have provided excellent relief.

Discussion

Hemifacial spasm (HFS) is a syndrome of partial or complete and painless involuntary contractions of one side of the face. The movements come on spontaneously or are triggered by facial movements (smiling, lip pursing) or emotion. The contractions can be sustained (tonic) or brief and repetitive (clonic). HFS can rarely be bilateral (less than 5%), in which case contractions on one side are asynchronous with the ones on the other side.

Prevalence of HFS is 11 per 100,000 persons. HFS affects individuals of all ages with a peak in the middle age. There is female preponderance (M/F: 1/2). The only acknowledged risk factor is hypertension. Rare familial cases have been reported. A less vigorous association has been postulated with migraine and trigeminal neuralgia.

HFS may start as a very restricted phenomenon, such as lower eyelid twitch, as seen in our patient, before it extends to the rest of the face. HFS is a stand-alone movement disorder, and it should not be accompanied by any symptom outside facial symptomatology, and there are no sensory features.

HFS originates in the transition zone of central and peripheral myelin or the more proximal root entry zone of the seventh cranial nerve, where it is being compressed by an aberrant or tortuous loop of a vessel of the vertebrobasilar system. The most common culprit vessels are the anterior-inferior cerebellar artery (AICA), the posterior-inferior cerebellar artery (PICA), and the vertebral artery. HFS, therefore, belongs to the family of neurovascular compressive syndromes that also include trigeminal neuralgia, glossopharyngeal neuralgia, and vestibular nerve compression syndrome (postulated as a potential cause of dizziness and vertigo). The vessel pressure generates ectopic firing in the facial nerve or hyperexcitability of the facial motor nucleus.

Other etiologies of HFS are much less common. They include cerebellopontine angle tumors, brain stem gliomas, multiple sclerosis, and CNS vascular insults. A very small number are familial, but the genetic abnormality is unknown.

HFS requires differentiation from other facial dyskinesias, especially facial synkinesis following Bell's palsy and other facial nerve injuries (trauma, surgery). A key distinguishing feature of HFS is its spontaneous contractions

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as opposed to the tight triggering by voluntary facial movements seen with facial synkinesis. HFS mimics include psychogenic hemifacial spasm, craniofacial dystonia (blepharospasm, orofacial dystonia, oromandibular dystonia), facial tic, facial myokymia, hemi-masticatory spasm, and oculomasticatory myorhythmia.

Diagnosis may begin and end with the clinical exam if the clinician feels comfortable with an otherwise typical presentation and where surgical decompression is not being entertained in the near future. Magnetic resonance imaging of the brain can be done if the clinician is concerned about nonvascular etiologies, while brain MRA may pinpoint the culprit vessel and the site of compression. It is not unusual that only at the time of neurovascular surgery can the compression be visualized. Cerebral angiography is only needed if surgery is seriously being considered and is required for surgical planning.

Our patient had clear evidence of vertebrobasilar dolichoectasia specifically of the left vertebral artery. Of interest was his substantially younger age than most reported cases (mean age in the 50s), which raises the question of other predisposing factors (genetic, small posterior cranial fossa) that might be of academic interest to pursue but that would have no bearing on treatment at this time.

Botulinum toxin injections represent the treatment of choice with a high rate of success (85–95%) accompanied by a low rate of reversible complications (ptosis, facial weakness). Repeat injections are usually required every 3–6 months.

I inject subcutaneously in four sites around the involved eye with doses between 1.25 and 5 units of onabotulinumtoxinA (or other neurotoxin equivalents). Two sites are located in the tarsal portion of the upper eyelid, one site in the lateral canthus and one site in the outer half of the lower eyelid. I might also inject additional sites including the corrugator and the midface (zygomaticus complex, nasalis, risorius) as well as the perioral muscles and mentalis (see Fig. 75.1).

Oral pharmacology with carbamazepine, clonazepam, baclofen, and gabapentin is notoriously disappointing. Surgery represents the only chance for a permanent solution. Under general anesthesia, a retrosigmoid craniotomy is performed, and a Teflon sponge is placed between the vessel and the facial nerve. Figures of recurrence are in the low single digits, but there are risks of temporary or permanent deafness and or facial paralysis (also in the single digits).

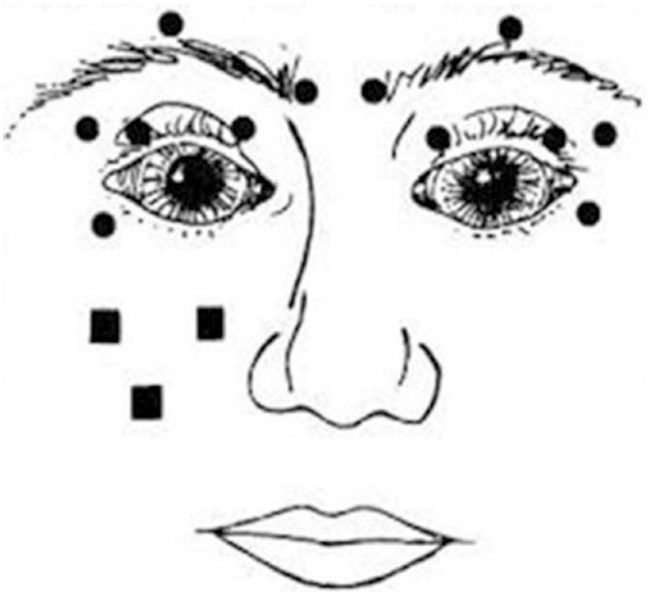

Fig. 75.1 Diagram of possible injection sites for a patient with a right hemifacial spasm. Two sites are located in the right upper lid staying away from the midline. One site is located above the right lateral canthus and another one in the lateral third of the lower eyelid. Other potential sites include the frontalis muscle above the eyebrow, the corrugator, and the midfacial area. The sites on the left side of the face would be considered in rare cases of alternating hemifacial spasm. (Reprinted from Taylor JD, Kraft SP, Kazdan MS, Flanders M, Cadera W, Orton RB. Treatment of blepharospasm and hemifacial spasm with botulinum A toxin: a Canadian multicentre study. Can J Ophthalmol. 1991 Apr;26(3):133–8. With permission from the Canadian Journal of Opthalmology)

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Treatment of Restless Legs Syndrome and Periodic Limb Movements

76

William G. Ondo

Case

This 56-year-old Caucasian woman was originally seen 15 years ago but now presents with worsening of restless leg syndrome (RLS). She first noticed a creeping and pulling sensation in both calves during pregnancies in her mid-20s. This seemed to resolve until about the age of 40 when she gradually began to have similar sensations that only occurred after 9 PM. This worsened over 4–5 years to the point where she experienced symptoms most nights, was developing sleep deprivation, and eventually sought medical care. Although she initially denied any family history of RLS, she later met several relatives at a family reunion with similar symptoms. At the initial visit, serum iron studies were normal, and she was placed on ropinirole 1 mg at night, which initially almost completely stopped all RLS symptoms. She returned a year later having increased the ropinirole to 2 mg secondary to breakthrough symptoms, with good results. She then switched care to her local primary care physician.

She now returns 10 years later, with markedly worsened RLS symptoms. They occur from about 11 AM until she finally falls asleep at 2 AM. Her entire legs and now arms are involved. In addition to the original creepy pulling sensation, she now has diffuse aching pain throughout her limbs. Over the last several years, she has increased the ropinirole to 4 mg in the evening and 4 mg at night. After each increase, she would usually demonstrate transient benefit for weeks to months but would then need to further increase the dose. On a couple of nights when she ran out of medicine, she did not sleep at all.

Examination shows an anxious-appearing woman who startles easily. When distracted, there were some arrhythmic stereotype movements in the legs. There was no evidence of neuropathy, and the remainder of her examination was normal. A sleep study showed delayed onset to sleep (2.5 h) and frequent periodic limb movements, some with awakening.

After long discussion about her RLS and the augmentation she is experiencing, we infused high-dose intravenous iron, then 3 weeks later quickly weaned off the ropinirole after starting low-dose methadone. Despite the iron and methadone, she still had a marked exacerbation of RLS for about four nights, including two with no sleep at all, but then rapidly improved. We stopped the methadone and started gabapentin enacarbil 600 mg at 6 PM. Her RLS is now largely controlled with occasional nocturnal breakthrough symptoms.

Discussion

The diagnosis of RLS relies entirely on the subjective report of (1) an urge to move the legs, which may or may not be associated with some other paresthesia; (2) worsening of symptoms with physical inactivity; (3) transient improvement of symptoms with physical activity; (4) worsening of symptoms in the evening and night, with improvement in the morning; and (5) the lack of a better explanation for symptoms. RLS can occur at any age, including children, and affects women somewhat more than men (1.5–2.5: 1). Diagnostic criteria in children are less clear, but there is a consistent association between RLS and attention deficit disorder. RLS is most commonly seen in people from Northern European ancestry, where the prevalence is about 15% of the population. In Asian countries the prevalence is much lower, typically 1–2%. There are currently 19 RLS genes, found mostly on GWAS studies, that confer risk for RLS, but none of them have very high penetrance, so it is not clinically indicated to assess for them.

The differential diagnosis for RLS includes akathisia associated with dopamine-blocking medications, which differs from RLS in that it affects the entire body rather than just the limbs and is not necessarily worse at night. Myalgia and other leg pain are also confused with RLS but can be differentiated from the lack of a true urge to move, even though repositioning may afford temporary relief.

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Neuropathic pain is typically superficial and worse in the feet, as opposed to RLS, which is usually deep and in the calves. True muscle cramps result in actual chaotic muscle contraction, which is not seen in RLS.

There are several medical conditions associated with RLS, including systemic iron deficiency, uremia, pregnancy, Parkinson's disease, essential tremor, and probably neuropathy. Of these, uremia is the most robust, as RLS affects about 30% of patients on dialysis, often very severely. Dialysis itself does not improve RLS, but successful kidney transplantation almost immediately and robustly stops symptoms. RLS is seen in about 30% of pregnant women, typically in the last trimester, and resolves within days of delivery in most cases. This can be problematic since most treatments for RLS are not established as safe during pregnancy. RLS is frequently worsened by antihistamine medicines, especially sedating antihistamines, which more readily cross the blood-brain barrier. Dopamine-blocking agents and serotonergic reuptake inhibitors can also potentially worsen RLS.

Evaluation of a typical RLS patient can be fairly minimal. Everyone should have serum iron studies, including ferritin, iron binding percentage, and a complete blood count (CBC). It is important to note that a CBC does not screen for iron deficiency and ferritin may be normal or even high despite reduced iron stores. Other evaluations are only done if clinically indicated. A polysomnogram often demonstrates periodic limb movements of sleep (PLMS), which are seen in approximately 90% of patients with RLS. Typically these are variations of a triple flexion response that occur every 5–90 s in stage 1 and 2 sleep. They can also occur during drowsiness. However, PLMS are not part of the diagnostic criteria for RLS. Many people have PLMS without RLS, as they are seen in normal aging, sleep apnea, and many neurodegenerative diseases. Therefore polysomnogram is usually reserved for people thought to have other concurrent sleep problems such as sleep apnea. Nerve conduction studies can be done if there is physical examination evidence of neuropathy.

The main pathology of RLS on autopsy studies is reduced brain iron, even in the setting of normal serum iron levels. Therefore, assessment of serum iron is only an indirect measure of what is thought to be truly associated with RLS. There is evidence for altered spinal cord activity, potentially mitigated by descending dopaminergic tracks. There is actually no evidence of overt dopamine deficiency, despite effective treatment with dopaminergic medications. There is evidence of increased dopamine turnover, suggesting increased activity of dopaminergic systems despite reduced functionality. Importantly, there is no evidence that RLS evolves into Parkinson's disease, although RLS may occur ephemerally as one of many non-motor features of Parkinson's disease.

Treatments for RLS are effective but not curative, so should be reserved for subjects whose symptoms are sufficient to justify chronic pharmacotherapy, most commonly when sleep deprivation occurs. First-line therapies include dopamine agonists (ropinirole, pramipexole, and rotigotine patch) and alpha-2-delta blockers (gabapentin enacarbil and pregabalin) (Table 76.1). Dopamine agonists work immediately and are especially effective for the pure urge to move and periodic limb movements. The oral drugs should be dosed 1–2 h before typical onset of symptoms and titrated to the lowest effective dose. Although initially very effective, dopaminergics can cause augmentation (earlier onset of symptoms, intensification of symptoms, spread to other parts of the body, and changed quality of symptoms) with chronic use (months to decades) [see case]. This can initially be treated with dose adjustments, usually earlier dosing, but only completely resolves with discontinuation of the dopaminergic, a very difficult process with marked rebound symptom exacerbation for up to 2 weeks, prior to improvement. Other possible side effects include sedation, edema, and impulse control disorders. Hallucinations and hypotension are rarely seen when these drugs are used for RLS.

Alpha-2-delta agonists improve RLS sensory symptoms to a similar degree as dopaminergics but do not improve PLMS as robustly. Unlike dopaminergics, they do improve sleep architecture, increasing deep slow wave sleep, and may improve painful symptoms. They have not been associated with augmentation but can cause sedation, "dizziness" edema, and weight gain.

Second-line therapies include Mu opioid drugs, especially low-dose methadone (5–20 mg/day), which has demonstrated little addiction or dependency in this population, and typically does not require any dose escalation over years. Oral iron is reasonable but poorly absorbed unless there is severe systemic iron deficiency, so not usually very effective. Iron salts are

Table 76.1 Drug therapy for RLS

Drug	Class	Initial dose	Typical dose range	Time
Ropinirole	Dopamine agonist	0.25 mg	1–4 mg	1–2 h before Sx onset
Pramipexole	Dopamine agonist	0.125 mg	0.25–1 mg	1–2 h before Sx onset
Rotigotine patch	Dopamine agonist	1 mg	1–4 mg	Any, 24 h patch
Gabapentin enacarbil	Alpha-2-delta	600 mg	600–1200 mg	5–6 PM with food
Pregabalin	Alpha-2-delta	50 mg	100–400 mg	2 h before Sx onset
Methadone	Opioid	5 mg	5–20 mg/day	2–3 h before Sx onset
L-DOPA	Dopamine precursor	25/100 mg	100–400 mg	1 h before Sx onset

Other opioid medications are used, with doses typically same as, or lower than, pain indications

absorbed best on an empty stomach, avoiding other divalent metals such as with a multivitamin. Iron in heme (blood/meat) is the best absorbed form. High-dose intravenous iron, specifically iron dextran or ferric carboxymaltose, may also improve RLS, even in subjects with normal serum iron studies. The peak improvement is seen 4–6 weeks post infusion.

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Treatment of Stiff-Person Syndrome

77

Marinos C. Dalakas

Case

A 62-year-old woman presented with trunk stiffness and rigidity manifested as slowly progressive difficulty turning and bending, slow-step walking, impaired balance, and sudden falls resulting in fear of walking alone, especially crossing a street or in crowded places. Her fears were interpreted as related to anxiety and depression, and she visited a neurologist who diagnosed "rigid parkinsonism." Brain MRI was normal, and a DaTscan was reported as suggestive of extrapyramidal disease. She was prescribed sertraline and carbidopa/levodopa, but there was no benefit. Over the ensuing 12 months, her symptoms worsened; the doses of both carbidopa/levodopa and sertraline were increased, and pramipexole was added, but again there was no benefit. When she came to see us, close to 2 years after symptom onset, there was prominent hyperlordosis with concomitant stiffness of both abdominal and lumbar paraspinal muscles. There was no cogwheel rigidity. She was talkative, with normal articulation, but very anxious, constantly emphasizing her fear to walk alone and her frequent falls especially in public spaces or with unexpected stimuli. The constellation of these symptoms raised the strong suspicion of stiff-person syndrome (SPS). We discontinued carbidopa/levodopa (over 1 month) and ordered anti-GAD antibodies which came back strongly positive at very high titers of 1:1000.0000. She also had history of thyroid disease with positive antithyroid antibodies. Pramipexole was also stopped. She was started on baclofen 10 mg TID along with diazepam 10 mg TID (first dose in the evening, increasing to TID over 3 weeks). After 6 weeks, she had clearly improved with better mobility, less stiffness, and reduced fear of walking. I asked her to increase the diazepam, but it made her sleepy; I added, instead, gabapentin 400 mg TID. She improved further, became able to walk easily without falling, moved about freely in open spaces without assistance, and was able to drive a car again. Sertraline was also discontinued. About 3–4 months after therapy, she became functional with minor limitations to the point that additional treatments were not deemed necessary. Because the improvement was clinically satisfactory and the drugs well tolerated, no need for immunotherapy was considered at this point.

Discussion

Stiff-person syndrome (SPS) is an autoimmune CNS disorder characterized by the triad of (1) *stiffness of truncal and proximal limb muscles* due to continuous co-contracture of agonist and antagonist muscles resulting in hyperlordosis, difficulty bending or turning, and slow, wide-based gait in an effort to improve balance; (2) *episodic spasms*, superimposed on the stiffness, precipitated by sudden unexpected noises and tactile and visual stimuli or emotional upset; and (3) *overt anxiety and task-specific phobias*, often leading to the erroneous diagnosis of a primary anxiety disorder and visits to psychiatrists. If anxiety dominates the clinical picture, SPS is discovered in retrospect when the administration of antianxiety agents, such as diazepam or alprazolam, improves the motor symptoms.

The symptoms vary in severity, from mild to severe, and can be fluctuating or fixed leading to disability. Up to 65% of SPS patients cannot independently perform daily activities because of body stiffness, phobias, anxiety-triggered muscle spasms, and frequent falls; others use walkers or wheelchairs, and still others are bedridden due to severe stiffness. At times, the muscle spasms are prominent and continuous and, if respiratory and thoracic paraspinal muscles are involved, may result in breathing difficulty, perfuse sweating, and other autonomic release phenomena ("status spasticus") requiring

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admission to the intensive care unit, intravenous diazepam administration, hydration, and supportive care.

The diagnosis of SPS is clinical, based on the aforementioned symptoms and signs, the exclusion of other neurological diseases that could explain stiffness and rigidity, and the absence of extrapyramidal or pyramidal tract signs. The diagnosis is aided by normal MRI of the brain and spinal cord; by the electrophysiologic recordings which demonstrate low-frequency motor unit firing at rest, simultaneously from agonist and antagonist muscles in spite of the patients' effort to relax (normally, when the agonist muscles contract, their respective antagonists are in a state of relaxation with no electrical activity); and the presence of high-titer antibodies against glutamic acid decarboxylase (GAD)-65 or against glycine receptors (other antibodies seen in rare SPS patients are listed on Table 77.1). SPS is frequently associated with other autoimmune diseases; among more than 100 patients we have followed, diabetes, thyroiditis, vitiligo, and pernicious anemia were the most common, with type I diabetes occurring in up to 35% of the patients. The presence of diabetes in a patient presenting with the aforementioned symptoms should raise the suspicion of SPS. Low titers of anti-GAD antibodies are also seen in diabetes as GAD is present in the β-cells of the pancreas, but there is distinction between the two antibodies; in diabetes the titers are low (below 1–2000 units), and the antibodies are directed against conformational GAD epitopes, while in SPS the titers are very high (above 5–10,000, usually in hundreds of thousands), and the antibodies are directed against linear epitopes.

Table 77.1 The spectrum and specificity of antibodies in stiff-person syndrome and other overlapping autoimmune CNS disorders

1. High titers of anti-GAD antibodies [>10 times, compared to the low titers (1–2000 units) seen in diabetes]
SPS, detected in 80% of patients (with IgG antibodies directed against linear GAD epitopes)
Limbic encephalitis
Myoclonus and temporal lobe epilepsy
Progressive encephalomyelitis with rigidity and myoclonus (PERM)
Cerebellar ataxia
Impaired eye movements with nystagmus and abnormal saccades
Neuromyotonia
Batten's disease (including the CLN3 knockout mice, the animal model of Batten's disease)
2. Low titers of anti-GAD antibodies
Insulin-dependent diabetes mellitus (in diabetes, serum IgG recognizes conformational GAD epitopes)
Other, autoimmune or not, disorders (these antibodies are transient or of unclear significance)
Transiently, after IVIg infusion because GAD antibodies are normally present within the various IVIg preparations
3. Anti-glycine receptor alpha 1 subunit (GlyRa1) antibodies
Seen in up to 10% of SPS patients (especially those with prominent spasms and phobias); they usually coincide with anti-GAD, but there may be rare SPS cases which are only GlyRa1-positive
Anti-GlyRa1 receptor antibodies are characteristic and diagnostic of PERM
4. Anti-GABARAP
Seen in up to 65% of SPS (in one series; not in clinical use)
5. Anti-amphiphysin
Seen in up to 5% of paraneoplastic SPS cases
6. Anti-gephyrin
Seen in a single case of paraneoplastic SPS
7. Anti-DPPX (dipeptidyl peptidase-like protein)
Seen in some patients with PERM. DPPX is an extracellular regulatory subunit of the Kv4.2 potassium channels present on neuronal surface and myenteric plexus that explains why patients may have gastrointestinal symptoms

Although high anti-GAD titers in the constellation of the aforementioned symptoms and signs secure the diagnoses of SPS, high tires of anti-GAD antibodies are also seen in other CNS autoimmune disorders including epilepsy, encephalitis, cerebellar ataxia, nystagmus, and myoclonus (Table 77.1). Among GAD-positive patients, there may be at times overlapping symptoms, most often SPS with epilepsy (in 5% of cases), ataxia (in 5–10%), and nystagmus. Diagnostic difficulties arise in about 10–20% of the patients who have the typical SPS clinical triad described above but have no detectable serum antibodies. In these cases of clinically "seronegative SPS," a trial with diazepam is advisable; a positive clinical response, objectively assessed after 6 weeks, is diagnostically helpful. Performing a spinal tap in seronegative patients to check for GAD antibodies in the CSF is not only difficult because of the stiffness but also uninformative, and I do not pursue it because GAD-seronegative patients are also GAD-negative in the CSF. At times, SPS starts focally in one lower limb ("stiff-limb syndrome"); these patients have mild disease, but many of them may later develop generalized symptoms. In 5% of patients, SPS is paraneoplastic, preceding or following certain cancers most often breast, lung, or thymomas. Paraneoplastic SPS is associated with either anti-GAD or more often with anti-amphiphysin or anti-gephyrin antibodies (Table 77.1).

Diagnostic errors are frequent; patients have been misdiagnosed as Parkinson's disease, primary lateral sclerosis, or multiple sclerosis. The prominent stiffness in the spine and the accompanying back pain has led patients to orthopedic surgeons and even to unnecessary surgery, including spinal fusion. The phobias and anxiety often lead to the diagnosis of a primary anxiety disorder and frequent visits to psychiatrists, only to discover in retrospect that after administration of diazepam for anxiety, the SPS improves. Although the phobias seem to stem from a realistic fear of falling caused by the stiffness and spasms, a concomitant primary anxiety disorder due to dysfunction of the CNS inhibitory pathways cannot be excluded. On the other end of the spectrum, there are patients with quite atypical symptoms, manifested with

clinically unusual or bizarre stiffness and painful spasms, often requiring narcotics, who either have very low anti-GAD antibody titers (which are not specific or diagnostic for SPS) or are GAD-negative; these patients do not have SPS but rather a complex functional disorder erroneously labelled "possible SPS."

In designing and understanding the rationale of therapies, the clinician needs to appreciate that two etiopathogenic factors are responsible for the SPS symptomatology; one is the reduction of GABA (presumably by antibodies against GABAergic pathways) which explains the stiffness, heightened sensitivity, phobias, and hyperexcitability and is helped by GABA-enhancing drugs and the second is the underlying autoimmunity which, like any other autoimmune disorder, requires immunotherapy. I typically start therapy with one to two GABA-enhancing drugs and I proceed to immunotherapy only if the response is unsatisfactory. My preference is to use a combination of two drugs, as follows:

(a) Diazepam, which is the initial treatment of choice. Because the doses required may at times be as high as 40–50 mg per day causing lethargy, drowsiness, and dependency, I try not to go higher than 10 mg TID. Similar compounds include clonazepam, alprazolam, lorazepam, and tetrazepam.
(b) Baclofen up to 50 mg daily; this is an excellent drug that I always start along with low doses of diazepam.
(c) Gabapentin up to 3–4000 mg daily. It helps the majority of patients in combination with the other two.
(d) Other GABA-enhancing drugs, such as levetiracetam, vigabatrin, or tiagabine, may offer supplementary benefit. In general, if the first three agents are not controlling the disease in a satisfactory manner, I proceed to immunotherapy. Anti-spasticity agents such as tizanidine and dantrolene offer minimal benefit. Botulinum toxin may help some patients, but the doses required are high and the benefit not overall substantial. I do not recommend intrathecal baclofen.

For immunotherapy, I start with intravenous immunoglobulin (IVIg), because in a controlled study, it was shown to be beneficial. I use 2gm/kg per month and try to maintain the improvement with 1 gm/kg as needed, usually every 2–3 months. For IVIg responders, I have tried to use as IVIg-sparing agents an immunosuppressant drug, such as CellCept or azathioprine, but their efficacy has been overall disappointing. For unclear reasons, corticosteroids are not very helpful. If IVIg is not helpful or sufficiently effective, I consider either plasmapheresis or rituximab, both of which can help a small number of patients. My personal preference is rituximab because in a controlled study we conducted, a small number of patients substantially improved with long-lasting benefit, even though the study did not overall demonstrate a statistically significant benefit owing to a strong placebo effect.

Suggested Reading

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