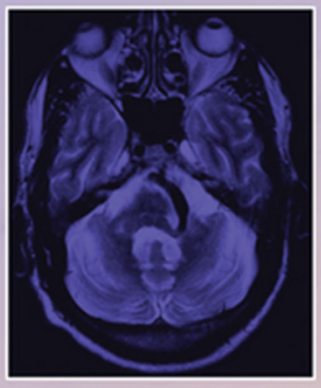
NEUROLOGY IN PRACTICE

Series editors **Robert A. Gross & Jonathan W. Mink**

Non-Parkinsonian Movement Disorders



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NEUROLOGY IN PRACTICE:

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Non-Parkinsonian Movement Disorders

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Series Foreword

The genesis for this book series started with the proposition that, increasingly, physicians want direct, useful information to help them in clinical care. Textbooks, while comprehensive, are useful primarily as detailed reference works but pose challenges for uses at the point of care. By contrast, more outline-type references often leave out the "hows and whys"—pathophysiology, pharmacology—that form the basis of management decisions. Our goal for this series is to present books, covering most areas of neurology, that provide enough background information to allow the reader to feel comfortable, but not so much as to be overwhelming, and to associate that with practical advice from experts about care, combining the growing evidence base with best practices.

Our series will encompass various aspects of neurology, with topics and the specific content chosen to be accessible and useful.

Chapters cover critical information that will inform the reader of the disease processes and mechanisms as a prelude to treatment planning. Algorithms and guidelines are presented, when appropriate. "Tips and Tricks" boxes provide expert suggestions, while other boxes present cautions and warnings to avoid pitfalls. Finally, we provide "Science Revisited" sections that review the most important and relevant science background material, and references and further reading sections that guide the reader to additional material.

Our thanks, appreciation, and respect go out to our editors and their contributors, who conceived and refined the content for each volume, assuring a high-quality, practical approach to neurological conditions and their treatment.

Our thanks also go to our mentors and students (past, present, and future), who have challenged and delighted us; to our book editors and their contributors, who were willing to take on additional work for an educational goal; and to our original publisher, Martin Sugden, for his ideas and support, for wonderful discussions and commiseration over baseball and soccer teams that might not quite have lived up to expectations. And thanks, too, to Claire Bonnett, our current publisher, for her efforts to bring this volume forward.

This volume represents the end of our series. As readers will recognize, neurology encompasses far more than we have presented; still, we hope that the high points encompassed by these books will serve well.

We have dedicated the series to Marsha, Jake, and Dan, and to Janet, Laura, and David. And also to Steven R. Schwid, MD, our friend and colleague, whose ideas helped shape this project and whose humor brightened our lives; but he could not complete this goal with us. Our thanks to them are undiminished.

Robert A. Gross
Jonathan W. Mink
Rochester, NY, USA

Foreword

Non-Parkinsonian Movement Disorders, edited by my colleagues, Drs. Brandon Barton and Deborah Hall, is a new entry in the larger series, *Neurology in Practice* and an immediate compendium of the *Parkinsonian Movement Disorders*. The topics covered in this volume provide the practicing neurologist, psychiatrist, and primary care health professional with expert reviews that cover both hypokinetic and hyperkinetic disorders. Hypokinetic disorders discussed include stiff-person syndrome, catatonia, and catalepsy as well as a variety of stiff-muscle conditions. For the hyperkinetic disorders, the editors have assembled a group of expert authors to cover tremors, myoclonus, tics, chorea, dystonia, and involuntary movements due to toxins and drugs. Importantly, because neurological disorders can be both out-patient and in-patient consultations, a chapter on ICU movement disorders emergencies is included, and an important chapter on the knotty and complex problem of psychogenic movement disorders that focuses on a variety of functional movements, both consciously and unconsciously generated.

Each presentation is anchored in very practical descriptions of phenomenology, key clinical information from the history and neurological examination that guide the physician to the correct diagnosis and treatment options. The text is enriched with tables and figures and a number of unique learning tools not found in other books on this topic. These tools include special boxed "Tips and Tricks" and "Caution" warnings that can help prevent errors. Besides the focus on practical clinical medicine, the authors provide two special highlights in each chapter, "Science Revisited" to remind clinicians of the scientific anchors related to the disorders and "Evidence at a Glance" where clinical trial evidence-based review information is provided. All these special additions allow a reader to study the full text, but also to retrieve rapidly needed key points.

With a long career devoted to the treatment of movement disorders, research, and education, I laud the editors and their recruited authors in providing the medical community with an accessible and accurate book with a unique format. In a busy environment, this text serves as a very solid neurological work with the essentials delivered in a succinct and highly readable format.

Because a movement disorders diagnosis always starts with accurate visual identification, a very strong advantage of this text is the video material that accompanies each chapter. The elegant examples assembled are well synchronized with the text materials and allow the reader to study very good examples of the disorders under consideration. I suggest that readers start a chapter with a short examination of the video materials, so as to be clear on the type of movement under discussion, then read the text, finally returning to the videos for a focused re-examination of the details of the carefully prepared examples. With this emphasis on the key role of expert visual recognition in movement disorders, the words of the celebrated nineteenth-century neurologist, Jean-Martin Charcot, resonate, and I offer this citation as the reader embarks on the very pleasant road of reading this volume:

> Let someone say of a doctor that he really knows his physiology or anatomy, that he is dynamic—these are not real compliments; but if you say he is an observer, a man who knows how to see, this is perhaps the greatest compliment one can make (Charcot, 1888, *Leçons du mardi)*.

Christopher G. Goetz, MD, Chicago, IL, USA, 2016

About the Companion Website

This book is accompanied by a companion website:

www.wiley.com/go/hall/non-parkinsonian_movement_disorders

The website includes:

Videos

1

Approach to Movement Disorders

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Introduction

Patients with movement disorders typically present with a change in their overall pattern of movements: this may represent an increase of movement (hyperkinetic), decrease (hypo- or akinetic), uncoordinated movement (ataxia), or a combination of the aforementioned. The initial task is to properly categorize the appearance or "phenomenology" of the movement disorder, as this is the essential step to guide the clinician in developing a differential diagnosis and treatment plan. Given recent advances in neurology, the majority of movement disorder patients are candidates for treatment, such as medication, physical therapy, or surgical interventions.

The first part of this book provides a short chapter on non-parkinsonian hypokinetic movement disorders; parkinsonian disorders are covered in another volume in this series. The second part includes hyperkinetic disorders. Part three includes various syndromes that do not fit into the other categories or that overlap between categories. Broader chapters in part four, on genetics, neuroimaging, rating scales, and videotaping suggestions, are intended to serve as clinician resources.

This introductory chapter provides an approach that will facilitate the evaluation of a movement disorder patient. The phenomenological categorization of the most common movement disorders falls into seven major categories: parkinsonism, tremor, dystonia, myoclonus, chorea, ataxia, and tics. Most of the commonly encountered disorders can be classified into one of these categories, but given the breadth of the diseases in the field, there are many unusual or rare types of movement that may not be easily categorized or may be consistent with more than one phenomenological category. A thorough history and examination are essential to defining the phenomenology. Home videotapes of the patient may also be useful if the movements are intermittent, variable, or not seen clearly in the office. Laboratory testing and imaging are necessary in some movement disorders, but are less helpful in many circumstances given that the disorders are diagnosed mainly on history and examination.

History

Start by asking *six questions* in the history.

1. Can you describe the movements?

Patients will usually be able to describe a decrease or increase (or both) in their overall movement from baseline, although often hyperkinetic aspects of abnormal movements can overshadow the hypokinetic movements from the patient's perspective. Hypokinetic movement disorders, also termed bradykinesia (slowed movement) or akinesia (loss of movement) are characterized by an overall decrease in the speed or amplitude of movement in any area of the body. Signs and symptoms could include decreased facial expression, slowed speech, reduced

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dexterity of the extremities, decreased arm swing, and slowed walking speed. Hyperkinetic movement disorders, also generally termed dyskinesia (abnormal movements), are characterized by an increase in baseline movements. Hyperkinetic movement disorders have highly variable manifestations, ranging from increased eye closure to arm flailing to jerking of the legs. Lastly, patients may complain of a change in the character of voluntary movements, such as becoming clumsy or unsteady with walking, which may be seen in ataxic disorders.

Certain features of abnormal movements are very important to elicit in the patient's description. Defining the conditions under which the movement occurs, such as with rest or with action, is necessary for accurate diagnosis and categorization of tremor. An ability to suppress the movement or an increase in the movement with suggestion are features common to tics. Specific triggers of the movements, especially with certain tasks, may be reported in dystonic disorders or paroxysmal movement disorders. Myoclonus can be triggered by startle. Asking about worsening of the disorder or improvement with certain foods or alcohol can narrow the differential diagnosis in forms of dystonia, myoclonus, or tremor disorders. A history of falls, especially the temporal course, is helpful in disorders that affect gait and balance, as falls are seen earlier or more frequently in some disorders as opposed to others.

2. When did the movements start and how have they changed over time?

Most movement disorders are subacute or chronic in nature. An acute onset is less common and may signify a secondary movement disorder related to an underlying inciting event, such as a stroke or medication change. Acute onset of movement disorders at maximal severity is also commonly seen in functional movement disorders, where patients will often present to emergency departments from the start. Most hypokinetic, hyperkinetic, and ataxic movement disorders will slowly worsen over time. Disorders that improve over time are less common; for example, tic disorders will typically improve from childhood into adolescence and adulthood. Static movement disorders may occur with birth injury or some dystonic disorders.

3. Are the movements continuous or intermittent?

Although many movement disorders start out as intermittent or suppressible, they tend to become more continuous or constant when they progress over time. The rest tremor seen in parkinsonian disorders is a classic example, where the tremor starts intermittently in a limb before becoming more regular and spreading to other limbs. Early on, this type of tremor can be sometimes voluntarily suppressed or decreased with movement, but later the tremor is continuous. Episodic movement disorders are much less common. Paroxysmal disorders, which are typically choreic or dystonic in nature, can many times be diagnosed by history alone if specific triggers such as sudden movements cause the disorder to occur. Functional (psychogenic) movement disorders are also frequently episodic. The circumstances under which the movement occurs can be particularly helpful. For example, restless legs syndrome worsens at night when the patient is laying down.

4. Is there a family history?

All modes of inheritance patterns are seen in movement disorders and the genetic basis of these disorders is rapidly being discovered. It is not sufficient to inquire only about the particular movement disorder seen in the patient, since broadening the questioning to other biological family members may yield additional important clues. For example, patients with grandchildren with intellectual disabilities may be at risk for fragile X-associated disorders. Tic patients may have associated diagnoses in the family, such as attention deficit hyperactivity disorder.

5. Are there other medical illnesses?

The majority of movement disorders are restricted to the nervous system, but systemic organ involvement may provide diagnostic clues. For example, patients with underlying cancers may be at risk for paraneoplastic disorders and iron deficiency anemia or diabetes may predispose to restless legs syndrome. The presence of cardiomyopathy is associated with Friedreich ataxia or mitochondrial disorders. Enlargement of visceral organs (spleen, liver) may suggest a lysosomal storage disease.

6. Have the movements been treated in the past and what was the response to treatment?

A response to dopamine medications may facilitate diagnosis of dopa-response dystonia. Paroxysmal movement disorders may be exquisitely responsive to antiepileptic medications. Other substances may improve movements, such as the improvement

of essential tremor, essential myoclonus, and myoclonus-dystonia with alcohol.

Examination

Depending on the movement disorder, abnormal movements may be present in focal or contiguous areas of the body or may be generalized. By determining the location and phenomenology of the movement, most patients can be placed into one of *seven distinct patterns* of abnormal movement.

Parkinsonism

The main features of parkinsonism are tremor at rest, bradykinesia or akinesia, rigidity, loss of postural reflexes, flexed posture, and freezing. Parkinsonism, in particular, Parkinson disease, is the most common disorder seen in movement disorder clinics and is covered by another volume of this series.

Tremor

This pattern is typically rhythmical and oscillatory and may affect more than one body part. Tremor should be classified on examination by the conditions under which it is activated: at rest, with posture, or with action. Tremor may be present in multiple conditions, for example, essential tremor, which is frequently seen with posture and action or intention. Tremors may also be task specific, such as the dystonic tremor of writer's cramp.

Chorea

Choreic movement is random in nature and is purposeless, non-rhythmic, and unsustained. It may appear to flow from one body part to another. Huntington disease is a frequent cause of chorea and manifests with brief, irregular movements. Chorea can be suppressed or camouflaged. It can be accompanied by "negative chorea" or motor impersistence.

Dystonia

In dystonia, agonist and antagonist muscles contract simultaneously causing twisting movements that are frequently sustained. The speed of the movement is variable and when sustained, can lead to abnormal postures and contractures. Dystonia is typically worsened with action, sometimes only occurring with specific actions. It can be classified by location, age of onset, and etiology, and the classification system has recently been revised.

Myoclonus

This pattern consists of brief, sudden, typically irregular jerks from muscle contraction. Myoclonus may be synchronized and triggered by action or startle. Negative myoclonus is caused by inhibition of the muscles, with the classic example being asterixis. Myoclonus can be rhythmic or oscillatory and occur in various parts of the body, either focally or generally.

Tics

Tics are abnormal movements (motor) or sounds (phonic) that are abrupt, usually transient, and can be simple or complex. Tics can vary over time and can be accompanied by an uncomfortable urge or feeling. Tics may be suppressible, although severe tics may be continuous. Gilles de la Tourette syndrome is characterized by the presence of both motor and phonic tics, present for more than one year, with young onset.

Ataxia

Lack of coordination of movement distinguishes ataxia from other movement disorders. The pattern of ataxic movement varies, but may include clumsy limb movements (dysmetria), dysarthria, ataxic eye findings such as abnormal pursuit, and uncoordinated walking. Kinetic tremor can also accompany ataxic signs. Ataxia can be localized to the peripheral or central nervous system so a thorough sensory and vestibular examination is necessary in these patients.

Other patterns of movements

There are several other types of abnormal movements that, despite being distinctly recognizable, do not fit well into the preceding patterns. These include stiff-muscles, akathetic movements, myokymia, paroxysmal dyskinesias, restless legs, and stereotypy. In addition, some movement disorders have more than one pattern of movement, such as in the myoclonus-dystonia disorders. Functional movement disorders frequently do not fit well into the above-described patterns, but caution must be maintained, since many unusual movement disorders can be labeled functional.

Diagnostic testing

Accurate description of the phenomenology of the abnormal movements as a result of the history and examination is the first and most fundamental step

in diagnosis of movement disorders. Additional diagnostic testing is not warranted in many situations, for example, in the classic appearance of Tourette syndrome. However, there are some studies that may enhance or confirm clinical diagnosis. For example, laboratory studies can be useful particularly with tremor. Abnormalities of the thyroid, evidenced by elevated or low thyroid stimulating hormone (TSH), may cause or worsen tremor. Wilson disease, diagnosed by abnormal copper levels (in serum and/or urine), low ceruloplasmin, and the presence of Kaiser–Fleischer rings; should be considered in younger patients who present with bizarre tremors or other unusual movement patterns/combinations.

Genetic testing is available for many movement disorders and is driven by family history, age of the patient, and financial resources. For the more rare movement disorders, such as the inherited ataxias and Huntington disease, it may be the only testing that can give a definitive diagnosis. For individuals who are considering family planning, it may be necessary that genetic testing be accompanied by genetic counseling.

Neurophysiological assessment may be helpful in myoclonus, where myoclonic jerks show brief electromyography (EMG) bursts of 10–50 milliseconds. Rhythmicity in tremor can be demonstrated on EMG, but this is not frequently ordered by clinicians when evaluating a patient with tremor. Electromyography may also be helpful therapeutically in dystonic patients when used in conjunction with botulinum toxin treatment. Nerve conduction studies may be used to evaluate ataxic individuals for sensory abnormalities in peripheral nerves.

Imaging can be valuable in movement disorders that do not fit classic patterns or presentations. The most common movement disorders typically show normal basal ganglia structures on routine imaging, as in essential tremor, and dystonia. However, patients with movement disorders that are localized to one side of the body, that have abrupt stroke-like onset, or that include ataxia should be imaged with computed tomography or preferably, magnetic resonance imaging. Atrophy of specific structures, such as the striatum in Huntington disease, or the cerebellum in degenerative ataxias, may support the clinical diagnosis. Functional or nuclear medicine imaging is playing an increasingly important role in diagnostics.

Treatment

The majority of treatment options in movement disorders are symptomatic, not curative. However, in a few circumstances, early intervention of treatable forms of movement disorders may be curative or halt the progression of the disease. While rare, such conditions should be considered in patients with particular disease profiles; examples include patients with young onset tremor, dystonia or parkinsonism (Wilson disease), or fluctuating dystonic and parkinsonian features (dopa-responsive dystonia).

The approach described in this chapter offers a straightforward approach to evaluating a movement disorder patient. Questions about the movements, course, family history, medical illnesses, and medication response will help the clinician with the evaluation. Correctly describing the phenomenology is key to narrowing the list of diagnostic possibilities and guides the need for additional testing. The subsequent chapters will fill in the details, and with this framework, the reader will gain an ease of diagnosis and treatment of movement disorders.

Further Readings

Fahn S, Jankovic J, Hallett M. *Principles and Practice of Movement Disorders*, 2nd ed. Philadelphia: Saunders, 2007.

Fernandez HH, Rodriguez RL, Skidmore FM, Okun MS. *A Practical Approach to Movement Disorders: Diagnosis, Medical and Surgical Management*. New York: Demos Medical Publishing, 2007.

Part 1

Hypokinetic

2

Hypokinetic (Non-Parkinsonian) Movement Disorders

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Introduction

Movement disorders can be broadly classified into two categories, based on the presence of excess movement or a deficiency of movement. Hyperkinetic movements involve the presence of excessive involuntary movements that may manifest as tremor, chorea-ballism, myoclonus, and tics, among other disorders. Hypokinetic movements show paucity of movement and are described with terms such as bradykinesia (slowness of movement) or akinesia (absence or extreme poverty of movement). The most common form of hypokinetic disorders are the parkinsonian syndromes, including idiopathic Parkinson Disease (PD), atypical parkinsonism, (multiple system atrophy, corticobasal syndrome, progressive supranuclear palsy, etc.), and secondary causes of parkinsonism (midbrain tumors, paraneoplastic disorders, etc.). These topics are covered in another book in this series. A different category of slowness comes from disorders that affect motor function to the extent of rendering it "parkinsonian" but that cannot be explained by traditional impairments in the basal ganglia circuitry. This chapter focuses on the *non-parkinsonian* causes of hypokinetic movement disorders, which may not be traditionally included in the differential diagnosis of parkinsonism.

This chapter aims to highlight some of the important and treatable causes of non-parkinsonian hypokinetic syndromes such as stiff person syndrome, primary lateral sclerosis, catatonia and psychomotor depression, hypothyroidism, and normal pressure hydrocephalus. These, along with other general causes, which can result in paucity or absence of movement, are listed in Table 2.1.

Stiff-person syndrome (SPS)

Moersch and Woltman described "stiff man syndrome" in 1956 in 14 patients who had progressively fluctuating rigidity and painful spasms affecting the muscles of the back and abdomen. An association between SPS and DM was established in the late 1980s; however, only a few of the originally reported patients had concomitant diabetes mellitus (DM). Solimena and colleagues later reported the presence of anti-glutamic acid decarboxylase (anti-GAD) antibodies in patients with SPS and DM. Since GAD is the rate-limiting enzyme for the synthesis of GABA, the major inhibitory neurotransmitter, in the central nervous system, GABAergic depletion at the cortical and spinal interneuronal level is central to the pathogenesis of SPS.

About 80% of SPS patients have a high titer of anti-GAD antibodies detectable in the serum or CSF.

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Table 2.1 Non-parkinsonian causes of hypokinesia

Stiff-person syndrome and related disorders
• Primary lateral sclerosis (PLM)
• Catatonia
• Neuromuscular causes: hypothyroidism, Brody syndrome, myotonia
• Akinetic mutism
Sequelae of vascular events (affecting anterior cerebral artery distribution)
Structural lesions: tumors, hydrocephalus, traumatic brain injury
Post-infectious: Creutzfeldt–Jakob disease, post-encephalitic parkinsonism
• Functional or psychogenic slowness

GAD is synthesized in the presynaptic GABAergic neurons in both the central nervous system and in the islet of Langerhans **β**-cells of the pancreas, hence the association with DM. There are two GAD isoforms—GAD65 and GAD67—but it is GAD65 that has been implicated in both SPS and DM. The GAD antibodies recognize different regions (epitopes) of the GAD molecule. The GAD antibodies in type 1 DM recognize the carboxy-terminal end or the center of the GAD molecule, while in SPS they recognize the amino-terminal fragment of GAD. Even though GAD antibodies are the most common antibodies associated with SPS, other proteins, both pre- and post-synaptic, in the GABAergic neuron have been implicated in the etiology of SPS or its variants (Box 2.1).

Clinical features

SPS disease is sporadic in nature, affecting women more often than men (in a recent series ~70% patients were women). Although the age of onset is variable, most of the afflicted adults are between 29 to 59 years of age. Symptoms start slowly and insidiously with episodic aching and stiffness of the axial musculature (paraspinal and abdominal muscles). Symptoms are usually symmetric and progress to involve the proximal muscles in all four extremities (Video 2.1). Typically the distal limb and facial muscles are spared. Patients have a characteristic hyperlordosis of the spine, which makes it very difficult for them to bend over to touch their toes. The hyperlordosis persists even when they are laying down. The rigidity and stiffness may fluctuate on an hour-to-hour or daily basis. If it affects the neck, patients should be counseled not to drive until adequately treated, as it may significantly limit their ability to turn their heads.

Superimposed on the stiffness, patients also have intermittent severe spasms. These can be precipitated by various triggers, such as loud noise, sudden movement, touch, stress, and fatigue. Spasms usually last for minutes and abate once the offending stimuli are removed. However, during the spasms, patients can experience significant pain. The spasms can be variable in magnitude and severity, may occur in rapid succession, leading to a "spasmodic storm," and can be severe enough to cause fracture of the long bones.

The fear of precipitating the spasms causes patients to have anxiety and task-related phobias. More than 50% of patients fear open spaces. The presence of phobias, excessive startle, and exacerbation of symptoms when emotionally upset many times leads to an erroneous diagnosis of a functional or psychogenic disorder and, unfortunately, delays proper treatment.

Electromyography (EMG) studies show the presence of continuous motor unit activity at rest without any abnormality in the motor unit morphology. Reflex-induced spasms are short-latency (<80 ms), stereotyped motor responses to nerve stimulation. These are expressed as one or more hypersynchronous bursts of EMG activity followed by short pauses and then slow cessation.

Box 2.1 Autoimmune antibodies in SPS and variants

Presynaptic:	GAD and amphiphysin
Postsynaptic:	GABA-A receptor associated protein, glycine and gephyrin

Diagnosis of SPS variants and related conditions

SPS is a clinical diagnosis. Dalakas and colleagues have outlined criteria, which can assist the clinician in making the diagnosis (Box 2.2). However, there are patients who do not meet all of these criteria or have other additional features: they are often categorized as SPS variants, which we describe below (Box 2.3).

Progressive encephalomyelitis with rigidity and myoclonus

Progressive encephalomyelitis with rigidity and myoclonus (PERM) variant of SPS (formerly, "stiff-person plus syndrome") is a rare paraneoplastic