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Movement Disorder Emergencies

Diagnosis and Treatment

2nd Edition

Humana Press

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For Rachel

Series Preface

This second edition to *Movement Disorder Emergencies* speaks to the great success of the first edition, which introduced a new clinical area in movement disorders in 2005. As the editor points out, this topic continues to be the basis of very popular courses at annual meetings of the American Academy of Neurology and the International Movement Disorders Society. The relative rarity of some movement disorders and the even greater rarity of the emergency complications, which sometimes arise, make this a crucial topic for the movement disorders specialist as well as the general neurologist, the internist, and emergency room physicians to understand and appreciate. Ideally, a copy of this book should be available in every emergency room.

Failure to properly diagnose and treat as well as failure to recognize the emergent situations that some of these disorders may place patients are again both emphasized. The current volume once again includes several patient vignettes at the start of each chapter to bring focus to the topic and highlight the urgency of the problem being presented. The availability of video illustrations further enhances the presentation. The discussion remains largely clinical but, where appropriate, basic mechanisms are also given proper attention. As the editor indicates, several brand new important topics have been added, which include psychosis in Parkinson's disease, anti-NMDA receptor encephalitis and other paraneoplastic movement disorders, and emergencies associated with Huntington's disease, deep brain stimulation, and psychogenic movement disorders. Suicide risk in Parkinson's disease, driving risk in patients with movement disorders, and emergent situations that arise during genetic counseling are other intriguing new topics that have only recently been receiving the attention they deserve. Once again the neurologic community owes a debt of gratitude to the editor of this book.

Boston, MA, USA — Daniel Tarsy M.D.

Preface

Movement disorders is a field firmly based in the outpatient clinic. The vast majority of patients with hypokinetic and hyperkinetic movement disorders receive their care in the neurologist's office, and, except for those patients who undergo deep brain stimulation, they rarely encounter the hospital or emergency room. It is precisely for this reason that a book devoted to movement disorder emergencies seemed appropriate over 10 years ago. Patients with movement disorder emergencies are uncommon, but the stakes are high—miss the diagnosis, and the patient can suffer irrevocable harm.

The first edition of *Movement Disorder Emergencies* was published in 2005, and it was generally well received. In the intervening half decade, there has been increasing attention devoted to this topic, with annual courses at the American Academy of Neurology's Annual Meeting and the Movement Disorder Society's International Congress. The structure of the book has been kept the same—clinical cases and vignettes are essential to each chapter. All of the topics have been updated by the authors to reflect the most current literature on etiology and treatment. The opportunity to produce a second edition also allowed inclusion of important topics that were missed in the first edition: psychosis in Parkinson's disease; emergencies in Huntington's disease; emergencies associated with deep brain stimulation; psychogenic movement disorders; NMDA receptor-mediated encephalitis; driving risk in movement disorder patients; genetics-related emergencies; and suicide and suicide risk.

As before, video examples of the most important movement disorder emergencies are presented in the accompanying video disc.

This book is dedicated to the patients presented within, who endure these unusual disorders with grace, courage, and resilience.

New York, NY, USA — Steven J. Frucht

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Chapter 1
A Brief Introduction to Movement Disorders

Steven J. Frucht

Abstract Movement disorders encompass a wide variety of diagnoses and clinical situations. Most patients with movement disorders are managed in the outpatient setting, and usually, time is not of the essence. However, certain conditions present urgently or emergently, and the consequences of missed or delayed diagnosis can be severe. We call these conditions *movement disorder emergencies*, and their diagnosis and management form the topic of this book.

Introduction

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

A *movement disorder emergency* is a neurological disorder, evolving acutely or subacutely, in which the clinical presentation is dominated by a primary movement disorder, and in which failure to accurately diagnose and manage the patient may result in significant morbidity or even mortality. Movement disorder emergencies include such diverse entities as acute forms of parkinsonism, chorea, and tics; disease-specific emergencies such as abductor paresis in multiple system atrophy; and conditions like Wilson's disease, NMDA-receptor antibody encephalitis, and

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dopa-responsive dystonia where failure to properly diagnose and treat the patient leads to unacceptable morbidity.

This short chapter begins with a clinical review of the approach to a patient with a movement disorder, and then reviews the major categories of movement disorders as a prelude to the chapters that follow. Video examples of the primary movement disorders are presented in the accompanying video disc. In addition, each chapter begins with one or more patient vignettes, and wherever possible video examples of the various movement disorder emergencies have been included in the video selection.

The Approach to the Patient with a Movement Disorder

Like all areas of neurology, the approach to the patient with a movement disorder begins with the patient's history. Certain elements of the history are particularly important in movement disorders. Patients presenting with an acute movement disorder emergency may be unable to provide a history; however, most patients referred for evaluation to an outpatient center can provide key elements of their stories. Patients and their spouses or companions should be asked to describe the time course in which symptoms developed (hours vs. days vs. months), whether the condition is getting worse, whether involuntary movements are suppressible, what factors trigger or ameliorate their symptoms, and whether movements are present only while awake or also while asleep. A complete review of past and present medications, including those purchased without a prescription, is critical. Exposure to environmental chemicals, occupational toxins, or illicit drugs, recent travel history, and family history of neurological disabilities are other important queries.

Examination of a patient with a movement disorder begins with careful observation. Start by simply watching the patient for at least 60 or 90 seconds in order to define the phenomenology of the movements. Unlike classical neurology's emphasis on localization, it is far more important to define the phenomenology of the movements than to determine their origin. Patients can be classified into two main groups—those who move too little (hypokinetic or parkinsonian) and those who move too much (hyperkinetic). Hyperkinetic disorders are further classified by the speed of the movements, their frequency and amplitude, whether they are regular or irregular, and their stimulus-sensitivity. Dystonia, chorea, tics, myoclonus, and tremor are the major forms of hyperkinetic movement disorders. Sometimes more than one movement disorder is present, such as in a patient with generalized parkinsonism and dystonia of the hand, or in a patient with myoclonus and dystonia.

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

Hypokinetic Disorders

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

Patients with parkinsonism can be classified by etiology into four groups. Primary parkinsonism (i.e., Parkinson's disease) is a neurodegenerative disorder characterized by loss of dopaminergic neurons within the substantia nigra and accumulation of Lewy bodies within the remaining neurons. Secondary parkinsonism includes drug-induced forms (i.e., neuroleptic-induced), toxin-induced parkinsonism (MPTP), post-encephalitic parkinsonism, and vascular parkinsonism. Parkinson-plus syndromes encompass a group of disorders that mimic Parkinson's disease, with the burden of additional neurological deficits. This group includes multiple system atrophy (an umbrella term including three conditions that share similar pathology: olivopontocerebellar atrophy, Shy–Drager syndrome, and striatonigral degeneration), progressive supranuclear palsy, and corticobasal ganglionic degeneration. Heredodegenerative parkinsonism includes a wide variety of disorders that are progressive, typically with other neurological deficits accompanying parkinsonism. Examples include Wilson's disease, X-linked dystonia parkinsonism (also known as Lubag), frontotemporal dementia, juvenile Huntington's disease, and neuroacanthocytosis, among others.

A variety of medications are available to treat parkinsonism. Levodopa is typically administered with carbidopa in the form of Sinemet (carbidopa/levodopa), in strengths 25/100, 25/250, and in controlled-release preparations (25/100, 50/200). A variety of dopamine agonists are available as well, including the ergot agonist bromocriptine, and the non-ergots pramipexole and ropinirole. Amantadine, selegiline, rasagiline, entacapone, and anticholinergics are often used as well. In general patients with Parkinson's disease enjoy the best response to these drugs, and patients with Parkinson-plus disorders and heredodegenerative forms of parkinsonism benefit either incompletely or not at all. Since its introduction more than 40 years ago, no drug has supplanted levodopa as the most effective and best-tolerated anti-parkinson agent.

Acute parkinsonism and the parkinsonism-hyperpyrexia syndrome will be discussed in Chaps. 2 and 3, and psychosis complicating Parkinson's disease (the most frequent reason for hospitalization) in Chap. 6. Parkinsonism is the dominant clinical phenotype of the neuroleptic malignant syndrome and malignant catatonia (Chaps. 4 and 5). Respiratory compromise resulting from abductor paresis is a treatable and life-threatening problem in patients with multiple system atrophy, and is considered in Chap. 7. The widespread availability of deep brain stimulation has transformed the treatment of advanced Parkinson's disease over the last decade. However, sometimes patients get into trouble with DBS, and emergencies associated with DBS will be reviewed in Chap. 20.

Hyperkinetic Disorders

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

Dystonia

Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures. The relatively long duration of movements, simultaneous contraction of agonist and antagonist groups, and sustained contractions in discrete muscle groups in an affected body part help distinguish dystonia from other hyperkinetic disorders. A *geste antagoniste* or sensory trick is a unique feature of dystonia; gently touching the chin in a patient with cervical dystonia or changing the grip of the pen in a patient with writer's cramp results in immediate improvement in dystonic contractions. Dystonia may be focal, affecting one body part: eyes (blepharospasm), neck (torticollis), vocal cord (spasmodic dysphonia), hand, foot, or trunk; segmental (affecting two continuous body parts); hemidystonic (affecting an ipsilateral hand and foot); or generalized.

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

Anticholinergics, baclofen, and clonazepam are most commonly used in patients with generalized dystonia, but side effects often limit their use in adults. Focal dystonia affecting the eyes, jaw, neck, vocal cords, or limbs is best treated with local injection of botulinum toxin, which directly chemodenervates the body part involved.

Injections are effective, safe, and virtually free of significant side effects except for the possibility of excess weakness in the muscles injected. They may be uncomfortable and thus difficult to use in children, and they must be repeated every 3–6 months. Recent experience suggests that deep brain stimulation is a highly effective treatment in patients with severe generalized primary dystonia, particularly DYT-1 patients.

Dystonia affecting the vocal cords may contribute to airway embarrassment; this is discussed in Chap. 8. Dystonic storm refers to uncontrolled, violent dystonic spasms that often require treatment in an intensive care unit (Chap. 9). Several conditions may mimic dystonia, such as tetanus and atlanto-axial rotatory subluxation; their management is reviewed in Chap. 10.

Chorea

Chorea refers to involuntary movements that are rapid, brief, unsustained, continuous, often flowing in quality, and typically moving from one part of the body to another. Chorea may occur in hereditary disorders such as Huntington's disease, neuroacanthocytosis, ataxia-telangiectasia, and benign hereditary chorea. It is more commonly encountered in the setting of metabolic derangements (hyperglycemia), as a para-infectious disorder (poststreptococcal chorea), or after exposure to drugs such as neuroleptics, (tardive dyskinesia), anticonvulsants, or noradrenergic stimulants.

Most neuroleptics will help to control chorea regardless of etiology; however, side effects may include depression, parkinsonism, and QT prolongation. These drugs carry a small but real risk of engendering tardive disorders, even with brief exposure. Valproic acid is another agent that has been used to control chorea, typically in poststreptococcal cases. Tetrabenazine is a dopamine depletor and blocker that does not induce tardive disorders, suggesting a unique position within this group. Severe chorea is an important movement disorder emergency, discussed in Chap. 11 (tardive disorders) and Chap. 12 (hemiballism-hemichorea). The management of Sydenham's chorea and other poststreptococcal movement disorders is discussed in Chap. 13. Huntington's disease is the most common cause of chorea in adults, and Huntington patients and those at risk for the illness present special problems for the managing physician—rare but important emergency scenarios in these patients are covered in Chap. 14.

Tics

Tics are relatively brief movements (motor tics) or sounds (vocal tics) performed in response to an internal urge, and they are often repetitive and gestural (stereotypic). Unlike dystonia, myoclonus, chorea, and tremor, tics can often be completely suppressed. Performance of the tic generally reduces the uncomfortable urge. Simple tics involve one muscle group (blinking, shoulder shrug), whereas complex tics are

sequenced activities that may replicate normal movements, save for their need to be repeated or their inappropriate content or context.

Although tics may occur after infection or medication exposure, most patients evaluated for tics have a primary tic disorder that, in its fully expressed state, is best known as Tourette's syndrome. Obsessive-compulsive symptomatology and attention deficit hyperactivity disorder are common comorbidities in this population. Clonazepam, clonidine, guanfacine, serotonin-specific reuptake inhibitors, neuroleptics, and tetrabenazine have been used to treat tics. When tics are severe and persistent, interfering with school performance or social life, they represent a tic emergency (Chap. 16). Vocal tics are especially disturbing to young children or working professionals, and they represent another movement disorder emergency (Chap. 17).

Myoclonus

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

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

Although no drugs are approved for the treatment of myoclonus, several antiepileptic agents have been borrowed to treat myoclonic disorders; these agents include valproic acid, clonazepam, levetiracetam, and zonisamide. Often, several drugs are required in combination to obtain adequate control. Patients with spasticity of

central origin often have accompanying myoclonus, such as stiff person syndrome. These patients are complex, and they may decompensate acutely from their disease or as a complication of treatment—these scenarios are covered in Chap. 15. Myoclonus is commonly seen in patients with serotonin syndrome (Chap. 18), principally affecting the legs. Exaggerated startle, a brainstem form of myoclonus, defines hyperekplexia, an inherited startle syndrome that is discussed in Chap. 19.

Tremor

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

"Don't Miss" Diagnoses

Included in this text are four disorders that might not, at first glance, appear to be true emergencies. NMDA-receptor-mediated encephalitis (Chap. 22), Wilson's disease (Chap. 23), dopa-responsive dystonia (Chap. 24), and Whipple's disease (Chap. 25) typically present to the outpatient clinic arena, and the time frame in which neurologic symptoms develop may be quite long (although typically short in NMDA-receptor syndrome). However, we have chosen to classify these disorders as emergencies for the following reasons: they are treatable, with the potential of return to baseline status; they are rare, with protean clinical presentations that make diagnosis difficult; and the consequences of a missed or delayed diagnosis can be severe. Because of these reasons, we thought that these "don't miss" diagnoses deserved to be included in a book on movement disorder emergencies.

Accidents and Suicide

Increasing attention is being paid to patient risks associated with movement disorders and their treatment. The issues of driving risk and accidents (Chap. 26), patient and family crises related to genetic counseling (Chap. 27), and suicidal ideation and attempts (Chap. 28) present an emergency for patients, their families, and the treating physician—certainly, disasters in these areas stay in the memory for a long time. These topics are thus included to complete this book.

Chapter 2
Acute Parkinsonism

Hubert H. Fernandez and Joseph H. Friedman

This chapter contains video segments that can be found on the accompanying DVD.

Abstract Acute onset parkinsonism is rare. The most common explanations are neuroleptic malignant syndrome, viral encephalitis, psychogenic, and catatonia. Testing, including cerebrospinal fluid analyses, toxicology, routine blood evaluations, imaging, and electroencephalograpy, assumes a much greater role than the evaluation of degenerative forms of parkinsonism. Acute parkinsonism should always be considered an emergency. Catatonia and neuroleptic malignant syndrome are treatable disorders that are often readily reversed. Viral encephalitis usually requires aggressive supportive care. Other, less common forms are also discussed in this chapter.

Patient Vignettes

Patient 1

A 75-year-old woman with a history of bipolar disease dating back to her twenties was admitted to the hospital after falling and breaking her hip while walking her dog. She had been living alone. She underwent a total hip replacement without incident, and remained at her mental and physical baseline postoperatively in the

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recovery room and postsurgical floor. Two days after surgery she suddenly became mute, stiff, and unresponsive. In addition to her usual regimen of lithium 600 mg, fluoxetine 20 mg, and trifluoperazine 4 mg daily, she had received a total of five doses of meperidine 50 mg/bolus intravenously for pain control. She kept her eyes open and responded to visual threat and deep pain but not voice. She was akinetic, and tone was markedly increased. When her arms were passively elevated, she slowly lowered them. Deep tendon reflexes were normal. Vital signs, laboratory tests including lithium levels, and a head CT were unremarkable. She remained in this state for 3 days before a movement disorder consultation was requested.

Patient 2

A 15-year-old girl developed a 4-day febrile illness accompanied by a diffuse erythematous, maculopapular rash, conjunctivitis, and headache. On the fifth day as her fever and rash resolved she became increasingly drowsy and difficult to arouse. When awake she followed commands very slowly. Her visual fields and eye movements were normal and no ptosis was noted. Her face was expressionless and her mouth was held partly open. She was diffusely rigid with asymmetry. A mild, intermittent resting tremor was noted in the left hand; no other adventitious movements were noted. Deep tendon reflexes were normal and plantar responses were equivocal. The remainder of her neurologic examination was unremarkable. Medical and family history was non-contributory.

Immunizations were up to date apart from measles. Her peripheral white blood cell count was 14.0×10^9/L with 45% neutrophils and 48% lymphocytes. Cerebrospinal fluid (CSF) analysis showed 20 white blood cells per millimeter (all lymphocytes), no red blood cells, and normal protein and glucose. Serum measles antibody titer (by complement fixation) 10 days after the rash was 1:160; 3 weeks later, the titer was 1:80. Electroencephalogram (EEG) and computerized tomography (CT) of the head were unremarkable. She was started on carbidopa/levodopa 25/100 mg at ½ tablets three times per day with significant improvement in her symptoms. Over the next 3 months, tremor, bradykinesia, and rigidity slowly resolved.

Introduction

Secondary parkinsonism, defined by having an identifiable non-degenerative disorder, is common, often occurring following exposure to medications that block dopamine D2 receptors [1]. In primary parkinsonism [2] the date of symptom onset is usually hard to pinpoint. In contrast, most secondary forms of parkinsonism including the drug-induced forms evolve over weeks or even hours. It may be difficult to recognize akinetic rigid syndromes early on, especially in patients who are systemically ill.

The major causes of acute parkinsonism are listed in Table 2.1. Parkinsonism may be a relatively minor aspect of a life-threatening disorder, or it may be the presenting and most obvious feature. In the latter, patients and families often note the

Table 2.1 Etiologies for acute parkinsonism

Infectious
Post-infectious
Autoimmune
Systemic lupus erythematosus
Medication
"Typical" side effects of anti-dopamine drugs
Idiosyncratic effects
Neuroleptic malignant syndrome
Serotonin syndrome
Chemotherapeutic drugs
Toxic
Carbon monoxide
Cadmium
MPTP
Ethanol withdrawal
Ethylene oxide
Methanol
Disulfiram
Bone marrow transplantation
Structural
Stroke
Subdural hematoma
Central and extra pontine myelinolysis
Tumor
Hydrocephalus
Psychiatric
Catatonia
Conversion
Obsessive-compulsive disorder (obsessional slowness)
Malingering

symptoms only when the patient is brought to medical attention after a fall or a spell of incontinence. With diligent questioning, one can usually determine that the process began much more distantly than originally reported.

Acute parkinsonism in psychiatric disorders occurs in two settings, catatonia and conversion disorder. While parkinsonism may accompany severe depression [3] (particularly in the elderly) as well as with severe obsessive-compulsive disorder [4], the onset is not usually acute.

Noninfectious Acute Parkinsonism

Structural Lesions

Normal pressure hydrocephalus often mimics parkinsonism, but the onset is insidious. In contrast, obstructive hydrocephalus is a well-known cause of acute parkinsonism [5]. Acute parkinsonism may occur in both adults and children, either due to shunt obstruction or at presentation. Obstructive hydrocephalus following meningitis

or subarachnoid hemorrhage may also cause parkinsonism. One 16-year-old patient had parkinsonism noted on awakening from repair of a shunt malfunction; the shunt was blocked although hydrocephalus was not present. Another case developed immediately after shunt revision. One developed acutely 1 year after shunting [6]. Some cases of obstructive parkinsonism are responsive to levodopa.

Vascular parkinsonism, previously called atherosclerotic parkinsonism, usually results from tiny lacunes in the basal ganglia compounded by microvascular white matter disease [7]. This is generally insidious in onset and slowly progressive, although sudden worsening may occur with new strokes. Acute parkinsonism following a single stroke is rare [8–16]. Kim described six patients who developed hemi-parkinsonism, three with rest tremor and cogwheeling rigidity [11]. Tremor and other signs of parkinsonism developed after weakness improved. Imaging studies revealed large infarcts involving the supplementary motor area or cingulate gyrus. Other frontal strokes have also caused acute parkinsonism [12, 13]. As one might expect, strokes in the substantia nigra may cause parkinsonism [8–10], but these are exceedingly rare. Interestingly, strokes in the lenticular nuclei do not cause parkinsonism [14]. Acute hemorrhage is a less common cause of acute parkinsonism [15].

Toxic/Metabolic

A number of poisons may induce parkinsonism. In some, like manganese, symptoms develop subacutely [17] or over long periods of time [18]. Parkinsonism may follow recovery from coma caused by carbon monoxide poisoning [19–21]. Carbon monoxide poisoning is a persistent problem in some countries, notably Korea, where faulty oil burning heaters are used. The globus pallidus is typically involved, but recent data suggests that white matter deterioration must also be present for parkinsonism to develop. Cadmium [22] and ethylene oxide [23], disulfiram (used to prevent alcoholics from imbibing) [24], and cyanide poisoning are other uncommon causes [25, 26].

MPTP has a special place in the history of movement disorders [27]. After its identification by Langston and colleagues as the source of a mini-epidemic of severe, acute parkinsonism in IV drug abusers in the San Francisco Bay area, it was developed as a tool for research in PD. The drug is taken up by glial cells and converted to MPP+, which is secreted and taken up by dopaminergic cells in the pars compacta of the substantia nigra. MPTP was the first systemically administered drug to selectively target these cells, and because it has a similar effect in other primates, it has been widely used to create animal models of PD. These models are superb for testing symptomatic treatments for motor dysfunction. The onset of parkinsonism occurs after the first few doses.

Acute parkinsonism is a rare complication of insect stings [28–30]. Acute parkinsonism developed within 3 days of a wasp sting [28] associated with pallidal necrosis, followed by acute deterioration 6 months later with degeneration of the nigrostriatal pathway. Bee stings have not been implicated.

Parkinsonism due to alcohol withdrawal has been reported rarely [31–34]. A follow-up of some of these patients one or more years later proved that this withdrawal phenomenon was not a premature unmasking of subclinical PD. Parkinsonism occurred early in withdrawal, and sometimes resolved within a week [31]. The mechanism is postulated to be a metabolic effect of ethanol on striatal dopamine or dopamine receptors.

Twelve days after overly rapid correction of hyponatremia, a 66-year-old woman became confused and developed parkinsonism. MRI revealed central pontine myelinolysis. She was responsive to very low doses of levodopa, and her parkinsonism gradually resolved [35]. Another similar case was also accompanied by pyramidal features [36]. Parkinsonism is however not a typical feature of central pontine myelinolysis [37]. Hypoxic insult to the basal ganglia may cause parkinsonism or dystonia [38–40]. This is uncommon and typically occurs after a major brain insult. The syndrome has occurred in children [39] as well as adults, and damage to the lenticular nuclei is clearly visible on MRI. Onset is usually delayed, but symptoms may develop rapidly.

Neuroleptic malignant syndrome (NMS) is variably defined, but generally requires the presence of fever, altered mental status, and rigidity (see Chap. 4 for a complete discussion of NMS) [41–43]. Many patients have extreme elevations of creatine phosphokinase (CPK) due to rhabdomyolysis, but this is not required for diagnosis. Elevations in the CPK to the 1,000–2,000 range are sometimes seen in otherwise normal, treated psychotic patients, even in the absence of signs or symptoms of muscle or tone abnormalities. It is critically important to exclude infection in patients presenting with fever, alteration in mental status, and CPK elevation. Infections frequently cause exacerbations of neurological syndromes, including parkinsonism, and both infection and NMS may occur in the same patient. NMS may begin at any point once a patient is treated with neuroleptics, but it usually occurs relatively shortly after initiation of the offending drug or after a dose increase. While there is a general sentiment that the newer atypical neuroleptics are less likely to cause NMS, there is as yet little data to support this.

The onset of NMS may be fulminant, progressing to coma over hours, but it usually develops over days. Patients develop fever, stiffness, and mental impairment with delirium and obtundation. The impaired mental state may initially be overlooked. Rigidity may be so severe that the limbs cannot be moved, and the stiffness may be fairly fixed. In some, muscle contractions may mimic a tonic seizure. Management of NMS requires excluding infection, identifying and discontinuing the offending drug, close monitoring of autonomic and respiratory parameters, and treatment with dopaminergic replacement (either levodopa or dopamine agonists).

Dopamine D2 receptor blocking drugs routinely cause parkinsonism [1]. This may also occur with lithium or valproic acid. The syndrome usually develops over the course of weeks, but may occasionally develop over 24 hours [44]. In patients who have a primary parkinsonian syndrome, a low-potency neuroleptic or even an atypical antipsychotic can induce acute parkinsonism. This is not uncommon when a patient with PD is treated with an antiemetic such as prochlorperazine or metoclopramide.

A handful of children who underwent bone marrow transplantation (BMT) and chemotherapy developed an acute parkinsonian syndrome, sometimes evolving over hours, 2–3 months after transplant [45, 46]. In addition to parkinsonism, cognitive and mental changes also occurred. No particular medication could be implicated, and one patient had an autologous transplant eliminating the possibility of a graft versus host reaction in that case. MRI revealed demyelination, and brain biopsies revealed regions of variably active inflammatory demyelinating lesions. Severe and persistent neurologic sequelae were common. Several reports in the literature describe an acute parkinsonian syndrome occurring with a variety of chemotherapeutic agents [47] and with cyclosporin [48]. Some of these patients responded very well to levodopa, and parkinsonism was not permanent.

A handful of teenagers with systemic lupus involving the nervous system developed acute parkinsonism in the setting of active CNS involvement [49, 50]. Chorea is a more common movement disorder associated both with systemic lupus and lupus anticoagulant antibody.

Psychiatric

Catatonia is an important diagnostic possibility to consider in the setting of acute parkinsonism [51–53]. Catatonia should be strongly considered in any patient with acute-onset akinesia without an obvious cause such as toxin exposure, hypoxic ischemia, CNS infection, or hydrocephalus. Concurrent use of neuroleptic drugs that may cause parkinsonism may complicate the diagnosis.

Although for many decades catatonia was considered a variant of schizophrenia, DSM criteria have been revised to recognize it as a manifestation of manic-depressive disorder as well. It is actually more common in the affective disorders. The patient may have experienced previous spells that may not have been recognized, or resolved over long periods of time. Catatonia may punctuate a manic spell or follow a bout of catatonic excitement. A catatonic, unlike someone with parkinsonism, will not attempt to move. He or she will not appear to be uncomfortable or become hungry. All studies will be normal and an EEG, if the eyes are closed, will be normal.

Most physicians incorrectly think of catalepsy as the defining characteristic of catatonia. Not all patients have waxy flexibility or maintain postures that are externally imposed. The hallmark features of catatonia are negativism, a refusal to cooperate generally manifested as mutism or minimal interaction, and lack of movement. Patients may be stiff, or in contrast exhibit “mit-gehen,” in which they move with the imposed movement, “helping” the movement. Thus one sees a patient who is not moving but may not be in the typical flexed posture of parkinsonism. There is no tremor, and, despite an alert status, little interaction with the environment. Patients will not follow commands and may not respond to pain. Since the patient may keep his or her eyes closed, coma and encephalopathy must be excluded. However if the eyes are closed and the patient is stiff, unresponsive to deep pain, the possibility of coma needs to be considered. If a patient is catatonic there may be no response to

deep pain but cranial nerve reflexes will remain intact. It is unlikely that a catatonic will respond to suggestion, but it is certainly worth trying. "If he is truly comatose/unable to move/stiff/etc., then he will keep his hand above his face when I drop it." If the patient is simply severely parkinsonian from neuroleptics then he or she should be able to comply with some requests, such as moving the eyes, raising a finger, etc.

Psychogenic parkinsonism is not common but should always be considered, especially in young patients. In studies of new referrals to movement disorder specialists, about 2–5% have presumed psychogenic diagnoses [54]. Acute-onset parkinsonism without a demonstrable cause is not likely organic. The behavioral causes are catatonia, conversion, and malingering. Conversion disorder is a type of somatoform disorder, in which patients express mental stress as physical disability [55]. It usually begins abruptly, helping to distinguish it from organic disorders [56, 57]. In idiopathic PD, tremor tends to vary throughout the day, often becoming prominent in time of stress and disappearing during periods of relaxation. These variations usually occur over minutes, whereas in conversion the symptoms tend to resolve for hours or even days at a time. Factors that typically worsen tremor in PD—cold, heavy lifting, excitement—do not necessarily affect conversion tremor. On exam, signs of conversion resolve with distraction and vary in frequency, while PD is usually invariant in frequency. The slowness of conversion disorders has a more deliberate character, especially during handwriting. Balance impairment is usually not present. The presence of a "belle indifference" attitude is often but not always present in conversion. Some patients with bona fide PD will mask their concern, either because they do not understand the implications of the diagnosis or are in denial. Often patients with conversion have a background in medicine, such as nursing, medical secretary, and lab technician, or have experience with the disorder from a relative. The single most common stressor in women with conversion is a history of childhood sexual or physical abuse.

Infectious Parkinsonism

Classification and Clinical Features

Since von Economo first described acute parkinsonism, similar illnesses have been reported with a myriad of infectious agents. In this section, we have divided the infectious causes of parkinsonism into seven categories (see Table 2.2).

Von Economo's disease, also called encephalitis lethargica (ED), was probably seen prior to his initial description of 13 cases with the onset between February and April 1917 in Vienna [58]. Urechia [59] probably described the first recorded credible case series of ED with the onsets in April and May 1915 in Bucharest. Somewhat later (1915 or 1916), cases were described in the French army [60, 61]. A massive encephalitis outbreak affecting 65,000 Chinese in the province of Yunnanfu caused devastation from 1917 to 1927 [53, 62]. By 1919, cases had been reported throughout

Table 2.2 Classification of infectious causes of parkinsonism

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

the world. The peak incidence in the United States was in 1923 with about 2,000 reported deaths. No major outbreaks of epidemic encephalitis occurred after 1926, and by 1935 the disease had virtually disappeared.

Von Economo was the first to recognize and classify three distinct forms of the acute illness, which he called "encephalitis lethargica." He described the *somnolent-ophthalmoplegic form*: a "prodromal phenomena consisting of general discomfort, shivering, headache and slight pharyngitis. The temperature is generally only a little raised. Within the next few days, somnolence begins to predominate. The patients, when left to themselves, fall asleep in the act of sitting and standing, and even while walking, or during meals with food in the mouth. If aroused, they wake up quickly and completely, are oriented and fully conscious, but soon drop back to sleep. Sleepiness in this form may last for weeks or even months but frequently deepens to a state of most intense stupor. Generally, during the first days of illness cranial nerve palsies appear. Ptosis is one of the first and most frequent symptoms. Rarely observed are supranuclear paralyses, paresis of convergence, nystagmus, optic neuritis, papilledema, pupillary disturbances and even Argyll Robertson's sign" [63].

In the *hyperkinetic form*, "chorea and hemichorea as well as myoclonic twitches were observed which may degenerate into wild jactations. On the other hand, it may find its mental expression in a general, curious restlessness of an anxious or hypomanic type. In most of these cases, there is a very distinct sleep disturbance and generally the condition is one of troublesome sleeplessness" [63].

Von Economo termed the least frequent form *amyostatic-akinetic*. He described it as "a rigidity, without a real palsy and without symptoms arising from the pyramidal tract. This form of encephalitis lethargica is particularly common in the chronic cases, dominating the clinical picture of parkinsonism. I reserve the name 'parkinsonism,' though symptomatically identical with the amyostatic-akinetic form, rather for the chronic cases. To look at these patients one would suppose them to be in a state of profound secondary dementia. Emotions are scarcely noticeable in the face, but they are mentally intact" [63].

ED was a serious, often lethal disease. "The prognosis of clinically well-documented cases of encephalitis lethargica is 40% mortality, 14% complete recovery, 26% recovery with defect, but able to work, and 20% chronic invalidity" [63].

It is estimated that more than 60% of ED patients who survived developed post-encephalitic parkinsonism (PEP). The sequelae occurred more often in adults than in children. The latency period was less than 5 years in 50% of cases and less than 10 years in 85% [64]. The average age of the onset of PEP was approximately 27 years. Resting tremor was the presenting symptom in two-thirds of cases while

akinetic-rigid features occurred alone in about one-third [65]. Symptoms were occasionally unilateral and often asymmetrical [66]. Other neurological abnormalities besides parkinsonism were present in most patients. One of the most notable features was the presence of oculogyric crises: "they consist of tonic visual convulsions, occurring in fits and generally lasting only a few minutes, during which the patients as a rule look upwards and sideways" [63]. Other features included dystonia (such as blepharospasm, torticollis, cranial and torsional dystonia), myoclonus (focal or generalized), facial and respiratory tics, choreoathetosis, obsessive-compulsive behavior, pyramidal signs [66, 67], supranuclear gaze palsy, and eyelid apraxia [68].

One study assessing the accuracy of diagnosis of PEP in pathologically proven cases showed a high reliability and sensitivity in diagnosis. The best predictors for the diagnosis included the onset below middle age, symptoms lasting more than 10 years, and oculogyric crisis [69]. Recent work has suggested that the relationship between ED and PEP is less clear [70].

The course of PEP is unclear. Duvoisin and Yahr [64] followed 49 patients with probable PEP and observed a stable course or very slow deterioration. On the other hand, Duncan [71] who studied 136 PEP inpatients in London was impressed with the progressive nature of parkinsonian disabilities. Calne and Lees [72] and Viereggel [73] both reported deterioration in motor function, generally late in life. The relatively uniform nature of the deterioration exceeded changes in motor function seen in normal elderly subjects and occurred without comparable age-related changes in intellect. In one report, the mean survival from the onset of symptoms was 23.2 years with the mean age at death of 74.3 years [65].

While there appears to be general agreement that ED and PEP share a viral etiology, no causative agent was ever identified. Its occurrence around the time of the influenza pandemic of 1918 and 1919 has led some to link ED/PEP to the influenza pandemic [74]. However, von Economo himself rejected this hypothesis on several grounds: (1) ED appeared prior to the influenza pandemic; (2) ED/PEP was not contagious, whereas influenza was highly so; (3) their clinical presentations were different; and (4) the pathology was different with typical midbrain lesions in ED/PEP contrasting with diffuse brain congestion in cases of post-influenzal encephalopathy [63]. Since the influenza pandemic affected at least 500 million persons [75] or over one-fourth of the world's population at that time, it is very possible that many individuals with ED may coincidentally also have had influenza [76].

Modern studies using immunocytochemistry and immunofluorescence to detect in situ antigens failed to consistently isolate influenza or any other virus in the remaining brain or CSF samples of neuropathologically confirmed ED and PEP [76–80]. Similarly, the search for autoantibodies did not support an autoimmune mechanism in PEP [81]. Finally, studies on genetic susceptibility of ED/PEP have been inconclusive. While Elizan [82] saw a highly significant increase in the frequency of HLA-B14 antigen in PEP cases, Lees [83] could not confirm this in their samples.

ED cases considered to be associated with the 1917–1927 pandemic occurred until the early 1930s, after which the disease disappeared. Thus assuming up to a 20-year latency, no PEP cases would be expected to appear after the middle 1950s. Several sporadic ED-like and PEP-like cases, unrelated to the pandemic, have been

reported with the onset after 1959 [84–91]. Other than one report of positive influenza A antibody titer (1:>160) [90] and another report of CSF cultures yielding coxsackie B4 enterovirus [91], attempts to identify the viral agent in ED-like cases have failed. Nonetheless, the clinical presentation, laboratory studies, imaging, and pathological findings are reminiscent, if not identical, to ED/PEP. To distinguish these cases from parkinsonism associated with viral encephalitides, Howard and Lees [88] proposed major criteria for the diagnosis of ED. The illness should comprise an acute or subacute encephalitic illness with at least three out of the following seven features: (1) signs of basal ganglia involvement; (2) oculogyric crises; (3) ophthalmoplegia; (4) obsessive-compulsive behavior; (5) akinetic mutism; (6) central respiratory irregularities; and (7) somnolence and/or sleep inversion.

Parkinsonism may occasionally accompany viral encephalitides [89]. Table 2.3 lists the viruses known to cause encephalitis with or without associated parkinsonism. In most instances, parkinsonism associated with viral infection occurs during the acute encephalitic phase or shortly thereafter. If the patient survives, the parkinsonism is usually transient, although it can take several months to resolve. Unlike EP or PEP, oculogyric crises, ophthalmoplegia, cranial neuropathies, or psychiatric/behavioral disturbances are rare.

In HIV-infected patients, parkinsonism may develop from exposure to dopamine blockers (such as prolonged use of metoclopramide); secondary to opportunistic infections (toxoplasmosis, progressive multifocal leukoencephalopathy, tuberculosis) affecting the basal ganglia [91–96]; or as part of HIV encephalopathy in the absence of opportunistic infections [97, 98]. The parkinsonian syndrome is often unresponsive to levodopa [99].

Rarely parkinsonism is associated with nonviral infectious agents: spirochetes (neurosyphilis and Lyme disease), mycoplasma pneumoniae, and opportunistic infections accompanying HIV. Most reported cases of parkinsonism from spirochetal [100, 101] and mycoplasma [102–106] infections present with acute onset and improve markedly with appropriate treatment, despite the severity of the initial clinical presentation. Of the five reported cases with mycoplasma, the presenting extrapyramidal features were parkinsonism and/or dystonia, accompanied by seizures in three cases. All patients were children or young adults, and in all cases, MRI revealed selective involvement of the corpus striatum except for one case with concomitant involvement of the substantia nigra and pallidum [103]. One patient [102] experienced severe dyskinesias and dystonia with levodopa therapy, but symptoms gradually resolved.

In patients with acquired immunodeficiency syndrome (AIDS), parkinsonism, hemichorea-athetosis, and ballismus have been described with opportunistic infection. Parkinsonism, in particular, has been reported with cerebral toxoplasmosis [93, 95], progressive multifocal leukoencephalopathy [107, 108], and cerebral tuberculosis [109]. All but one case presented with bilateral lesions in the basal ganglia. One patient with mycobacterium tuberculosis involving the left lentiform nucleus only developed parkinsonism when the right lentiform nucleus was superinfected with toxoplasma [96]. There is only one reported case of parkinsonism following herpes ophthalmicus [110].

Table 2.3 Causes of viral encephalitis

Virus	Parkinsonism	Author
California encephalitis (LaCrosse virus)	Not reported	
Coxsackie virus	Acute	Walters [128]
	Acute, transient	Posner et al. [129]
Cytomegalovirus	Not reported	Giraldi et al. [130]
Eastern equine encephalitis (EEE)	Not reported	
Herpes virus	Not reported	Ickenstein [131]
Human immunodeficiency virus	Secondary to opportunistic infection	Nath et al. [91]; Carrazana et al. [92]; Navia et al. [93]; Noel et al. [4]; Maggi et al. [96]; De la Fuente et al. [107] Singer et al. [108]; Werring and Chaudhuri [109]
	Part/feature of HIV encephalopathy	De Mattos et al. [97]; Mirsattari et al. [98]
Epstein–Barr virus	Acute, transient	Hsieh et al. [132]
Influenza virus	Acute, transient	Isgreen et al. [133]
Japanese B encephalitis	Followed acute phase without interval	Shiraki et al. [134]
	Chronic phase with interval	Ishii et al. [135]
	Acute, persistent	Shoji et al. [136]
	Acute, transient	Pradhan et al. [137]
Lymphocytic choriomeningitis	Acute, transient	Scheid et al. [138]
	Chronic, persistent	Adair et al. [139]
Mumps	Not reported	
Murray valley encephalitis	Reported	Bennett et al. [140]
Papovavirus	Not reported	
Poliovirus	Acute, transient	Bickerstaff and Clarke [141]; Thieffrey [142]
	Acute	Barrett et al. [143]; Duvoisin and Yahr [64]
	Parkinsonism in late life with history of polio as a child/young adult	Vincent and Myers [144];
Rubella	Not reported	
Rubeola, measles	Post-measles, transient	Mellon et al. [145]; Meyer [146]
Russian spring-summer encephalitis, European tick-borne encephalitis	Acute, transient	Henner and Hantal [147, 148]
	Tremor only	Radsel-Medvescek et al. [149]
St. Louis encephalitis	Tremors	Cerna et al. [150]; Wasay et al. [151]
	Dystonia with tremor as sequelae	Finley [152]; Finley and Rigs [153]
Varicella-zoster virus	Not reported	
Venezuelan equine encephalitis	Not reported	
Western equine encephalitis	Reported	Fulton and Burton [154]
	Chronic, persistent	Mulder et al. [155]

A 5-year-old boy developed isolated fever 15 days after a measles vaccine shot and then developed persistent parkinsonism. MRI showed hyperintense signal affecting the substantia nigra bilaterally. He responded to levodopa but dyskinesias appeared even at low doses [111]. The only other reported case was that of a 38-year-old man who experienced fever, sweats, palpitations, diplopia, and leg tremor within hours of receiving the last of three tetanus vaccinations. Within 1 week, he developed severe parkinsonism with resting tremor, generalized rigidity, and bradykinesia, which responded well to levodopa and a dopamine agonist. Unlike the previous case, parkinsonism was transient [112].

Neuropathology and Imaging

The pathological features of ED differ from those of other viral encephalitides (usually characterized by diffuse brain congestion and edema). In ED, pathology typically consists of non-hemorrhagic involvement of the gray matter, preferentially in the midbrain. Although the brainstem and basal ganglia bear the brunt of the burden, the cerebral cortex and spinal cord can be affected as well. The pathological hallmark of the disease is cytoplasmic inclusions of neurofibrillary tangles (NFTs) within the substantia nigra (SN), associated with severe neuronal loss [69, 113, 114]. Lewy bodies are not present. In the chronic state (PEP), inflammation is often replaced with degeneration of neurons and gliosis throughout the central nervous system, particularly the midbrain [115]. NFTs occur in the absence of senile plaques [65, 116]. Unlike Alzheimer's disease, they do not stain for alpha synuclein or amyloid [117], but similar to progressive supranuclear palsy, they are ubiquitinated and tau-positive on immunohistochemistry [118, 119].

MRI findings from cases of parkinsonism associated with viral encephalitis as well as ED/PEP-like cases usually reveal bilateral, symmetrical basal ganglia involvement, predominantly with signal hyperintensities in the SN but may also involve the striatum and lenticular nucleus [120]. When symptoms resolve, these MRI lesions can be transient as well. On fluorodopa positron emission tomography, PEP differs from idiopathic PD. Uptake in the putamen of PEP patients is homogenously reduced, without the anterior–posterior gradient typically seen in PD [90, 121]. This may be due to the more diffuse involvement of the SN pars compacta in PEP compared to the ventrolateral predominance in PD.

Evaluation

A young patient with acute or subacute onset of parkinsonism associated with a febrile illness should have a complete blood count, and blood chemistries including liver, renal, thyroid function tests, antinuclear antibodies, erythrocyte sedimentation rate, chest radiography, electrocardiogram, and blood and urine cultures. CSF should be sent for cell count, glucose, protein, and extra tubes for CSF gram and

acid-fast bacilli stain, VDRL, Lyme titers, and serologies (for herpes simplex virus, herpes zoster, mumps, measles, adenovirus, enterovirus, cytomegalovirus, Epstein–Barr virus, toxoplasmosis, etc.). Serum ceruloplasmin, 24-h urine copper and heavy metals, toxicology, HIV test, tuberculin-purified protein derivatives test, and serum VDRL may be necessary. An EEG may define seizure activity and helps grade the level of encephalopathy. Brain imaging with contrast can define ring-enhancing or granulomatous lesions. Rarely, duodenal biopsy (to rule out Whipple's disease), blood smear (for malaria), and CSF 14-3-3 protein (for prion disease) may be of value.

Treatment

Comments on Patient 1: This patient had been taking trifluoperazine and lithium, both of which may cause parkinsonism, but she had been taking both for many years, had not had an increase in dose recently, and her lithium level was not elevated. Since her symptoms occurred 2 days after surgery, a direct result of the surgery was unlikely. Meperidine may trigger severe reactions with MAO inhibitors, but this has not been reported with the drugs she was taking. The absence of any fever argued strongly against serotonin syndrome or NMS. The fact that she was awake, blinked to threat, moved in response to pain, had a non-focal exam, and a normal brain CT pointed to a probable psychiatric cause. Given the history of bipolar disease requiring an antipsychotic, catatonia was considered, and in fact she met criteria for this syndrome. After a baseline EEG was obtained, which was normal, an infusion of lorazepam was given. Two minutes later she awoke and was manic. This confirmed the diagnosis of catatonia and pointed to the need for more aggressive psychiatric treatment. When the effects of the lorazepam wore off within a few hours, she became catatonic again.

Establishing the etiology of acute parkinsonism is of paramount importance. NMS is treatable, usually with levodopa or dopamine agonists. In cases of profound rigidity and fever the patient may be paralyzed or treated with dantrolene sodium. Unlike malignant hyperthermia, the muscles in NMS are normal, hence responsive to depolarizing drugs. Catatonia often responds to intravenous lorazepam [53]; however patients may require prolonged treatment to prevent recurrence. Patients who do not respond to lorazepam should be considered for electroconvulsive therapy which has been reported as successful in treating this disorder as well as NMS.

Toxic, metabolic, infectious, post-infectious, and structural akinetic rigid syndromes are usually not responsive to symptomatic therapies. Levodopa requires conversion to dopamine by intact nigral cells, suggesting that dopamine agonists may be more effective when the nigra is fully depleted. Unfortunately the general experience with dopaminergic agents in akinetic rigid syndromes is that levodopa works faster and has fewer side effects; we therefore advocate trials of levodopa for all parkinsonian syndromes except NMS, where a dopamine agonist is our drug of choice. When levodopa is not helpful, we advocate a trial of amantadine

200–400 mg/day in patients with normal renal function. Although amantadine has anti-influenza properties, there is no reason to believe it is useful for other viral syndromes. Dopamine agonists should be initiated at low doses and slowly titrated. Since patients with acute parkinsonism may improve on their own, it may be difficult to gauge the response to a slowly increasing dose of dopamine agonists. Once a patient has improved, our general approach is to slowly taper the medicines, as many patients improve spontaneously.

Comments on Patient 2: This 15-year-old girl developed acute parkinsonism immediately following a presumed viral encephalitis. Measles antibody titers suggested a resolving measles infection. Her parkinsonism gradually resolved over 3 months and was not associated with oculogyric crisis, ophthalmoplegia, myoclonus, or other movement disorders. The presentation is therefore not consistent with ED or PEP. In addition to supportive measures during the acute encephalopathic phase, delivery of the appropriate antibiotic/antiviral agent may suffice to resolve parkinsonism associated with known viral or bacterial encephalitis. When symptoms persist, levodopa alone or in combination with other adjunctive anti-PD agents may be used. Anticholinergic drugs [122], amantadine [123], bromocriptine, and deprenyl [124], have all been reported to augment levodopa response.

ED and PEP patients are extremely sensitive to anti-PD drugs, with dyskinesias and motor and psychic fluctuations occurring even at very low doses. Calne et al. [125] reported a 6-week double-blind, placebo-controlled trial of levodopa in 40 PEP patients, with frequent adverse events among those who received levodopa. Patients experienced chorea, tics, respiratory crises, excess sweating, and psychiatric disturbances. Only a minority gained useful and enduring benefit of levodopa throughout the study. Sacks [126] reported an enormous range of levodopa-induced behavioral and motor abnormalities where patients alternated between a severe "off" state and an emotionally labile "on" state. Unlike PD where patients often chose to be "on" with dyskinesias, PEP patients preferred to be "off" to avoid emotional lability. Similarly, Duvoisin [127] reported 63% of patients with increased involuntary movements and 33% with psychic manifestations among 26 PEP patients treated with levodopa. Slower titration enabled some patients to enjoy a sustained response. There is one report of PEP in which oculogyric crises resolved and tremor and rigidity improved with unilateral thalamotomy [67]. Since parkinsonism in PEP is probably progressive, or, at the very least, persistent, and since patients experience extreme motor fluctuations on low-dose levodopa, stimulation of the subthalamic nucleus might also be an option.

Conclusion

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

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Chapter 3
Parkinsonism-Hyperpyrexia Syndrome in Parkinson's Disease

Daniel E. Huddleston and Stewart A. Factor

This chapter contains video segments that can be found on the accompanying DVD.

Abstract Parkinsonism-hyperpyrexia syndrome (PHS) is a rare but potentially life-threatening complication of Parkinson's disease (PD). PHS was first described in 1981 and has been reported in dozens of cases since then. The clinical presentation of PHS includes hyperpyrexia, rigidity, altered consciousness, dysautonomia, leukocytosis, and elevated creatine kinase. Although PHS and NMS are phenotypically nearly identical, PHS is a distinct entity in that it is triggered by removal or effective loss of dopaminergic therapy in a parkinsonian patient. The mainstay of PHS treatment is rapid replacement of effective anti-parkinsonian therapy. While abrupt levodopa withdrawal is the classic trigger of PHS, a variety of other inciting scenarios have been described. The pathophysiology underlying PHS is generally accepted to be a hypo-dopaminergic state, and its clinical features can be explained as sequelae of central dopamine depletion. PHS is a neurological emergency, with significant morbidity and mortality. Early recognition and rapid reintroduction of anti-parkinsonian medications are keys to the successful management of this syndrome.

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Patient Vignette [1]

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

He had been fully able to communicate, perform activities of daily living, and ambulate 48 hours prior to presentation. He had recently been incarcerated, and during his confinement his medication doses were abruptly and substantially diminished for unclear reasons. His usual dosing schedule included carbidopa/levodopa (C/L) 25/100 one tablet every 2 hours starting at 6:00 a.m. to 8:00 p.m., with two tablets at 10:00 p.m., midnight, and 2:00 a.m. In addition, he was also prescribed pergolide 1 mg three times/day, and quetiapine 25 mg five 1/2 tablets each day in divided doses. In July 2000, he underwent deep brain stimulation (DBS) surgery, with bilateral leads placed in the subthalamic nuclei. They were operational as of the last office visit. DBS surgery led to improved off times and less dyskinesias, but allowed only minimal change in levodopa dose.

In the emergency department, the patient appeared acutely ill. He was febrile, with a temperature of 101 °F, heart rate of 100 bpm, blood pressure of 140/90, and respiratory rate of 24. He was awake but confused and unable to follow commands or intelligibly communicate. His mucus membranes were dry. He appeared diffusely stiff, with severe rigidity of the neck and limbs. A coarse tremor was present in both upper extremities, but no other involuntary movements were seen. No signs of trauma were found. Pupils were symmetrical and reactive to light, and fundoscopic exam was normal. Reflexes were present and symmetric, with no pathologic reflexes.

Laboratory studies revealed a white blood cell count (WBC) of 16,000 cells/mm^3, blood urea nitrogen of 39 mg/dl, and normal red blood cell indices. No iron indices were measured. Creatine kinase (CK) was >4,000. A cranial CT revealed bilateral DBS leads without acute pathology. A lumbar puncture with CSF analysis was normal. The diagnosis of parkinsonism-hyperpyrexia syndrome (PHS) was made: a nasogastric tube was placed and levodopa and pergolide were reinstituted, with intravenous fluids. Despite treatment, his condition worsened, with medically refractory hypertension, respiratory distress, seizures, and ultimately renal failure. He expired 3 days after presentation. Postmortem exam revealed bilateral pulmonary emboli with infarction. Examination of the brain revealed marked depigmentation of the substantia nigra and the locus ceruleus, with Lewy bodies confirming the diagnosis of PD.

Introduction

Neuroleptic malignant syndrome (NMS) is a potentially fatal drug-induced movement disorder that was first described by Delay and associates in 1960 [2, 3]. These authors reported it as the "most serious but also rarest and least known of complications of neuroleptic chemotherapy" [3]. Since the 1980s, it has been a considerable concern in relation to the treatment of psychiatric patients because of its potentially high mortality rate of 5–20% [4, 5]. The characteristic clinical features include hyperthermia, muscle rigidity, dysautonomia, and mental status change. Hyperthermia is present in nearly all cases of NMS, and muscle rigidity is reported in more than 90% of patients [4–8]. Alterations in mental status can range from fluctuating alertness, to agitation and delirium, to frank stupor or coma [7, 9]. Muteness is also seen, although less commonly than catatonia. Unstable blood pressure, cardiac arrhythmia, dyspnea, pulmonary edema, and bladder incontinence are common signs of dysautonomia, and diastolic hypertension possibly being a specific feature [4]. Several laboratory abnormalities support the diagnosis, including elevated creatine kinase, elevated WBC count, and diminished serum iron [4].

It was initially believed that NMS only occurred in psychiatric patients, particularly those with schizophrenia and affective disorders who were treated with neuroleptics. Although particular risk factors in these patient populations have been delineated, it has become clear that any patient exposed to these agents is at risk for developing NMS [4]. This constellation of symptoms has since been recognized in patients exposed to other agents such as dopamine depleters (tetrabenazine) [10], a related syndrome (serotonin syndrome) associated with exposure to serotonin-specific reuptake inhibitors [11], and cocaine [12].

In 1981, a similar disorder was described in a patient with PD triggered by sudden withdrawal of dopaminergic medications, specifically levodopa, amantadine, and biperiden. Several dozen other cases have since been reported. The syndrome seen in PD has been reported under a variety of different names, including NMS, neuroleptic malignant-like syndrome (NMLS) [13, 14], levodopa-withdrawal hyperthermia, PHS [15], lethal hyperthermia [16], dopaminergic malignant syndrome [17], and acute dopamine depletion syndrome [18]. PHS is the most specific and clinically descriptive term and the one currently most accepted for this disorder. As we will show, levodopa withdrawal is not the only cause of this entity, and the word dopaminergic pertains to any NMS-like syndrome. It is important to draw a distinction between true NMS and PHS. From this point forward, when discussing this syndrome in parkinsonian patients we will use the term PHS. This chapter reviews the clinical entity of PHS and discusses its management. Interest in this syndrome has been on the rise in recent years, evidenced by the publication of several review articles on the subject [19–22].

Clinical Features

Although PHS is rare, several situations are common triggers. The scenario most commonly reported is the "levodopa holiday" [14, 23–25]. These cases were all reported in the 1980s when drug holidays were still utilized for therapeutic purposes. They were recommended in patients with intractable "off" periods and psychosis, although their utility was controversial [26, 27]. Drug holidays often involved rapid reduction and complete cessation of dopaminergic medication. Patients would remain off for up to 14 days, despite well-known risks associated with immobility such as aspiration pneumonia and pulmonary embolism. Drug holidays are no longer used; however there are other situations when dopaminergic medications are discontinued posing an equal risk. In several reports, the medications were abruptly stopped by the patients themselves because of side effects, misunderstanding in medication instructions, or a desire to try alternative treatments [13, 17, 18]. In one case the medications were stopped because physicians thought that the patient had psychogenic parkinsonism [18]. PHS has also been seen in PD patients with partial withdrawal of dopaminergic therapy, or when medication regimens were substantially changed. Iwuagwu [28] described a case with the onset linked to discontinuing tolcapone. When the patient became confused, the treating physician thought that this was exacerbated by levodopa; after it was stopped, PHS escalated. Cunningham [29] described a patient who developed hyperthermia, rigidity, and dysautonomia when immediate-release levodopa was switched to controlled release, and bromocriptine was tapered off from 40 mg/day to 0 in a few days. Peak serum levodopa levels are notably lower with controlled-release formulations than immediate release. Keyster [18] reported a similar case where PHS occurred when a patient was switched from levodopa to bromocriptine.

Another situation where PHS has been reported is in PD patients treated for a coexisting psychiatric disorder with neuroleptics. One such patient with schizophrenia and PD treated with neuroleptics for their primary psychotic disorder became gravely ill after cessation of anti-parkinsonian medications [30]. In another case, a patient admitted to the hospital for drug-induced psychosis had their levodopa stopped and haloperidol started at the same time. It is not unreasonable to refer to these cases as NMS also, since it is unclear if symptoms started because of dopaminergic drug withdrawal or neuroleptic initiation. Severe "off" periods associated with motor fluctuations can also trigger such events. Pfeiffer and Sucha [16] reported a single patient developing repeated PHS features with "off" episodes. Events occurred for years, lasting 1 or 2 h and clearing when he turned "on." He ultimately died during a severe episode associated with a fever of 107 °F.

Three other situations have been reported in single cases that occurred without change in medication regimen. One involved peri-menstrual "off" times with symptoms of PHS [31]. In this case, it is believed that elevated estrogen and progesterone levels may have decreased CNS dopaminergic stimulation in a manner similar to cutting medication doses. Another case involved metabolic alteration, particularly hypernatremia [32]; the mechanism by which this caused PHS is unclear. In a third

case a patient in the intensive care unit developed the symptoms of PHS after his enteric feed was changed from a formulation with lower protein content to one with higher protein content [33]. The PHS cleared after the enteric feed was changed back to the formulation with lower protein content. His home regimen of PD medications was continued unchanged throughout his course. In this case the development of PHS was attributed to decreased absorption of his PD medications caused by increased protein content in his enteric nutrition. Despite these cases and others like them, it should be noted that PHS, for the most part, refers to a disorder that occurs with withdrawal of CNS dopaminergic stimulation. Metabolic changes and infection may increase the risk for PHS. However, while they can, on their own, cause worsening of parkinsonian symptoms, it is unclear if they do so via the same mechanism. Therefore, we propose that the term PHS should have a specific meaning, indicating the presence of the NMS-like constellation of symptoms on the background of dopaminergic drug withdrawal.

Our patient vignette suggests an additional risk for PHS in PD patients. DBS of the subthalamic nucleus (STN) is not infrequently used as a treatment for advanced fluctuating PD. When performed properly it leads to a substantial decrease in "off" time and severity. This improvement can in turn lead to a decrease in levodopa requirements by about 30% [34]. Some authors advocate discontinuing levodopa altogether [35], but others have voiced concern regarding this objective [36]. Our patient had subthalamic DBS implanted and abruptly stopped medications, although not as part of the programming plan. He developed PHS and pulmonary embolism, which was ultimately fatal. Other scenarios leading to PHS surrounding DBS have more recently been described. One case report (see Case 4 in Section "Illustrative Cases from the Literature" below) describes a patient who developed PHS repeatedly after his STN DBS was turned off for repeated stimulation-associated manic episodes [37]. One could assume that stopping DBS would have an equivalent effect of dopaminergic drug withdrawal. In another case report the authors describe the onset of PHS following medication withdrawal preoperatively in preparation for DBS surgery the night before [38].

The frequency of PHS in PD has not been studied formally, but the disorder appears to be rare. We identified more than 80 cases reported in the literature. The details of the cases were varied. One paper was a therapeutic trial that included 40 cases [39]; two papers reported 11 cases each [17, 40]; two reports described 3 cases each [14, 18]; and the rest were single case reports. Serrano-Duenas [17], with one of the larger cohorts, reported that 11 cases accounted for 3.6% of his PD patient population and 0.04% of total patient consultations for PD. In the study by Sato [39] 40 cases were seen over a 3-year period. These findings may suggest that PHS may be more prevalent than previously recognized but this requires further study.

Patients developing PHS were male (47 of 83 (56%) reported) or female, with duration of PD ranging from 2 to 16 years and baseline levodopa dose at the time of onset ranged from 200 to 2,100 mg/day. Not all patients had motor complications. In the report by Ueda [40] only 4 of 11 cases experienced this problem at the onset of PHS.

The clinical features of PHS are nearly identical to NMS, and the clinical presentation seems fairly stereotyped. The time of onset of symptoms after change in dopaminergic therapy ranged from 18 hours to 7 days. The initial feature in most patients was severe rigidity along with tremor, with progression to an immobile state [17, 18, 40]. Within 72–96 hours, most patients were hyperpyrexic with altered mental status ranging from agitation and confusion to stupor and coma. Autonomic signs such as tachycardia, tachypnea, labile blood pressure, urinary incontinence, pallor, and diaphoresis often accompany this. In some cases hyperthermia, mental status changes, and autonomic dysfunction may occur from the outset, along with worsening of parkinsonism [40]. Temperatures as high as 107 °F have been reported [14, 16]. Laboratory findings usually reveal leukocytosis (as high as 26,000) and elevated CK (ranging from 260 to 50,000 in reported cases). There have been no reports where iron levels were examined. Respiratory distress is not uncommon, and mechanical ventilation may be necessary [23, 30]. Mutism, as part of the mental status derangement, was reported by several authors [13, 29, 32]. Other neurological features include seizures [24] and myoclonus [15].

Although this description seems very similar to NMS, there appear to be some differences. Serrano-Duenos [17] performed a comparison looking at 11 PHS patients and 21 NMS patients. They found that the latency to the onset of symptoms after the inciting event was twice as long (93 h vs. 49 h) for PHS than NMS. In addition, in PHS the elevation of CK and WBC was significantly less robust. The duration of hospitalization was also shorter (8.4 days vs. 12.2 days). As expected, PHS patients were older than the NMS group. These findings suggest that NMS is a more aggressive disorder than PHS, and caries a poorer prognosis.

As with NMS, PHS may be associated with serious long-term effects. Some patients only partially recover from the event, and are left with significantly worse parkinsonism [17, 18]. In one case a patient at Hoehn and Yahr stage 2 prior to the incident became wheelchair-bound (stage 5) afterwards [17]. Medical complications are also a concern. Deep venous thrombosis is a serious complication, and may ultimately result in pulmonary emboli (as occurred in our illustrative case). Several patients have developed aspiration pneumonia during a bout of PHS and two cases developed renal failure [14, 18], complications well described in NMS. Finally, four of the reported cases (including ours) were fatal [14, 16, 23]. Two died in hyperthermic coma with no other explanation, one died with aspiration pneumonia and renal failure, and one from pulmonary embolism [1].

Illustrative Cases from the Literature

The following four cases from the literature illustrate this disorder, three from drug withdrawal and one related to DBS. In addition, Table 3.1 summarizes the time frame involved in development of PHS after dopaminergic drug withdrawal, and recovery after therapy in six representative cases [17, 18].

Table 3.1 Summary of selected clinical cases from two publications [17, 18] illustrating the time frames involved in the onset and recovery of PHS

Patient demographics	Medication discontinued	Clinical features within 24 h	Clinical features within 96 h	Improvement within 24 h	Improvement within 96 h
75-Year-old man with PD for 1 year	C/L 300 mg/day	None reported	Weak, rigid, tremulous, diaphoretic	None reported	Full resolution within 5 days
67-Year-old woman with PD and schizophrenia	C/L 250 mg/q.i.d	Febrile (41.2°C) Mute, tremulous, rigid	Same	Afebrile, improved sensorium	Full resolution within 48 h
64-Year-old man with PD for 7 years	C/L 250 mg/q.i.d. Benz. 2 mg/day Trihex. 4 mg/day	Tremulous, rigid	Febrile (39.4°C) Mute, confused, severe tremor, and rigidity	Less rigid and tremulousness, improved sensorium	Progressive improvement without return to baseline after 10 days
74-Year-old woman with PD (H&Y III)	C/L 750 mg/day Seleg. 10 mg/day	Rigid, unable to ambulate or feed self	Febrile (37.9°C) Stupor, severe rigidity	Afebrile, alert, much less rigid	Progressive improvement without return to baseline after 10 days
69-Year-old man with PD (H&Y II)	C/L 750 mg/day Bromo. 7.5 mg/day	Severe rigidity, unable to ambulate	Febrile (38.7°C) Somnolent, severe rigidity	Afebrile, alert, much less rigid	Progressive improvement without return to baseline after 10 days
69-Year-old woman with PD (H&Y IV)	C/L 1,125 mg/day Seleg. 10 mg/day	Febrile, severe rigidity, unable to ambulate	Febrile (39.2°C) Stupor, severe rigi dity	Afebrile, alert, much less rigidity	Progressive improvement without return to baseline after 10 days

C/L carbidopa/levodopa, *Ama* amantadine, *Seleg* selegiline, *Bromo* bromocriptine, *H&Y* Hoehn and Yahr

Case 1: [18] A 75-year-old man with a diagnosis of PD was treated with immediate release carbidopa/levodopa 25/100 one tablet three times per day for 1 year. When amantadine 100 mg was added for symptomatic benefit, the patient mistakenly discontinued his C/L. Within 5 days he became tremulous, weak, pale, diaphoretic, and dyspneic. Amantadine was increased without clinical benefit. It was discovered that C/L had been discontinued and it was restarted but only at twice-daily dosing. Over the ensuing week, the patient became progressively confused, resulting in the cessation of C/L. Within 48 hours, he worsened considerably and because of continued confusion 9 mg of haloperidol was given. Soon after, the patient became mute, agitated, and severely rigid with a diffuse coarse tremor. Laboratory review revealed leukocytosis, hypernatremia, and an elevated CK (452 U/L). Within 5 hours of this evaluation, the patient's temperature rose to 38.5°C. Bromocriptine (2.5 mg every 6 hours) was started, and within 72 hours, the patient's condition markedly improved. C/L was subsequently restarted, and the patient fully recovered.

Case 2: [17] A 74-year-old woman abruptly stopped taking her anti-parkinsonian medication. She had advanced disease (Hoehn and Yahr stage 3), and had been taking C/L 750 mg/day, selegiline 10 mg/day, and propranolol 80 mg/day. She decided to begin an alternative, natural treatment for PD and did not discuss this first with her treating physician. Within a short time, she became markedly rigid, and was unable to walk or feed herself. Within 96 hours, she was diaphoretic, somnolent, febrile (37.9°C), rigid, and stuporous and had a serum CK of 759 U/L on presentation to a local hospital. A diagnosis of PHS due to abrupt medication withdrawal was made, a nasogastric tube was placed, and dopaminergic medication was restarted. Within 9 hours she became alert, and rigidity lessened within 15 hours. On discharge 9 days later, rigidity was worse than prior to the incident.

Case 3: [23] A 51-year-old man with a 9-year history of PD was admitted to the hospital because of severe levodopa-induced dyskinesias. His medications on admission included C/L 25/250 three times per day and diphenhydramine 50 mg four times per day. C/L was reduced by one-half for 3 days, and then stopped altogether (drug holiday) and diphenhydramine was cut to BID. Two days later the dyskinesias stopped and were replaced by rigidity, bradykinesia, and tremor. On the third day his temperature rose to 38.2°C, heart rate was 120/min, respiratory rate was 28/min, and he was diaphoretic. The temperature increased further to 40.4°C by day 10 and he remained confused and disoriented. Anti-PD medications were restarted, and intravenous fluids and low-dose heparin were begun. By day 10 CK was 260 U/L and on day 14 WBC was 13,200/mm [3]. Workup for infection was negative, and antibiotics were initiated empirically. Despite therapy, he remained febrile and stuporous. He was intubated and placed on a ventilator, but died in hyperthermic coma on day 15 after discontinuing medications.

Case 4: [37] A 60-year-old man with a 17-year history of PD developed severe motor fluctuations and dyskinesias 9 years after disease onset. He was levodopa responsive, and underwent bilateral STN DBS placement. With stimulation, his motor symptoms improved, but he also developed mania. His mania increased 2 years after the DBS placement and he was admitted to the hospital where the stimulators were

turned off in light of the mania, which was attributed to the stimulation. On the third hospital day, the patient's manic symptoms disappeared, but he developed somnolence, immobility, and rigidity. He became febrile with a temperature of 38.7°C. Heart rate was 120, WBC count was 12,600/μL, and serum CK was elevated to 1,878 U/L. PHS was considered and treatment with medical therapy initiated, and by day 6 in the hospital the patient was afebrile with normal mental status. DBS was then turned back on and the patient had improvement in rigidity and akinesia. However, over the next several years he experienced several more episodes of mania, which did not respond adequately to antipsychotic drugs or DBS stimulation site adjustment. During each episode his DBS had to be turned off, and each time this was done he experienced recurrence of PHS, which responded each time to IV fluids followed by the reintroduction of DBS. His most recent manic episode was reversed by lowering the voltage of the stimulation, not completely turning it off, without emergence of PHS.

Risk Factors and Pathogenesis

In practice, many PD patients have their doses of dopaminergic medications decreased or stopped and yet only a very small fraction experience PHS. On the other hand, some patients are susceptible enough to develop this with minor medication changes or wearing off. There have been attempts to evaluate potential risk factors in PD patients [40–43]. The most ambitious of these was a study by Ueda [40], examining clinical and neurochemical features over a 3-year period in 98 consecutive hospitalized PD patients. Demographics, disease severity, and cerebrospinal fluid monoamine metabolites including HVA, MHPG, and 5-HIAA were evaluated. Eleven of the ninety-eight had a history of PHS (either remote or leading to the study admission). The PHS group had significantly worse parkinsonism and a greater daily levodopa dose. No difference was seen between groups with respect to gender, age, duration of disease, or maximum levodopa dose. HVA spinal fluid levels were significantly lower in the PHS group, the only feature independently related to the occurrence of PHS. A second study by the same group [41] examined CSF HVA levels in 9 patients during and after an episode of PHS, and compared them to 12 PD patients with simple worsening of PD with discontinuing medications. HVA levels were significantly lower in the PHS group. The authors suggested that the lower baseline level left a "narrow safety margin," leading to an increased susceptibility to the occurrence of PHS. Other studies [42, 43] suggest that the presence of motor fluctuations, psychosis, and dehydration prior to the event represent other possible risks. Overall it appears that those with more severe disease and more profound dopaminergic depletion are at greater risk. Support for this comes from the ELLDOPA trial where 361 early PD subjects treated with up to 600 mg of levodopa for 9 months were withdrawn over a few days. No cases of PHS occurred [44].

It is generally accepted that alterations in dopaminergic transmission in the brain are the primary pathogenic mechanism of NMS [4, 45]. Abnormalities in muscle membrane function, changes in peripheral and central sympathetic outflow, and

alterations in central serotonin metabolism have also been implicated [4]. The occurrence of PHS (a clinically identical syndrome to NMS) with dopaminergic drug withdrawal in PD indicates that a hypodopaminergic state alone is sufficient to trigger both disorders.

The clinical features of PHS can be explained by central dopamine depletion. The motor features of PHS are exaggerated PD symptoms related to decreased dopaminergic activity in the nigrostriatal system. The role of dopamine in thermal regulation is also well known. These dopamine pathways within the hypothalamus include the preoptic area, the anterior hypothalamus concerned with thermal detection, and the posterior hypothalamus involved with generation of effector signals. The thermosensitive neurons respond to local changes in blood temperature as well as to afferent information from peripheral thermosensors. Dopamine and dopamine agonists modulate hypothalamic temperature regulation, while dopamine receptor antagonists block this ability [4]. Dopaminergic depletion can also explain mental status changes through modulation of mesolimbic and mesocortical pathways [4].

Treatment

PHS is a neurological emergency. The key to treatment is early recognition of the syndrome and rapid reintroduction of withdrawn anti-parkinsonian medication (see Table 3.2). If there is no history of medication schedule alteration, then other causes must be sought including the use of neuroleptics or inadvertent shutting off of their DBS device (drained battery for example). When discontinuation of medication is the cause, the drug most commonly responsible is levodopa, and it should be reinstituted first, via nasogastric tube if necessary. Since PHS has occurred in two patients because of poor absorption of levodopa relating to diet this is an important consideration. Beyond that, the treatment is similar to NMS, including rehydration with intravenous fluids, treatment of hyperthermia with anti-pyretics and cooling blankets, as well as supportive measures such as mechanical ventilation, cardiovascular monitoring, intravenous access, nasogastric suctioning/feeding, and prevention of thrombophlebitis. Metabolic evaluation and workup to exclude infection are necessary. Since these patients are at risk for infection such as aspiration pneumonia, it is reasonable to initiate antibiotic therapy while the workup is under way. Additional medical therapy with bromocriptine or other dopamine agonists and dantrolene should be considered, although there have been no controlled trials. Bromocriptine is orally administered, with an initial dose of 2.5 mg t.i.d., and titrated for effect in increments of 2.5 mg t.i.d. every 24 hours. Dantrolene, a muscle relaxant initially used to treat malignant hyperthermia, is a parental compound typically dosed as 10 mg/kg/day in 3–4 divided doses. With proper therapy, symptoms will reverse in 10 hours to 7 days. Most of the patients described ultimately required a fairly lengthy hospital stay (5–22 days).

One study examined the use of methylprednisolone pulse therapy as an added regimen for PHS in PD [39]. In a randomized trial, all patients received levodopa,

Table 3.2 Steps in the management of PMS in PD

Recognition of the disorder
Verification of patients' medication regimen/compliance
Reintroduction of anti-parkinsonian medications
Supportive measures: Anti-pyretics/cooling blankets
Rehydration
ICU monitoring/management (see text)
Clinical evaluation for possible comorbid conditions
Bromocriptine 2.5 mg po t.i.d., titrated by 2.5 mg t.i.d./daily as necessary
Dantrolene sodium 10 mg/kg/day IV in divided doses (t.i.d./q.i.d.) as necessary

bromocriptine, and dantrolene sodium and patients were randomized to receive placebo or 1,000 mg of methylprednisolone for 3 days. Results suggested that steroid pulse therapy might shorten the course of the illness, perhaps by as much as 10 days, although notable overlap between groups was seen. This is the only double-blind, placebo-controlled trial in PHS or NMS, and further investigation is warranted.

Conclusion

PHS is a neurological emergency caused by the abrupt withdrawal of dopaminergic therapy that has the potential to end in fatality. In all likelihood, it is under-recognized and more common than the literature might suggest. The use of several terms to describe the diagnosis in the literature has contributed to the confusion. A unifying term could improve awareness, especially if the term relates specifically to those patients with underlying parkinsonism. That is why we believe that PHS, recommended by Gordon and Frucht [15], fulfills that role.

There are several ways to prevent PHS. First, drug holidays are no longer considered an appropriate treatment approach in PD. If reduction in dopaminergic therapy is needed, gradual reduction is mandated and patients should be made aware of the possible occurrence of PHS. This applies to patients with multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration [46]. When lowering doses patients need to remain adequately hydrated. In addition patients should be advised not to stop taking their medications on their own, and the dangers of this should be spelled out. It is important to avoid the use of standard neuroleptics in these patients since they are already at risk for NMS or PHS. Even atypical antipsychotics have the potential to lead to NMS in PD. The agents best tolerated by PD patients are quetiapine and clozapine [47], but they should also be prescribed with caution. Although patients with more severe disease and those taking larger daily levodopa doses are at greater risk [40–43], even patients with early PD taking low doses of levodopa can develop PHS. Once the syndrome does occur, recognition is paramount and rapid reintroduction of dopaminergic medications imperative.

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Chapter 4
Neuroleptic Malignant Syndrome

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Abstract Since the original description of neuroleptic malignant syndrome (NMS) over 50 years ago, a wealth of clinical data has accumulated on the clinical features, treatment, and pathogenesis of this uncommon but potentially lethal drug reaction. As a result, substantial progress has been achieved in reducing the incidence and mortality of NMS by increasing acceptance, awareness, and recognition of the disorder, more conservative prescribing practices, reduction of proposed risk factors, and development and marketing of newer antipsychotics with less liability for extrapyramidal side effects. Early diagnosis, cessation of neuroleptic medications, prompt medical intervention, and consideration of specific remedies comprise the mainstay of management. Nevertheless, vigilance must be maintained, as NMS remains obscure to most clinicians in practice. It is therefore essential for all physicians to become familiar with the diagnosis and treatment of this serious and treatable drug reaction.

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Clinical Vignettes

Case A

A 16-year-old woman who lived on a farm and spent time outdoors had been well with no psychiatric history until 1 week prior to admission. She developed difficulty sleeping and bizarre behavior including assaultiveness, sobbing, undressing in public, and thoughts of suicide, prompting admission to the hospital. On examination, she was labile, agitated, and delusional and experienced tactile, visual, and auditory hallucinations. Neurologic exam revealed impaired recall, dyscalculia, and right-sided sensory deficits. Haloperidol 2 mg orally BID was started, and she also received 5 mg intramuscularly for worsening agitation. Within a few hours, she developed a temperature of 39.8 °C, tachycardia, diaphoresis, boardlike rigidity with cogwheeling, tremors, and mutism. A generalized seizure was observed. Despite administration of diphenylhydantoin, steroids, diazepam, benztropine, and three electroconvulsive treatments, she remained rigid and unresponsive with temperatures rising to 40.5 °C.

Laboratory examination revealed elevated serum creatine phosphokinase (CPK) (44,000 IU) and peripheral leukocytosis. Serial electroencephalograms (EEGs) showed diffuse generalized slowing, and computed tomography (CT) scan of the head was normal. Lumber puncture on three occasions revealed 30–70 WBC/mm^3 (98% lymphocytes) with normal pressure, glucose, and protein. Cultures, stains, serology, and polymerase chain reaction for viral antigens were negative. Haloperidol was discontinued, and dantrolene and amantadine were administered. Over 2 weeks, she became alert, verbal, and ambulatory, and memory deficits and dysarthria resolved after 6 months.

Case B

A 65-year-old man with a history of alcohol dependence was admitted with a complaint of abdominal pain and nausea. Observation of a mass on a magnetic resonance imaging scan of the abdomen led to surgery for a perforated diverticulum. Postoperatively, he appeared restless, agitated, and delirious. He received haloperidol 2 mg and lorazepam 2 mg intravenously every 2 h. Within 24 h, he became unresponsive, tachycardic, hypotensive, tremulous, rigid, and febrile with temperatures reaching 41.5 °C. Laboratory examination revealed hypoxia, metabolic acidosis, elevated serum CPK (21,500 IU), and leukocytosis. An EEG showed diffuse generalized slowing and a CT scan of the head demonstrated mild cortical atrophy. Haloperidol was discontinued, but he developed sudden respiratory arrest requiring intubation. Lorazepam was continued and dantrolene and bromocriptine were administered. Subsequently, he was treated for acute renal failure and disseminated intravascular coagulation. He gradually improved over 4 weeks, but continued to exhibit persistent dysarthria and mild ataxia several months later.

Introduction

Neuroleptic malignant syndrome (NMS) was first identified by Delay and colleagues during early trials of haloperidol [1]. Although subsequently studied in France and Japan [2, 3], NMS remained obscure for an additional two decades until a cascade of hundreds of published clinical reports increased recognition and confirmed acceptance of NMS as a severe drug reaction associated with neuroleptic drugs [4–9]. The resistance and prolonged delay in acceptance of NMS as an iatrogenic condition occurred in part because it was often misdiagnosed as a form of malignant catatonia stemming from psychosis or schizophrenia, leading to tragic and fatal consequences of continued or even more aggressive antipsychotic treatment [6, 10].

In the intervening years, the accumulation of published clinical observations enabled a more precise definition of NMS, clarified risk factors and treatment strategies, renewed interest in related hyperthermic disorders, and shed light on the pathophysiology of the syndrome. Increased awareness facilitating early diagnosis, more conservative use of antipsychotic medications, and introduction of newer antipsychotics with reduced extrapyramidal effects have reduced the incidence and mortality of NMS. Nevertheless, the evaluation, differential diagnosis, and treatment of NMS in medical as well as psychiatric settings remain obscure to most practicing physicians. This is alarming, given that NMS remains potentially lethal if unrecognized, and underscores the need for increased awareness of this serious drug reaction.

Epidemiology

Incidence

Although NMS occurs infrequently, the widespread use of neuroleptics in medicine and psychiatry suggests that the absolute number of cases is quite large. For example, data from the US Agency for Healthcare Research and Quality indicate that about 2,000–2,500 cases of NMS are diagnosed annually in hospitals in the United States. Annual healthcare costs of $70 million and a mortality rate of 10% underscore the continuing public health impact of this drug reaction (http://hcup.ahrq.gov/HCUPnet.asp).

The incidence of NMS varies depending on the sample size and risk of the population studied, prescribing practices and methods of case ascertainment. Combining data from published studies of NMS occurring among groups of psychiatric patients treated with neuroleptics, we previously estimated the incidence of NMS to be about 0.2%, while other estimates reported in the literature ranged even higher [7]. However more recent rates reported in two large-scale prescription database studies were lower by a factor of 10–0.02%, equivalent to one case developing in 5,000 patients receiving neuroleptics [11, 12]. The apparent reduction in the incidence of

NMS over time may be the result of more conservative dosing of neuroleptics, minimizing risk factors, early recognition of incipient cases, and widespread use of newer and less potent antipsychotic drugs. As an example of the effect of drugs with less affinity for the dopamine receptor, Stubner found a tenfold lower incidence of NMS with clozapine compared with haloperidol [11].

Risk Factors

Several small controlled studies have been conducted to identify reliable risk factors for the syndrome [13, 14]. NMS has been reported in both sexes and all age groups. Although elevated environmental heat and humidity have been proposed as contributing factors in a few cases, NMS occurs independent of ambient conditions. NMS is not limited to specific neuropsychiatric diagnoses. It has developed in patients treated with neuroleptics for diverse psychiatric illnesses, as well as in patients without any evidence of brain or behavioral disorders who received dopamine antagonists (promethazine, droperidol, prochlorperazine, metoclopramide) for agitation, sedation, or gastrointestinal disorders [15]. Previous authors have proposed an increased risk of NMS in patients with schizophrenia, mood disorders, developmental disorders, organic brain syndromes, preexisting catatonia, and disorders affecting the basal ganglia [8, 16, 17]. Several systemic and metabolic factors have been correlated with the risk of NMS including exhaustion, agitation, dehydration, low serum iron, and use of physical restraints [2, 7, 8, 18].

Pharmacologically, about 15–20% of patients who develop NMS experienced a similar episode during prior exposure to neuroleptics, suggesting a trait susceptibility to the disorder [19]. Virtually all classes of drugs that induce dopamine receptor blockade have been associated with NMS. This includes all neuroleptics used as antipsychotics, although higher potency antipsychotics are probably associated with greater risk; haloperidol has accounted for about half of all reported cases [11]. Although the newer, less potent antipsychotics have also been associated with NMS in sporadic case reports, their liability for inducing NMS is likely smaller [11, 20]. Whereas cases meeting diagnostic criteria for NMS have been reported with clozapine, risperidone, and olanzapine, unequivocal reports implicating monotherapy with quetiapine, ziprasidone, aripiprazole, iloperidone, asenapine, and paliperidone remain scarce.

NMS cases, including some that were fatal, have also been reported in association with other neuroleptic drugs prescribed by medical and surgical practitioners as mentioned above [15]. These include prochlorperazine, metoclopramide, droperidol, and promethazine. Haloperidol is also frequently used in critical care settings for management of agitation and delirium. We believe that cases of NMS in these settings remain seriously underreported and unrecognized.

NMS is not a result of overdosage with neuroleptics, usually occurring within the therapeutic range. Several studies have suggested that patients who develop NMS are more likely to have received relatively higher doses, more rapid titration,

and more parenteral injections of neuroleptics compared to controls [13, 14]. It is currently unknown whether or not adjunctive or concomitant medications (e.g., anti-parkinsonian drugs or lithium) increase or decrease the risk of NMS. Recently, the FDA required manufacturers of antidepressants to add a warning to their package labeling about NMS-like reactions associated with these drugs when used either alone or in combination with neuroleptics. Concurrent administration of neuroleptics and other drugs, including lithium, SSRIs, or SNRIs, may increase the risk of NMS, but alternatively these events may actually be instances of serotonin syndrome [21].

It is important to realize that the association of these risk factors with NMS in a few patients does not outweigh the benefits of neuroleptic therapy for the vast majority of patients for whom they are properly indicated [9].

Pathophysiology

Several lines of evidence provide compelling support that a reduction in dopamine levels in the brain is the trigger underlying NMS [8, 22]. All neuroleptics implicated in NMS share the characteristic of dopamine receptor blockade. Clinical studies indicate that the risk of NMS correlates with dose, potency, rate, and route of administration of dopamine antagonists [13]. Dopaminergic drugs have been administered empirically and found to be an effective therapy for NMS in some studies [23–25]. Most convincingly, patients with Parkinson's disease have developed a hyperthermic-parkinsonian syndrome that is indistinguishable from NMS following abrupt withdrawal of dopamine agonists. Patients with lesions interrupting dopamine pathways have developed a syndrome of akinetic mutism and hyperthermia resembling NMS. Studies of neurotransmitter metabolites in cerebrospinal fluid obtained from patients with acute NMS reveal central dopamine hypoactivity as a possible trait marker for NMS, based on comparatively low concentrations of the dopamine metabolite homovanillic acid [26, 27]. A few preliminary studies have also suggested abnormalities in the dopamine D2 receptor gene of patients who recovered from NMS episodes, although results have not been consistently replicated [8]. Studies of clinical correlates of frontal-subcortical circuits provide a framework within which individual NMS symptoms may be mapped to perturbations in specific dopamine pathways [22]. Finally, changes in dopamine pathways in response to stress may be implicated as an additional state-related cofactor involved in the triggering of NMS [22].

Although the evidence for a central role of dopaminergic mechanisms in the pathophysiology of NMS is persuasive, other mechanisms have been proposed. These include a relative excess of glutaminergic transmission secondary to dopamine blockade, effects of low serum iron on dopamine receptor function, effects of reduced activity of gamma aminobutyric acid, and dysregulation of the sympathetic nervous system [18, 22, 27–29].

Finally, even though NMS and malignant hyperthermia induced by anesthetics (MH) differ in pharmacologic triggering mechanisms—MH attributed to a primary

pharmacogenetic defect in skeletal muscle—their similar clinical presentations of a hypermetabolic syndrome suggest potential parallels. Clinical reports of a risk of NMS following administration of neuroleptics in patients with MH-susceptibility, preexisting myopathies, or unexplained CPK elevations lend support to overlapping or convergent mechanisms between NMS and MH [8, 15, 30, 31]. This clinical evidence combined with reported pharmacologic effects of neuroleptics on CPK levels, membrane permeability, calcium regulation, and contractility in skeletal muscle is intriguing and merits further investigation [32].

Clinical Characteristics

Prodromal Signs

In addition to the development of reliable risk factors, it would be useful to identify early signs of NMS in order to abort the progression of the syndrome by discontinuing triggering drugs. Although occasional cases of NMS may have a fulminant onset within hours after drug administration, the initial progression of symptoms is usually insidious, occurring over days. Neurologic signs of muscle rigidity and altered mental status occur early, followed by autonomic changes and hyperthermia; in over 80% of cases in which a single presenting sign was reported, rigidity or mental status changes constituted the initial manifestation [33]. Other prodromal signs may include obtundation, catatonia, tachycardia, tachypnea, labile blood pressure, dysarthria, dysphagia, diaphoresis, sialorrhea, incontinence, rigidity, myoclonus, tremors, low-grade fevers, or serum CPK elevations. Clinicians should be prepared to diagnose NMS early and to document the rationale for cessation versus continuation of neuroleptic therapy. However, these early signs are not specific for NMS, do not necessarily progress to NMS, and do not invariably precede the syndrome [7].

Signs and Symptoms

Clinical features of NMS are listed in Table 4.1. NMS may be conceptualized as a form of drug-induced hyperthermia, usually associated with profuse sweating. Extreme temperature elevations represent a medical emergency and predispose to complications, including irreversible brain damage if not reduced immediately. There are few disorders that result in extreme elevations in temperature, signifying an underlying disruption of thermoregulatory systems, as occurs in NMS due to drug effects on hypothalamic centers; thus, the diagnosis of NMS is more likely in a patient with very high temperatures, whereas the differential diagnosis in a patient with low-grade temperature elevations is quite broad. Generalized rigidity, often described as “lead-pipe,” is a core feature of NMS, and is usually associated with rhabdomyolysis. Cogwheeling, spontaneous and action myoclonus of multifocal

Table 4.1 Clinical features of NMS

Administration of neuroleptics, particularly high-potency agents
Signs and symptoms
Hyperthermia (>38 °C)
Muscle rigidity ± cogwheeling
Tremor, myoclonus
Mental status changes (stupor, mutism, delirium)
Autonomic instability (tachycardia, labile blood pressure)
Tachypnea, dyspnea
Diaphoresis, sialorrhea, incontinence
Dysarthria, dysphagia
Positive laboratory findings
Muscle enzyme elevations (CPK, LDH, transaminases, aldolase), myoglobinuria, leukocytosis, metabolic acidosis, hypoxia, low serum iron, elevated serum catecholamines, slowing on EEG
Complications
Cardiorespiratory arrest, acute renal failure, rhabdomyolysis, pulmonary emboli, aspiration pneumonia, disseminated intravascular coagulation, limb contractures, ischemic brain damage
Exclusion of other central, systemic, and toxic causes of hyperthermia

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

Laboratory Evaluation

Although several laboratory abnormalities have been reported in NMS, none are specific or pathognomonic for the diagnosis [8]. Instead, a comprehensive laboratory evaluation is essential in excluding other causes of hyperthermia and detecting medical complications. Serum CPK is usually moderately elevated but occasionally reaches extraordinary levels reflecting massive rhabdomyolysis. Rhabdomyolysis is multifactorial in origin, stemming from rigidity, immobility, hyperthermia, ischemia, and possibly direct drug effects on skeletal muscle. Although elevations in CPK are not specific to NMS, monitoring of the enzyme level remains important as a measure of the severity of rhabdomyolysis and the attendant risk of renal failure. Rhabdomyolysis is also manifested by increases in serum myoglobin, aldolase, transaminases, and lactic acid dehydrogenase concentrations. Other frequently described laboratory abnormalities include metabolic acidosis, hypoxia, decreased serum iron concentrations, elevated serum catecholamines, electrolyte abnormalities, leukocytosis with or without a left shift, and coagulopathies including those associated with disseminated intravascular coagulation.

Nonfocal generalized slowing on EEG, consistent with encephalopathy, has been reported in over half of NMS cases [19]. Brain imaging studies, cerebrospinal fluid examination, and sepsis evaluation are negative, allowing for the exclusion of other causes of fever and neurologic deterioration [19].

Diagnostic Criteria

Although a number of rating scales and diagnostic criteria sets have been proposed [8, 34, 35], the degree of agreement between them is only modest [36]. To address this issue, an international, multispecialty panel of NMS experts was convened recently to reach a consensus using a standardized Delphi process regarding the clinical features that are most valuable in making a diagnosis of NMS, their relative importance, and corresponding critical values [37]. The key features of NMS that were agreed upon included the following: exposure to a dopamine antagonist, or dopamine agonist withdrawal, within the past 72 hours; hyperthermia (>100.4 °F or >38.0 °C on at least two occasions, measured orally); muscle rigidity; mental status alteration (reduced or fluctuating level of consciousness); CPK elevation (at least four times upper limit of normal); evidence of sympathetic nervous system lability and hypermetabolism; and a negative workup for infectious, toxic, metabolic, or other neurologic causes.

Clinical Course and Outcome

NMS results from neurochemical changes induced by neuroleptics during the initial stages of treatment or after dosages are increased. In a review by Caroff and Mann [19], 16% of patients developed NMS within 24 hours of initiating neuroleptic treatment, 66% by 1 week, and 96% within the first 30 days. It would be unusual for NMS to develop later than 1 month after treatment initiation, unless the dose was increased or another neuroleptic was added. Only 4% of reported cases developed NMS beyond 30 days. Conversely, once neuroleptics were discontinued, NMS is self-limited barring complications. Following discontinuation of oral neuroleptics, the mean recovery time has been estimated at 7–10 days [7]. About 63% of patients recover within 1 week, and nearly all within 30 days [19].

In some cases, the course of NMS may be prolonged. For example, patients receiving long-acting depot neuroleptics may remain ill nearly twice as long [7]. Occasional patients may develop a residual catatonic-parkinsonian state that can persist for weeks to months if left untreated after the acute hyperthermic and hypermetabolic symptoms of NMS subside [38]. Although dopamine agonists and benzodiazepines have been advocated for treatment of this residual state, electroconvulsive therapy (ECT) appears to be more rapidly effective with reduced mortality in reported series [38].

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

Evaluation and Differential Diagnosis

The differential diagnosis of NMS encompasses a broad range of disorders presenting with fever, necessitating a thorough medical and neurologic evaluation. Despite careful investigation, the cause of the syndrome in some patients may remain unclear or reflect multiple determinants. Other disorders that can resemble NMS include primary disorders of the brain, and systemic disorders that secondarily affect brain function. Among the former are infectious encephalitis, structural lesions, and rare cases of non-convulsive status epilepticus [7, 8].

We have been consulted on several cases resembling the patient described in our first clinical vignette (Case A), in which a patient with underlying encephalitis is initially misdiagnosed with a psychiatric condition and then develops NMS following administration of neuroleptics [17, 39]. Most often, a causative pathogen is not identified, or these cases are found to represent autoimmune or paraneoplastic encephalitides [40]. These observations led us to underscore the importance of considering encephalitis in the differential diagnosis of patients who present with the new onset of psychosis, especially if they develop NMS after treatment with neuroleptics. Such cases imply that encephalitic patients may be at increased risk for NMS and other neuroleptic-induced extrapyramidal disorders.

Advanced stages of psychotic disorders associated with excited or stuporous catatonia (delirious mania or malignant catatonia) can progress to exhaustion, hyperthermia, and death [41, 42]. Although the incidence of malignant catatonia has decreased, it still occurs and can be indistinguishable from NMS. Indeed, NMS has been conceptualized as a drug-induced iatrogenic form of malignant catatonia. In either NMS or malignant catatonia, neuroleptics should be discontinued because most NMS episodes are self-limited and should subside within 2 weeks after drug discontinuation, and in malignant catatonia, neuroleptics appear to be ineffective and even detrimental. In contrast, ECT appears to be the treatment of choice in malignant catatonia, and is often also effective in NMS [25].

In relation to systemic disorders, patients with common and benign forms of neuroleptic-induced parkinsonism or catatonia may develop fever from coincidental infections or dehydration and be mistakenly diagnosed as having NMS. Neuroleptics have also been associated with rhabdomyolysis alone without other features of NMS, and the relationship between these two drug-induced phenomena is unclear.

Hyperthermia may be observed in patients with thyrotoxicosis and pheochromocytoma, which can be distinguished from NMS by the absence of rigidity. Systemic lupus erythematosus or other autoimmune diseases affecting the brain may present with fever and neurologic signs. Heatstroke may develop in patients during hot weather and be confused with NMS [43]. Furthermore, neuroleptic treatment may predispose to heatstroke by blocking central thermoregulatory heat loss pathways. Unlike NMS, muscle rigidity is unusual in heatstroke.

Diverse toxins and drugs have been associated with hyperthermia and must be considered in the differential diagnosis of NMS. Volatile anesthetics and succinylcholine are associated with MH during surgery, which can be confused with NMS if neuroleptics are administered peri-operatively [15]. Although NMS has been reported before and after surgery, it appears unlikely to develop intra-operatively, in contrast to MH. Furthermore, centrally derived muscle rigidity associated with NMS can be reversed by neuromuscular blockade, whereas rigidity associated with MH reflects a defect within skeletal muscle which does not respond to paralyzing agents.

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

Finally, serotonin syndrome is often considered in the differential of NMS, and has been increasingly reported in association with serotonergic agents introduced for the treatment of depression or migraine headaches, and subsequently expanded to use in many disorders [44]. Although serotonin syndrome can present as an NMS-like hypermetabolic state in its most severe form associated with monoamine oxidase inhibitors, it usually presents with milder and more transient symptoms indicative of an agitated delirium.

Our second vignette (Case B) illustrates the need to exclude several of these conditions before settling on the diagnosis of NMS. This is a particularly challenging task in critical care units where fever commonly occurs as a result of infections or drug reactions. It is unusual for MH to occur postoperatively and therefore MH was an unlikely diagnosis in this case. In contrast, NMS has been reported in the context of neuroleptic treatment of postoperative agitation. Furthermore, this patient was alcohol dependent raising the possibility of a withdrawal reaction. Although CPK elevations can be observed in alcoholics as well as in patients with NMS, the characteristic rigidity of NMS is not a typical feature of alcohol withdrawal. However, we have previously suggested that patients with severe withdrawal from alcohol or sedatives may be at increased risk of developing NMS [8]. Both clinical vignettes illustrate the fact that NMS is a diagnosis of exclusion, stemming from primary or acquired subcortical brain dysfunction and neuroleptic-induced effects on the brain.

Treatment

The mainstay of treatment of NMS includes risk reduction, early diagnosis, cessation of neuroleptic medications, and provision of intensive medical and nursing care [9, 25]. There is less evidence and consensus concerning the comparative efficacy of specific pharmacologic agents and ECT in the treatment of NMS. This derives from the fact that with early recognition and prompt cessation of neuroleptics, NMS is a self-limited disorder in most cases, regardless of specific therapies. Furthermore, there are no controlled, comparative, treatment trials. It is difficult to compare any specific treatments because NMS is rare, self-limited, and heterogeneous and unpredictable in the onset, progression, and outcome. Nevertheless, there are rational theories and empirical clinical data that lead to consideration of specific pharmacologic agents and ECT in the treatment of NMS.

Based on available evidence, we recommend that specific treatment of NMS should be individualized and based empirically on the character, duration, and severity of clinical signs and symptoms (Table 4.2) [9, 25, 45]. In many cases, supportive care alone after drug cessation with close monitoring for progression of symptoms or complications may be sufficient until recovery occurs. Benzodiazepines are effective in reversing catatonia, easy to administer, and can be tried initially in most cases. Trials of bromocriptine, amantadine, or other dopamine agonists may be a reasonable next step in patients with moderate symptoms of NMS that include prominent parkinsonian signs, or when withdrawal of dopamine agonists is involved. When severe symptoms render treatment by the oral route impractical, intravenous or subcutaneous administration of dopamine agonists, e.g., lisuride or apomorphine, may be an option [46]. In addition, newer dopamine agonists are being developed for transdermal delivery that will facilitate parenteral administration of dopaminergic drugs under extreme circumstances.

Dantrolene appears to be beneficial primarily when significant rigidity and severe hyperthermia develop as manifestations of a full-blown hypermetabolic state [23, 24, 47, 48]. An inhibitor of skeletal muscle hypermetabolism, dantrolene has been associated with rapid reduction of extreme temperature elevations in many case reports. None of the above medications have been reliably effective in all reported NMS cases in which they have been administered, and they are often administered in more severe or refractory cases after supportive management has failed to reduce symptoms. Furthermore, positive drug effects are usually reported during the first few days of treatment of NMS, whereas delayed administration is unlikely to produce a response.

If symptoms of NMS persist despite supportive care and pharmacotherapy, ECT may be effective even late in the course. ECT may be preferred if idiopathic malignant catatonia cannot be excluded, if NMS symptoms are refractory to other measures, in patients with prominent catatonic features, and in patients who develop a residual catatonic-parkinsonian state or remain psychotic after NMS has resolved [25, 38, 41].

Table 4.2 Proposed treatment algorithm for NMS [9]

Woodbury stage [45]	Clinical presentation	Supportive care	First-line interventions	Second-line interventions
Stage I: Drug-induced parkinsonism	Rigidity; tremor	Reduce or switch antipsychotics	Anticholinergic agents	
Stage II: Drug-induced catatonia	Rigidity; mutism; stupor	Discontinue, reduce, or switch antipsychotics	Lorazepam (1–2 mg i.m. or i.v. every 4–6 h)	
Stage III: Mild or early NMS	Mild rigidity; catatonia or confusion; temperature >38 °C (100.4 °F); heart rate >100 bpm	Discontinue antipsychotics; carefully monitor for progression; correct risk factors	Lorazepam (1–2 mg i.m. or i.v. every 4–6 h)	
Stage IV: Moderate NMS	Moderate rigidity; catatonia or confusion; temperature 38–40 °C (100.4–104 °F); heart rate 100–120 bpm	Discontinue antipsychotics, manage fluids, initiate cooling measures, correct risk factors, provide intensive care	Lorazepam (1–2 mg i.m. or i.v. every 4–6 h), bromocriptine (2.5–5 mg p.o. or by nasogastric [NG] tube every 8 h), or amantadine (100 mg p.o. or by NG tube every 8 h)	Consider electroconvulsive therapy (6–10 bilateral treatments)
Stage V: Severe NMS	Severe rigidity; catatonia or coma; temperature >40 °C (104 °F); heart rate >120 bpm	Discontinue antipsychotics, manage fluids, initiate cooling measures, correct risk factors, provide intensive care	Dantrolene (1–2.5 mg/kg i.v. every 6 h for 48 h), bromocriptine (2.5–5 mg p.o. or by NG tube every 8 h), or amantadine (100 mg p.o. or by NG tube every 8 h)	Consider electroconvulsive therapy (6–10 bilateral treatments)

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Among patients who recover from NMS, there is a 30% risk of recurrent episodes following subsequent neuroleptic rechallenge [7]. However, the majority of patients who require neuroleptic therapy can be safely treated, provided precautions are taken. To minimize risk of recurrence, clinicians should; review records for accuracy of diagnosis of previous episodes of NMS; document indications for use of neuroleptics; consider alternative medications; obtain informed consent from patients and caregivers; reduce risk factors; allow 2 weeks to elapse before rechallenge; use low doses of low-potency conventional neuroleptics or atypical neuroleptics after a test dose; and monitor patients carefully for signs of incipient NMS.

Conclusions

Neuroleptics are highly effective and safe medications that have achieved widespread use in medicine and psychiatry. However, they have been associated with NMS in about 0.02% of psychiatric patients who receive them. Significant progress has been achieved in recognizing, managing, and understanding this drug reaction since it was first described over 50 years ago. Introduction of newer antipsychotics with reduced extrapyramidal liability, conservative prescribing guidelines, reduction of proposed risk factors, and education of staff have reduced the incidence of this disorder. Early diagnosis, cessation of neuroleptic medications, prompt medical intervention, and consideration of specific remedies can reduce morbidity and mortality when NMS occurs. It is essential for all physicians and nurses to become familiar with the diagnosis and treatment of this uncommon but potentially lethal drug reaction.

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Chapter 5
Malignant Catatonia

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

Abstract Malignant catatonia (MC) represents a life-threatening neuropsychiatric disorder that was widely reported both in the United States and abroad long before the introduction of antipsychotic drugs. Lack of recognition probably accounts for the relative paucity of contemporary North American reports on MC. Furthermore, MC is a syndrome rather than a specific disease entity that may occur as an outgrowth of diverse neuromedical illnesses as well as with the major psychoses. From this perspective, neuroleptic malignant syndrome (NMS), a potentially deadly complication of antipsychotic drug treatment, may be conceptualized as a drug-induced form of MC. The hypothesis that MC and NMS share a common pathophysiology, involving reduced dopamine functioning in the frontal-subcortical circuits, provides additional support for a view of NMS as a subtype of MC. Electroconvulsive therapy is the preferred treatment for MC stemming from a major psychotic disorder, and appears also effective in cases caused by neuromedical illnesses. Antipsychotic drugs should be withheld whenever MC is suspected.

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Clinical Vignettes

Patient 1

A 27-year-old female with a personal and family history of bipolar disorder has taken no psychiatric medications for the past 6 months. One week prior to admission, she develops elevated mood, pressured speech, and flight of ideas. Over the ensuing days, she grows markedly agitated and unable to sleep, talks constantly, paces relentlessly, and refuses to eat or drink. On admission to the psychiatric unit, she requires four-point restraints. She is confused and intensely hyperactive with periods of incoherent chatter alternating with hostile verbal outbursts. She frequently thrashes from side to side, is delusional, and appears to be responding to both auditory and visual hallucinations. She exhibits muscular rigidity, posturing, echolalia, and echopraxia. Temperature is 39 °C with tachycardia, tachypnea, profuse diaphoresis, and a blood pressure of 170/120 mm Hg. Laboratory abnormalities include leukocytosis, elevation in creatinine phosphokinase (CPK) (2,800 IU), and serum transaminases and a serum iron of 38 μg/dl (75–175 μg/dl). Lumbar puncture, EEG, and CT scan of the head are normal.

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

Patient 2

A 46-year-old male schizophrenic patient has taken no psychiatric medications for the past 2 years. He is admitted to the Intensive Care Unit with a 1-week history of progressive mutism, immobility, negativism, and staring. On exam, he exhibits marked muscular rigidity. Temperature is 40.1 °C with tachycardia, tachypnea, diaphoresis, and a blood pressure of 190/110 mm Hg. Laboratory evaluation reveals elevated CPK and leukocytosis. All other studies are noncontributory. Malignant catatonia is diagnosed. Intravenous lorazepam 2 mg, administered four times daily for 2 days, is without benefit. He is referred for bilateral ECT and responds promptly.

Introduction

Catatonia is a syndrome of striking motor and behavioral abnormalities that may occur in association with diverse neuromedical, drug-induced, and psychiatric illnesses. Furthermore, catatonia may be conceptualized as a continuum, with milder forms at one end (termed *simple* or *benign*) and more severe forms, involving hyperthermia and autonomic dysfunction (termed *malignant*), at the other [1]. In 1934, Stauder [2] described *lethal catatonia*, characterized by extreme motor excitement followed by stuporous exhaustion, coma, cardiovascular collapse, and death. The entire course involved progressive hyperthermia, autonomic dysfunction, clouding of consciousness, and prominent catatonic features. In those cases ending in death, the paucity of findings was puzzling and in sharp contrast to the catastrophic clinical manifestations. In fact, this disorder had been discussed previously by Calmeil (1832) [3] and Bell (1849) [4] and was the subject of numerous North American and foreign publications during the pre-antipsychotic drug era. Other names used to describe this same disorder included *Bell's mania*, *acute delirious mania*, *delirium acutum*, *delire aigu*, *psychotic exhaustion syndrome*, and *Scheid's cyanotic syndrome*, among others [5–10]. More recently, stressing that not all cases are fatal, Philbrick and Rummans [1] have promulgated the term *malignant catatonia* (MC).

Although the incidence of MC has likely declined worldwide following the introduction of modern psychopharmacologic agents, it has remained widely reported in Europe and Asia. In contrast, contemporary North American publications on MC have now become more limited with an almost complete lack of reference to the current foreign work or the large North American literature from the pre-antipsychotic drug era. In this chapter we review the historical and modern world literature on MC. On the basis of this review, we conclude that MC continues to occur and represents an uncommon but potentially fatal neuropsychiatric disorder. Lack of recognition appears to account for the scarcity of recent North American reports on MC.

Furthermore, our data indicate that MC, like simple catatonia, represents a syndrome rather than a specific disease. Although most often presenting as an outgrowth of the major psychoses, MC may also occur in association with diverse neurologic, infectious, and toxic-metabolic conditions. From this perspective, neuroleptic malignant syndrome (NMS), a life-threatening complication of antipsychotic drug treatment [8, 11], may be viewed as a drug-induced form of MC. In addition, findings from our review indicate that MC and NMS share a common pathophysiology involving reduced dopaminergic neurotransmission within the basal ganglia-thalamocortical circuits. Recognition of the clinical features of MC and an appreciation of its diverse etiologies are essential for the effective management of patients who develop this catastrophic reaction.

Clinical Presentation: Pre-antipsychotic Drug Era

Despite the diversity of nomenclature, there is considerable consistency to early accounts of MC [5–10]. A prodromal phase was observed in most, but not all, cases. It lasted an average of 2 weeks and involved insomnia, anorexia, and labile mood. In roughly 90 % of cases, the disease proper began with a phase of intense motor excitement that then continued almost without interruption (as exemplified by Patient 1). Features of this excited phase included refusal of foods and fluids, clouding of consciousness, tachycardia, tachypnea, cyanosis, labile or elevated blood pressure, and profuse perspiration. Acrocyanosis and spontaneous hematomas of the skin were frequently noted. At times, excitement might be interrupted by periods of catatonic stupor and rigidity. Other catatonic signs, such as mutism, catalepsy, posturing, echolalia, and echopraxia were often present. Thought processes became increasingly disorganized and speech grew progressively incoherent. Auditory and visual hallucinations accompanied by bizarre delusions were frequently prominent.

In this "classic" excited phase of MC, excitement was always associated with hyperthermia that could attain levels approaching 43.3 °C prior to the final stuporous phase of MC. This presentation differs phenomenologically from NMS in that although NMS is often preceded by a period of hyperactivity, hyperthermia first emerges concomitantly with, or shortly after, the onset of stupor and rigidity. The excited phase of MC was noted to vary in duration but lasted an average of 8 days [12].

In the final phase of MC, excitement gave way to stuporous exhaustion and extreme hyperthermia, often followed by coma, cardiovascular collapse, and death [5]. In all of Stauder's 27 cases [2], rigidity of the skeletal muscles was described during this terminal stupor, similar to that seen in NMS. Although other accounts of MC echoed the findings of Stauder, some reports described flaccid muscles in contrast to NMS [12]. About 10 % of cases reported during the pre-antipsychotic drug era involved hyperthermia and a primarily stuporous course unassociated with a preceding hyperactive phase (Patient 2).

During the pre-antipsychotic drug era, MC was reported fatal in 75–100 % of cases [5]. It was observed to occur predominantly in young adults between the ages of 18 and 35 and involved women roughly seven times more often than men. During this period, MC was estimated to account for 0.25–3.5 % of admissions to psychiatric hospitals and occurred with equal frequency throughout the seasons [5]. Stauder [2], and others, reported findings consistent with a familial pattern of occurrence.

Kraepelin [13], who called this disorder *delirium acutum*, considered it a nonspecific syndrome that could occur as an outgrowth of neuromedical illness as well as the major psychoses. In contrast, most early French authors viewed MC as an unusual but deadly form of encephalitis preferentially involving the hypothalamus [14]. Subsequent to Stauder's [2] publication, however, MC was increasingly seen as confined to the major psychoses, although Stauder himself never fully dismissed the possibility that some or all of his patients may have had encephalitis.

Most German and American authors emphasized lack of autopsy findings that could account for death, with the CNS abnormalities reported by the French either unconfirmed or deemed trivial. Bronchopneumonia and other infections were considered "opportunistic," occurring in an already exhausted and compromised host.

Contemporary Presentation

In 1986, we identified a series of 292 MC cases reported between 1960 and 1985 [5]. Two hundred and sixty-five cases came from 20 reports representative of more than 50 publications from Europe and Asia. The remaining 27 cases came from just 12 articles found in an exhaustive search of the North American literature. Most patients had received antipsychotic drug treatment. Since then, we have identified 107 additional cases reported in the world literature between 1986 and 2010, thus extending our series to 399 total cases [8–10, 15–32]. Although MC remains more frequently mentioned in the foreign literature, the disparity in these more recent 107 cases appears somewhat reduced, suggesting improved recognition of this disorder in North America.

Among 341 cases in which sex was specified, 218 (64 %) were female. The mean age of occurrence was 33, compared with 25 during the pre-antipsychotic drug era. Of considerable interest, mortality, which exceeded 75 % during the pre-antipsychotic drug era, remained at 60 % between 1960 and 1985 [5] and has fallen to 10 % in the 107 cases reported since 1986 [8–10, 15–32]. This recent decline is striking and presumably reflects enhanced awareness of MC, early diagnosis, and rapid institution of appropriate treatment. Nevertheless, MC continues to represent a potentially lethal disorder. Among cases reported since 1960, MC was estimated to occur in 0.07 % of psychiatric admissions [33] or annually in 0.0004 % of community adults [34].

Table 5.1 summarizes the clinical features of MC. Along with catatonic stupor and hyperactivity, they remain to be hyperthermia, altered consciousness, and autonomic instability manifested by diaphoresis, tachycardia, labile or elevated blood pressure, and varying degrees of cyanosis. Catatonic signs aside from stupor and excitement continue to be noted. One large series [35] identified 62 patients with psychogenic MC and reported that each exhibited at least three catatonic features. In our 107 most recent cases, muscle rigidity was present in 41 of 48 (85 %) cases in which muscle tone was characterized.

Among the 107 recent MC cases, CPK was elevated in 45 of 48 patients (94 %) in whom it was tested. Leukocytosis was reported in 24 of 35 patients (66 %) and serum transaminases were elevated in 13 of 29 patients (45 %). Serum iron levels were obtained in only eight patients, but were decreased in all eight. Less consistent findings among the 107 recent cases included non-focal generalized slowing on electroencephalography, elevated erythrocyte sedimentation rates, mild hyperglycemia, elevated serum creatinine, hyponatremia, hypernatremia, and dehydration. Philbrick and Rummans [1] found that three of five MC cases treated at their facility

Table 5.1 Clinical features of malignant catatonia

Signs and symptoms
Hyperthermia
Catatonic excitement and/or stupor
Other catatonic features (e.g., mutism, negativism, catalepsy, posturing, echolalia, echopraxia, staring)
Muscular rigidity (variable)
Altered consciousness
Autonomic instability
Profuse diaphoresis
Tachycardia
Labile or elevated blood pressure
Tachypnea, cyanosis (variable)
Positive laboratory findings
Most consistent—CPK elevation, leukocytosis, low serum iron levels
Less consistent—elevated serum creatinine, hyponatremia, hypernatremia, dehydration, frontal atrophy on CT or MRI, decreased frontal perfusion on SPECT
Outgrowth of diverse neuromedical, drug-induced, and psychiatric conditions

had evidence of frontal atrophy on CT scans of the head. Furthermore, one patient with a normal head CT had decreased frontal perfusion on posttreatment SPECT imaging.

In 60 (15 %) of the 399 contemporary cases, a preexisting neuromedical illness was believed to have initiated the full syndromal picture of MC. Reports of infectious causes predominated, including 25 cases of acute or post-infectious viral encephalitis [8–10, 16, 20, 21, 28, 31]; single cases of Borrelia encephalitis, general paresis, bacterial meningoencephalitis, and viral hepatitis; and bacterial septicemia that evolved from five cases of endometritis, and from single cases each of pyelonephritis, tuberculosis of the large intestine, aortitis, cholangitis, endocarditis, and gingival abscess [5–10]. In two cases of septic origin, the original focus of infection was not indicated [5]. Cerebrovascular thrombosis [5] and paraneoplastic limbic encephalitis accounted for two cases each [17, 22], and MC developed in the context of normal-pressure hydrocephalus and multiple sclerosis in single cases [9, 26]. Two cases occurred secondary to hyperthyroidism, and single cases were attributed to uremia, systemic lupus erythematosus, and cerebral anoxia [5, 9]. Reports of toxic causes included single cases due to tetraethyl lead poisoning, barbiturate withdrawal, clonazepam withdrawal, renal transplantation, toxic epidermal necrolysis, therapeutic ingestion or overdose of cyclobenzaprine, and intrathecal administration of Ziconotide [5, 9, 15, 27].

Three hundred and thirty-nine of the 399 cases (85 %) were considered as the outgrowth of a major psychotic disorder, diagnosed as schizophrenia in 127 cases, mania in 22 cases, major depression in 31 cases, psychotic disorder not otherwise specified in 22 cases, and "periodic catatonia" in 10 cases. Among these 339 MC cases arising from the major psychoses, 167 (49 %) ended in death and 104 went to autopsy.

Seventy-nine of the 104 proved autopsy negative. In the remaining 20 cases, however, death could be attributed to specific consequences of catatonic immobility, such as deep venous thrombosis with pulmonary embolism. These cases of simple (benign) catatonia rendered fatal by severe intercurrent medical complications were differentiated from "genuine" psychogenic MC.

The Malignant Catatonia Syndrome

Our review of the modern world literature supports Kraepelin's [14] conceptualization of MC as a nonspecific syndrome that may occur in association with diverse neurologic, medical, drug-induced, and psychiatric illnesses. Table 5.2 summarizes known causes of the MC syndrome.

Consistent with this view, it is appropriate to consider the relationship between MC and NMS. Among the 399 contemporary MC cases, the "classic" excited form (Patient 1) involving extreme hyperactivity and progressive hyperthermia prior to the onset of stupor has continued to predominate with 66 % of cases presenting in this fashion. However, 34 % of patients exhibited a primarily stuporous course. This represents a change from the pre-antipsychotic drug era when only about 10 % of patients presented as primarily stuporous [9]. Furthermore, a selective analysis of the 107 cases reported since 1986 indicates that this trend has continued, with only 56 % exhibiting excitement and 44 % presenting as stuporous (Patient 2).

In many of these cases involving a stuporous course, stupor and hyperthermia developed only following the initiation of antipsychotic drug treatment, giving rise to questions concerning the differentiation of MC from NMS. Furthermore, the clinical features of the presentation of classic excited MC, once stupor emerges, appear equally difficult to distinguish from those of NMS. Viewing MC as a syndrome, we have suggested that NMS represents an antipsychotic drug-induced toxic or iatrogenic form of MC. Accordingly, the emergence of NMS as a subtype of MC could help explain the increased percentage of primarily stuporous MC cases reported in the contemporary literature.

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

Table 5.2 Disorders associated with malignant catatonia syndrome

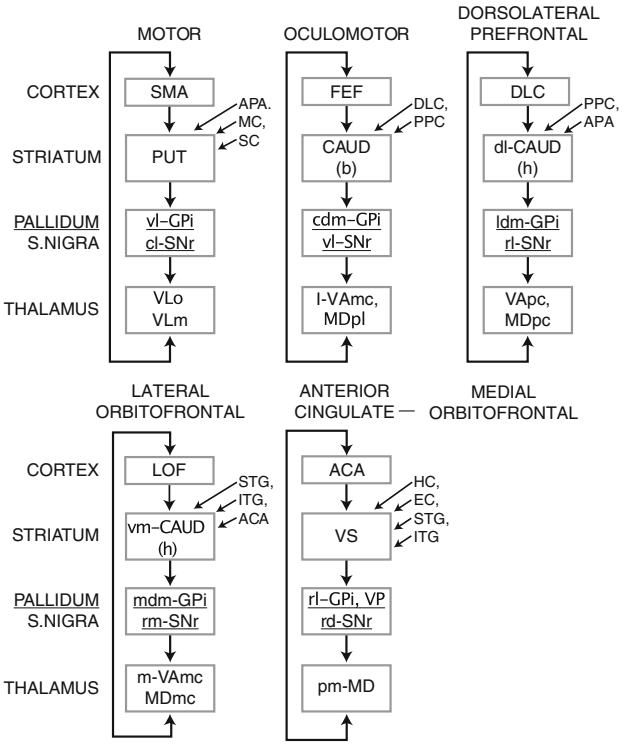
Psychiatric disorders
Schizophrenia
Mood disorders
Periodic catatonia
Psychotic disorder not otherwise specified
Cerebrovascular disorders
Basilar artery thrombosis
Bilateral hemorrhagic infarction of the anterior cingulated gyri
Bilateral hemorrhagic lesions of temporal lobes
Other central nervous system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

Clearly, it is difficult for clinicians to accept that high fever and confusion may occur as a direct outgrowth of a psychiatric condition. Hafner and Kafner [34] concluded that even in Germany, where MC appears better recognized, neurologists and internists rather than psychiatrists now more commonly care for patients who previously would have been diagnosed with MC. These patients are likely to receive diagnoses such as "nonspecific organic encephalopathy with fever." Conversely, reports resembling those on viral encephalitis "imitating" catatonic schizophrenia indicate that failure to recognize MC may result in a narrow focusing on behavioral manifestations, with neglect of ominous physical signs [36]. Once developed, MC, independent of etiology, assumes an autonomous and frequently fatal course. Only with prompt recognition of this distinctive syndrome can the proper diagnostic evaluation and treatment be initiated.

Pathophysiology

A consideration of the pathogenesis of MC with a particular focus on the dopamine system further supports a view of NMS as a subtype of this disorder. A number of authors have posited a key role for dopamine hypoactivity in triggering MC [5, 8, 9, 37, 38]. Furthermore, there is compelling clinical evidence implicating antipsychotic drug-induced dopamine receptor blockade in the pathogenesis of NMS [8, 39]. Fricchione [37, 38] along with our group [8–10] proposed that the onset of MC coincides with a reduction in dopaminergic activity within the frontal subcortical circuits. As elucidated by Alexander [40, 41], these circuits represent one of the brain's principal organizational networks underlying brain–behavior relationships. Five circuits connecting the basal ganglia with their associated areas in the cortex and thalamus have been identified and are named according to their cortical site of origin (see Fig. 5.1). They include the "motor circuit," the "oculomotor circuit," the "dorsolateral prefrontal circuit," the "lateral orbitofrontal circuit," and the "anterior cingulate-medial orbitofrontal circuit." Each circuit involves the same member structures, including an origin in a specific area of the frontal cortex; projections to the striatum (putamen, caudate, and ventral striatum); connections to the globus pallidus interna and the substantia nigra pars reticulata; which, in turn, project to specific thalamic nuclei; and a final link back to the frontal area from which they originated, thus creating a feedback loop.

Dopamine is in a key position to influence activity in each of the circuits. Mesocortical dopamine pathways project directly to circuit areas of origin in the supplementary motor area, frontal eye fields, and the three prefrontal cortical areas. Additionally, dopamine modulates each circuit through its projections to the striatum [42]. The motor, the anterior cingulate-medial orbitofrontal circuit, and the lateral orbitofrontal circuits represent the most likely candidates for involvement in the pathogenesis of MC.



ACA=anterior cingulate area
APA=arcuate premotor area
CAUD=caudate
(b)=body
(h)=head
DLC=dorsolateral prefrontal cortex
EC=entorhinal cortex
FEF=frontal eye fields
GPi=internal segment of globus pallidus
HC=hippocampal cortex
ITG=inferior temporal gyrus
LOF=lateral orbitofrontal cortex
MC=motor cortex
MD=medialis dorsalis
MDpl=medialis dorsalis pars paralamellaris
MDmc=medialis dorsalis pars magnocellularis
MDpc=medialis dorsalis pars parvocellularis
PPC=posterior parietal cortex
PUT=putamen
SC=somatosensory cortex
SMA=supplementary motor area
SNr=substancia nigra pars reticulata
STG=superior temporal gyrus
VAmc=ventralis anterior pars magnocellularis
VApc=ventralis anterior pars parvocellularis
VLm=ventralis lateralis pars medialis
VLo=ventralis lateralis pars oralis
VP=ventral pallidum
VS=ventral striatum
cl=caudolateral
cdm=caudal dorsomedial
dl=dorsolateral
l=lateral
ldm=lateral dorsomedial
m=medial
mdm=medial dorsomedial
pm=posteromedial
rd=rostrodorsal
rl=rostolateral
rm=rostromedial
vm=ventromedial
vl=ventrolateral

Fig. 5.1 Proposed basal ganglia-thalamocortical circuits. Parallel organization of the five basal ganglia-thalamocortical circuits. Each circuit engages specific regions of the cerebral cortex, stiatum, pallidum, substantia nigra, and thalamus (adapted from [40] with permission)

Specifically, the onset of hypodopaminergia in the motor circuit may underlie muscular rigidity [8, 9, 39]. In addition, hypodopaminergia developing in the anterior cingulate-medial orbitofrontal circuit could participate in causing diminished responsiveness, akinesia, and mutism and contribute to hyperthermia and autonomic dysfunction. Bilateral lesions of this circuit have been associated with akinetic mutism, which involves severe hyomotility, diminished arousal, and mutism and has been mistaken for simple catatonia [42]. Furthermore, certain cases of akinetic mutism have presented with hyperthermia and autonomic dysfunction, making them difficult to distinguish from MC [8, 9, 39]. In this regard, it is of considerable interest

that the anterior cingulate-medial orbitofrontal circuit contains a spur from the ventral pallidum to the lateral hypothalamus [43]. This suggests that reduced dopamine activity could cause hyperthermia and autonomic dysfunction in MC by disrupting anterior cingulate-medial orbitofrontal circuit transmission to the lateral hypothalamus.

Lastly, hypodopaminergia involving the lateral orbitofrontal subcortical circuit may mediate selected catatonic features observed in MC. Dysfunction in the lateral orbitofrontal circuit has been associated with utilization and imitation behaviors [44]. These behaviors involve automatic imitation of the gestures and actions of others or inappropriate use of objects such as tools or utensils. Utilization and imitation behaviors reflect enslavement to environmental cues [44] and share striking clinical similarities with catatonic features such as echopraxia, echolalia, gegenhalten, all of which are viewed as stimulus bound or motor perseverative phenomena consistent with frontal lobe dysfunction [44]. Utilization and imitation behaviors may also occur in association with dorsolateral prefrontal circuit dysfunction.

We have proposed that in addition to dopamine-2 receptor blockade, NMS is the product of preexisting central dopamine hypoactivity that represents a trait vulnerability marker for this disorder, coupled with state-related downward adjustments in the dopamine system occurring in response to acute or repeated exposure to stress [8, 9, 39]. Here, we suggest that such state- and trait-related factors are also critical in causing hypodopaminergia in the frontal subcortical circuits in MC. A number of lines of evidence indicate that certain individuals may exhibit baseline hypodopaminergia, including reduced homovanillic acid (HVA) levels in post-NMS patients; reduced striatal HVA levels or lack of elevated HVA-to-dopamine ratios in patients who died from MC or NMS; lower cerebrospinal fluid HVA levels and more severe baseline parkinsonian symptoms in patients with Parkinson's disease following recovery from NMS; and reports of abnormalities in the dopamine-2 receptor gene in NMS [8–10, 39].

Furthermore, the enhanced responsiveness of the dopamine system to stress may be implicated as a state-related cofactor predisposing to MC. In particular, the dopaminergic innervation of the medial prefrontal cortex in the rat is unique in that it is activated by very mild stressors such as limited footshock or conditioned fear [45]. In addition, there is considerable data indicating a functional interdependence of dopamine systems innervating the medial prefrontal cortex and subcortical dopamine systems; changes in the medial prefrontal cortex dopamine system appear to have an inverse relationship with dopamine turnover in the dorsal and ventral striatum [46]. Consistent with this, lesions of the mesocortical dopamine pathway to the medial prefrontal cortex in the rat result in increased indexes of subcortical dopamine functioning [46] (see Fig. 5.2).

Conversely, increased mesocortical dopaminergic neurotransmission to the medial prefrontal cortex has been associated with decreased indexes of subcortical dopamine functioning [46, 47]. Accordingly, if stress activates the stress-sensitive mesocortical dopaminergic pathway to the medial prefrontal cortex, it could have feedback effects in both the dorsal and ventral striatum, rendering these areas hypodopaminergic and predisposing to MC and NMS in individuals with preexisting central dopaminergic hypoactivity (see Fig. 5.3).

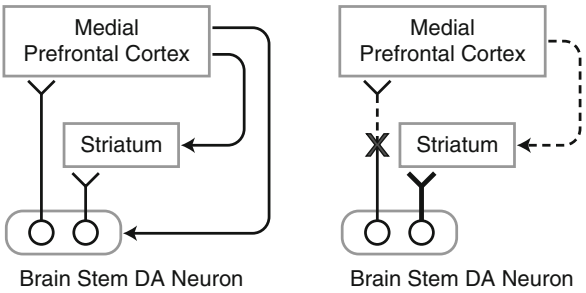


Fig. 5.2 Interdependence of Medial Prefrontal and Subcortical Dopamine System: Normal State (*right*) and after lesioning of the dopamine input to the Medial Prefrontal Cortex (*left*) (adapted from [46]. Copyright 1987, American Medical Association, All rights reserved

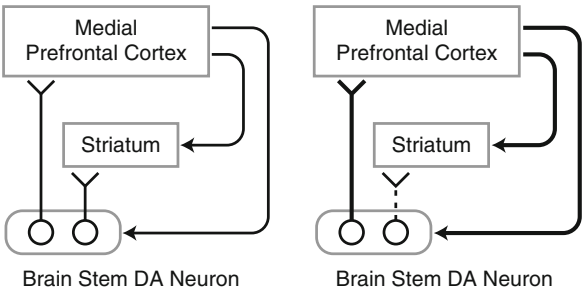


Fig. 5.3 Interdependence of Medial Prefrontal and Subcortical Dopamine System: Normal State (*right*) after stress-inducted activation of dopamine input to the Medial Prefrontal Cortex (*left*) (adapted from [46]. Copyright 1987, American Medical Association, All rights reserved

Evaluation and Treatment

Familiarity with the distinctive clinical features and varied etiologies of MC is essential for effective management of this potentially fatal condition. In both clinical vignettes, it was critical to exclude neuromedical or drug-induced causes of MC before assigning a psychiatric etiology. The potential for severe autonomic symptoms and high rates of medical complications dictate early institution of intensive medical care focusing on fluid replacement, reduction of temperature, and support of cardiac, respiratory, and renal functions. Careful monitoring for complications, particularly aspiration pneumonia, thromboembolism, and renal failure, is essential. Many clinicians, not recognizing the syndrome they are witnessing, are apt to treat the patient's unusual symptoms with antipsychotic drugs. However, the bulk of evidence indicates that the dopamine receptor blocking effects of antipsychotics are likely to aggravate MC episodes, as in NMS, where continuation of antipsychotic drug treatment clearly increases the likelihood of death. Antipsychotics should be withheld whenever MC is suspected.

Benzodiazepines have been highly effective in the treatment of simple (benign) catatonia, including antipsychotic drug-induced catatonia [37, 38]. Philbrick and Rummans [1] observed that the benefits of benzodiazepines in MC appeared less uniform than in simple catatonia but were nonetheless impressive at times. They asserted that even a partial response might be beneficial and retard the progression of MC until more definitive treatment can be instituted. Fricchione [37, 38] suggested that if simple catatonia proves unresponsive to benzodiazepines after 5 days of treatment, ECT should be considered as a definitive measure. In MC, however, these researchers argued against a 5-day wait and urged that ECT be started if benzodiazepines do not briskly reverse the MC process. Such was the case in Patient 2 where 2 days of intravenous lorazepam therapy was without benefit. Lack of response led to early initiation of ECT followed by dramatic resolution of MC.

Indeed, ECT has been viewed as a safe and effective treatment for MC when it occurs as an outgrowth of a major psychotic disorder [5–10]. Although controlled studies are lacking, case reports as well as series of consecutive cases indicate excellent results with its use. Among 50 patients reported in four large series [5], 40 of 41 patients treated with ECT survived. In contrast, only five of nine who received only antipsychotics and supportive care recovered. Similarly, in Philbrick and Rummans [1] review of 18 MC cases, 11 of 13 treated with ECT survived, compared to only 1 of 5 who did not receive ECT.

However, ECT appears effective only if initiated before severe progression of MC symptoms. Sedvic [48] reported that the onset of coma or a temperature in excess of 41 °C predicts a poor response even to ECT. Arnold and Stepan [12] found that in 19 patients starting ECT within 5 days of the onset of hyperthermia, 16 survived, whereas in 14 patients who began treatment beyond this 5-day point, ECT had no effect in preventing a fatal outcome. Although earlier protocols called for particularly intensive treatment [12], recent trials have indicated that ECT can be efficacious when given once or twice daily or every other day for a total of 5–15 treatments (usually bilateral) [5–10]. Substantial improvement often becomes evident after one to four treatments. There can be little doubt that prompt initiation of ECT represented a life-saving intervention in both of our clinical vignettes.

Other data, also anecdotal, suggests that MC due to the major psychoses can be effectively treated with adrenocorticotropic hormone (ACTH) and corticosteroids [5–10]. However, since severely ill patients have tolerated ECT without incident, and since the utility of hormonal therapy is less well documented, ECT appears to be the preferred treatment. ACTH and corticosteroids may be used if ECT proves ineffective.

Several investigators have suggested that ECT in combination with dantrolene, a drug that inhibits contraction and heat production in muscle, represents the optimal treatment for MC [5–10]. Additional cases have involved successful treatment with dantrolene alone; bromocriptine, dantrolene, and ECT; bromocriptine and benzodiazepines; and dantrolene and bromocriptine; as well as artificial hibernation [8–10].

In MC occurring as an outgrowth of a neuromedical illness, treatment must obviously be directed at the underlying disorder. Nevertheless, anecdotal reports have described ECT as dramatically effective in suppressing the symptoms of MC-like

states complicating a diversity of neuromedical conditions [5–10]. In such cases, the efficacy of ECT appears largely independent of the underlying illness, and improvement is likely to be transient if the neuromedical condition persists. If, however, the underlying disorder either remits or is corrected, permanent recovery may be possible. Along these lines, ECT has been used effectively in the treatment of NMS.

Conclusions

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

Furthermore, MC represents a nonspecific syndrome that develops as an outgrowth of neuromedical illness as well as the major psychoses. From this perspective, NMS may be conceptualized as an antipsychotic drug-induced form of MC. The hypothesis that MC and NMS share a common pathophysiology involving reduced dopamine functioning with the frontal-subcortical circuits provides additional support for a view of these disorders as manifestations of a unitary diagnostic entity. ECT appears to be the preferred treatment for MC stemming from a major psychotic disorder and it may also be effective in cases caused by neuromedical illness. Antipsychotic drugs should be withheld whenever MC is suspected.

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Chapter 6
Psychosis and Parkinson's Disease

Christina L. Vaughan and Jennifer G. Goldman

Abstract The clinical spectrum of Parkinson's disease (PD) psychosis ranges from mild illusions to formed hallucinations or even frank delusions. Hallucinations occur in about one-third of PD patients treated with chronic dopaminergic therapy and are most often visual. Delusions are less common but typically consist of well-systematized, thematic ideas such as paranoia or infidelity. PD psychosis may be due to extrinsic (i.e., pharmacological treatment) and/or intrinsic (i.e., disease-related) factors. Risk factors for the development of psychosis include older age; advanced disease; akinetic-rigid motor phenotype; concomitant cognitive impairment, depression, or sleep disturbances; and multiple medical problems. When psychosis in PD develops acutely, becomes troublesome or frightening, or poses a safety risk, medical attention is necessary. Medical management of acute psychosis typically includes the following: identifying and addressing specific causes (e.g., infection, medications), reducing or discontinuing medications for PD and other conditions that may aggravate psychosis, and introducing antipsychotic medications. Since antipsychotics with dopamine-blocking properties may worsen parkinsonism, medications with greater serotonergic properties such as clozapine and quetiapine are favored. Effective and well-studied treatments that improve PD psychosis without worsening motor function are still needed.

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Patient Vignettes

Patient 1

A 67-year-old man with a 7-year history of Parkinson's disease (PD) presented to the emergency department with agitation. For the past 2 weeks he had accused his wife of having an affair with the neighbor, believed that strangers were living in his house, and insisted that the dog gates were installed to prevent him from leaving the house. He had threatened family members, and finally his wife called the paramedics to bring him to the hospital. His medications included the following: carbidopa/levodopa 25/100 mg—2 tablets every 4 h (total eight tablets daily) along with entacapone 200 mg with each dose, carbidopa/levodopa CR 50/200 mg nightly, amitriptyline 25 mg nightly, and aspirin. His medical history revealed frequent urinary tract infections. On examination, he was confused and exhibited motor features of PD including bradykinesia, rigidity, and rest tremor. He was afebrile, and laboratory tests revealed normal blood counts and electrolytes. Urinalysis was suspicious for infection with positive leukocyte esterase and increased white cells. Neuroimaging did not reveal intracranial hemorrhage or evidence of acute stroke. He was admitted to the psychiatric ward for further management of his psychosis.

Patient 2

A 70-year-old man with a 15-year history of akinetic-rigid PD presented to the emergency department after lighting his bedspread on fire to kill the insects which he thought were infesting his bed. En route, he called the police claiming that the ambulance driver had kidnapped him against his will. Over the past year, he was reported to spend most of the day in his bedroom obsessing about "bugs" on his skin. He had arranged an elaborate system of locks and alarms to protect his belongings from intruders and believed that his wife was an imposter. His nightly sleep was poor, and he took frequent short naps throughout the day. His medication regimen included carbidopa/levodopa 25/100—2-½ tablets five times daily (total 12½ tablets daily). A prior trial of quetiapine up to 200 mg daily failed to improve his psychosis. On examination, he was agitated and had marked generalized dyskinesias. He repeatedly insisted that he had been kidnapped against his will although he was alert and fully oriented, with no evidence of dementia. Vital signs and basic laboratory studies including toxicology screen were unremarkable.

Introduction

Psychiatric symptoms are among the most common reasons for emergency department visits by Parkinson's disease (PD) patients. The disorders most likely to result in a visit are psychosis, acute confusion, and panic attacks [1]. Psychosis is a

frequent and troublesome complication in PD, often associated with increased morbidity, mortality, nursing home placement [2], caregiver stress [3, 4], and worsened quality of life [5]. Revised criteria for PD psychosis were recently proposed by a NINDS-NIMH working group: these include illusions, a false sense of presence, hallucinations, and delusions occurring chronically and in the setting of a clear sensorium [6]. While illusions and a sense of presence may be part of the PD psychosis spectrum, in this chapter we will focus on hallucinations and delusions as they may present an emergency for patients and their caregivers. Hallucinations can be very frightening and distressing to both the patient and caregiver, though in some cases they may be "benign" or even pleasant. Delusions, or false fixed beliefs, are often paranoid in nature and can be especially disruptive. When psychosis develops acutely or suddenly worsens, becomes troublesome or frightening, or poses a safety risk, urgent attention is required.

Hallucinations and delusions in PD may be acute or chronic, occur with clear or clouded sensorium, or retained or absent insight. Dopaminergic medications influence these scenarios, but other factors play a role as well. We will review the phenomenology, epidemiology, and pathophysiology of PD psychosis, and then discuss its evaluation in the emergency setting.

Phenomenology

The clinical spectrum of PD psychosis ranges from mild illusions to formed hallucinations or even frank delusions. Illusions and benign hallucinations (passage or presence, defined below) are often grouped together and called "minor" hallucinations [7]. Illusions are misperceptions of real stimuli, including phenomena such as interpreting inanimate objects as living beings (e.g., a chair mistaken for a dog, a lamppost mistaken for a tree). "Passage" hallucinations involve the sensation of a person or animal passing in the person's peripheral visual field, and "presence" hallucinations involve the sense that someone is present close by when no one is really there. These "minor" hallucinations are usually not troublesome for the patient or caregiver, and unlikely to constitute a movement disorder emergency.

Hallucinations are spontaneously fabricated perceptions occurring while the patient is awake. Most hallucinations in PD are visual in nature, although other sensory modalities may be involved [6]. Hallucinations in PD may be categorized as simple or complex. Simple hallucinations lack form and frequently include photopsias such as flashes of light or color, while complex hallucinations include visions that are clearly defined, taking the shape of animals, humans, or objects [8]. Examples of complex visual hallucinations in PD include mice scurrying on the floor or children playing in the house, but they can be frightening, including distorted, grotesque, or bizarre figures. Hallucinations in PD usually are not threatening, occurring with a clear sensorium [9, 10]. They are typically brief, lasting seconds to minutes, and may occur or increase at night. By their recurrent and stereotyped character, the hallucinatory figures may become familiar to the patient, who may

even observe them with sympathy [11]. These seemingly benign hallucinations, however, often progress into more elaborate hallucinations, particularly in the setting of a clouded sensorium or when accompanied by delusions [12]. Not all hallucinations are benign, and as insight decreases, their content may become frightening. The phenomenology of hallucinations also may change with advancing disease, becoming "malignant," disabling, and intermingled with paranoid thoughts of suspiciousness, sexual accusations, and contamination [13]. In general, hallucinations tend to occur when the patient is in a low sensory environment and thus, can be more dependent on sensory state than dopaminergic drug dose [14]. Visual hallucinations frequently manifest in dim light, or when vision is compromised [15]. Visual hallucinations are more common in PD, whereas auditory hallucinations are more common in schizophrenia [16].

Hallucinations in nonvisual modalities also occur, but they generally accompany visual hallucinations [11]. When they begin, older patients more frequently experience nonvisual or mixed hallucinations rather than purely visual ones, suggesting that age may influence their phenomenology [17]. Unlike visual hallucinations, auditory hallucinations are often vague; for example, auditory hallucinations commonly feature the din of a party heard coming from another room, people talking indistinguishably outside, or music of various types [7]. Rarely do auditory hallucinations interact with the patient, or involve back and forth conversation [13]. Auditory hallucinations in PD thus differ from those of schizophrenia. Auditory hallucinations in PD are not usually threatening and are less likely to be the sole modality of hallucinations present. Tactile or olfactory hallucinations are less common in PD, but they may occur. Tactile hallucinations often involve a feeling of contact with small animals or being touched by someone else [18]. Olfactory hallucinations may be pleasant or unpleasant in smell, even involving one nostril more than the other [15, 19].

Delusions are less common than hallucinations, affecting about 5–10% of drug-treated PD patients [20]. In PD, delusions often consist of well-systematized ideas focused on a single theme. Common delusional themes include the following: jealousy or spousal infidelity; paranoia; fears of being poisoned, injured, or filmed; elaborate schemes about conspiracies; stealing; abandonment; or somatic illnesses [15]. In a small cohort of PD patients with psychosis, systematized paranoid delusions (i.e., a single delusion with multiple elaborations or a group of delusions related to a single event or theme) were more common than nonspecific paranoid ideation (56 vs. 44%) [21]. A persistent suspicion may evolve into a fixed delusion, which may escalate causing injury or hospitalization. While delusions of persecution are common in both schizophrenia and PD, delusions in schizophrenia more frequently encompass themes of grandiosity, reference, and bizarre beliefs such as thought broadcasting, thought withdrawal, and thought insertion [22].

Misidentification syndromes are a specific type of delusion that present a particularly challenging situation for the patient and caregiver. Two common misidentification syndromes include the following: Capgras syndrome, in which the patient thinks that his recognizable spouse is an imposter, [23] and Fregoli syndrome,

in which the patient believes that familiar people are, often malevolently, disguised as strangers [24]. These misidentification syndromes have been reported in PD, particularly in the setting of PD dementia (PDD). In one report of a PD patient with Fregoli syndrome, symptoms completely resolved with reduction in levodopa dose [24]. In a prospective study of demented PD patients, Pagonabarraga reported a prevalence of delusional misidentification syndromes of 16.7% [25]. Roane described three cases of misidentification associated with parkinsonism, all of whom were demented [26]. In addition to PDD, delusions may accompany other parkinsonian disorders. Delusions have been reported in about 80% of patients with dementia with Lewy bodies (DLB) [27].

Epidemiology

Methodological differences among studies complicate attempts to estimate the frequency of PD psychosis. These differences include the following: the population source (community vs. movement disorder clinic-based), design (retrospective vs. prospective), types of prevalence values (point, period, or lifetime), symptoms included (illusions, hallucinations and/or delusions), and measurements or rating scales used. Further, reliance on the subjective accounts of the patient and/or caregiver makes identifying and rating psychosis challenging. As a result, prevalence estimates of PD psychosis in the literature vary greatly, ranging from approximately 20–60% [7, 10, 20, 28–31]. Many studies are clinic-based and cross-sectional, thereby providing point prevalence rates in PD patients on dopaminergic treatment [20]. In a clinic-based cross-sectional study of 116 consecutively seen PD patients, 60% met NINDS-NIMH criteria [6] for PD psychosis [32]. In an earlier cross-sectional study of 129 patients, Graham established a prevalence of 25% [10]. Several studies provide longitudinal information on the development of hallucinations. In a prospective, longitudinal cohort study, 60% of PD patients developed hallucinations or delusions at 12 years, and 42% of the cohort developed new psychosis during the study, occurring at a mean of 13 years after motor symptom onset [33]. In a long-term follow up study of PD patients initially free of hallucinations, Goetz found that at 10 years, 93% of the original 60 non-hallucinating PD patients had hallucinations on at least one interview. The prevalence of hallucinations increased from 33% at baseline to 63% at 10 years, and the odds of having hallucinations increased annually by a factor of 1.26 [34]. In the Sydney Multicenter Study which followed a cohort of initially levodopa-naïve PD patients, at 15 years follow-up, 50% of patients had formed visual hallucinations, with a mean time to onset of hallucinations of 10.7 years [35]. Among the survivors of the same cohort, 74% experienced visual hallucinations at 20 year follow-up, requiring reduction of dopaminergic medication in all, and initiation of an atypical antipsychotic in ten patients [36].

Factors Which Influence Development of PD Psychosis

A number of factors may influence the development of PD psychosis. In general, risk factors for developing hallucinations include older age, concomitant depression, and coexistent cognitive impairment [7, 28]. Other studies have reported greater axial rigidity, increased dopaminergic medication doses, sleep disturbances, and multiple medical problems in affected individuals [7, 8, 10, 31, 33, 37–40] (Table 6.1). While hallucinations occur more often in demented PD patients, they may occur in up to 17% of non-demented PD patients, as demonstrated in a large prospective study of 1,351 patients [41]. In a 10-year longitudinal study, Goetz found that time influenced their development, while sleep fragmentation, overall sleep function, total daily levodopa dose, Unified Parkinson's Disease Rating Scale (UPDRS) motor score, and Mini-mental State Examination score did not [34]. In another long-duration longitudinal study, Forsaa found that baseline levodopa equivalent dose, age at PD onset, and probable rapid eye movement (REM) sleep behavior disorder independently increased the risk of hallucinations. A secondary analysis of data from the CALM-PD study revealed that older age and the existence of multiple medical problems were associated with the development of hallucinations [42].

Pathophysiology

PD psychosis may be caused by extrinsic (i.e., pharmacological treatment) and/or intrinsic (i.e., disease-related) factors. It is well-known that dopaminergic medications can induce psychosis in PD by stimulating or inducing hypersensitivity of mesocorticolimbic dopamine receptors [43]. Virtually all classes of anti-parkinsonian medications may produce psychosis. Some studies suggest that dopamine agonists are more likely culprits than levodopa [42, 44–46], and anticholinergics are a frequent trigger especially in elderly PD patients [47]. While dopaminergic medications contribute to PD psychosis, several intrinsic factors also play a role [42–49].

Table 6.1 Risk factors for PD psychosis

- Older age
- Older age at PD onset
- Worse motor function, particularly axial function
- Higher baseline levodopa equivalent dose
- Advanced disease
- Lower cognitive status
- Concomitant dementia
- Concomitant depression
- Sleep disturbances (e.g., REM sleep behavior disorder)
- Multiple medical problems

Investigations of PD psychosis have focused on three primary areas: primary visual system, brainstem and cortex [12]. Dysregulation in these areas often manifests as visual disturbances, sleep or mood disorders, or cognitive impairment—suggesting abnormalities in "top-down" and/or "bottom-up" processing.

The visual system may be affected in PD patients at multiple levels, and hallucinations are associated with ocular and retinal dysfunction in addition to central processing deficits [50, 51]. Dopaminergic innervation around the fovea is reduced in PD, and this contributes to altered visual processing at the level of the receptive fields of ganglion cells [52]. Retinal dopaminergic dysfunction reduces meaningful information for central visual processing such that finer details of visual stimuli are blurred, and contrast and color discrimination are reduced [53]. Compared to PD patients without hallucinations, PD hallucinators have reduced visual acuity [30, 54] and impaired contrast sensitivity [53].

Cortical dysregulation has been suggested on the basis of functional and metabolic neuroimaging studies that showed different responses to visual stimuli or perfusion patterns in PD hallucinators compared to PD non-hallucinators. In a functional magnetic resonance imaging (fMRI) study, Holroyd and Wooten showed that PD hallucinators demonstrated increased activation in the visual association cortex and deficits in the primary visual cortex [55]. Stebbins found that hallucinating PD patients had more frontal and subcortical activation and less posterior cortical activation than non-hallucinating PD patients [56]. These studies suggest that retinal dopamine deficiency or decreased visual input (afferent abnormalities), or disruptions in the pathways mediating visual attention may alter how the visual cortex processes stimuli. Significantly reduced occipital–inferior temporal–parietal perfusion patterns have been shown in PD patients with visual hallucinations using *n*-isopropyl-*p*-[^{123}I] iodoamphetamine single photon emission computed tomography (^{123}I-IMP SPECT) [54] and ^{18}F-deoxyglucose positron emission technology (^{18}F-FDG PET) [57]. In a study using ([^{123}I]IMP) SPECT, Matsui found that PD hallucinators had significant perfusion reductions in the bilateral inferior parietal lobule, inferior temporal gyrus, precuneus gyrus, and occipital cortex compared to PD non-hallucinators. Using ^{18}F-FDG PET, Boecker found significant metabolic abnormalities in regions of the dorsal and ventral visual streams, but not in primary visual cortex in PD hallucinators compared to PD non-hallucinators; they did not find increased glucose metabolism in frontal regions, although this has been demonstrated in some studies. The two principal visual processing routes may be especially relevant to PD hallucinations as the ventral stream is involved in object and form vision, and the dorsal stream in spatial location and motion vision [57].

While the loss of substantia nigra pars compacta dopaminergic neurons is a neuropathologic hallmark of PD, it is well-recognized that PD pathology extends well beyond the nigrostriatal system [58]. Post-mortem studies have shown increased extranigral Lewy body burden in PD patients with visual hallucinations, including the ventral temporal lobe [59]. PD cases with well-formed visual hallucinations contained high densities of Lewy bodies in the amygdala and parahippocampus, with early hallucinations associated with higher densities in parahippocampal and inferior temporal cortices [60]. Brainstem changes with loss of noradrenergic

neurons of the locus ceruleus, serotonergic neurons of the raphe nuclei, and the cholinergic parabrachial and pedunculopontine nuclei may also play a role in PD hallucinations [16, 58].

The relationship between hallucinations, sleep, and brainstem dysfunction has been based on observations that hallucinations can occur as rapid-eye movement (REM) intrusions, and that hallucinating PD patients have altered sleep-wake patterns [12]. Visual hallucinations in PD may represent intrusions of REM sleep into wakefulness, and the hypothesis of visual hallucinations as overflow dream phenomena has been supported by several studies [61, 62]. This concept has focused anatomic attention on the reticular activating system and the parapontine nucleus [34]. Also hypothesized is a link between hallucinations and REM sleep behavior disorder (RBD) [63]. In a prospective study of PD patients, RBD significantly correlated with hallucinations independently of age, gender, PD duration or PD stage, and also correlated with dopaminergic dose [37]. The underlying mechanisms of RBD may relate to brainstem alterations of cholinergic [62] or noradrenergic activity [37].

PD psychosis is closely linked to cognitive impairment and dementia. Neuroimaging studies comparing hallucinating PD and non-hallucinating PD patients demonstrate greater volume loss in temporal and parietal lobes as well as limbic regions in PD hallucinators [64, 65]. In addition, post-mortem studies reveal Lewy body pathology in temporal and limbic regions, areas associated with memory function, in PD hallucinators [59, 60]. Clinically, many PD patients may lose insight into their psychosis when they develop cognitive impairment [7]. Cognitive deficits in PD hallucinators frequently affect visual and verbal memory, executive function, and visuoperceptive–visuospatial tasks [66]. In demented PD patients, hallucinations may be more complex, more frequent, and more likely to be perceived as unpleasant [67]. In a prospective study of PD patients with and without visual hallucinations, Llebaria showed that PD patients with hallucinations without insight were impaired in cognitive tasks reflecting posterior cortical dysfunction [68]. PD patients with major hallucinations and intact insight, however, had frontal-subcortical impairment reflecting executive dysfunction. Posterior cortical dysfunction may be a risk factor for both PD dementia [69] and hallucinations [57, 68]. Thus, the close relationship of hallucinations and cognitive impairment in PD may reflect shared neuroanatomical substrates.

Evaluation

When a PD patient presents with acute psychosis, several medical and neurological conditions may be entertained in the differential diagnosis. A toxic-metabolic encephalopathy may occur in patients who are medically ill, infected, or acutely overmedicated. In these cases, delirium is frequently present, and hallucinations may be associated with confusion, agitation or myoclonus. The medication regimen must be carefully reviewed, with attention to recent changes in drugs or doses,

Table 6.2 Evaluation of acute PD psychosis

Differential diagnosis
P—Parkinson's disease medications
SY—Systemic illness
C—Centrally acting medication
H—Hepatic, renal, or other metabolic dysfunction
O—Overdose of medications or intoxication
S—Sensory deprivation (hearing, visual impairment)
I—Infection (urinary tract infection, pneumonia)
S—Structural lesions (stroke, subdural hematoma, intracranial hemorrhage, trauma)
Proposed tests, depending on scenario:
• Labs: complete blood count, comprehensive metabolic profile, thyroid function, toxicology screen, urinalysis, urine culture, cerebrospinal fluidanalysis
• Imaging: head computed tomography or magnetic resonance imaging, chest X-ray
• Other: electroencephalogram

or drug–drug interactions (e.g., serotonin syndrome). In cases of anticholinergic toxicity, psychosis may be accompanied by dry skin, urinary retention and mydriasis [11]. Early identification and treatment of delirium is essential. Frequently, delirium or an acute change in mental status indicates a "medical" explanation (Table 6.2). Particularly with concomitant delirium, evaluation for acute psychosis requires basic laboratory studies, work-up for infection, toxicology screens, and neuroimaging for evaluation of intracranial hemorrhage or infarct. It is helpful to learn if the patient has previously experienced similar presentations, particularly urinary tract infections or noncompliance with medications.

For those PD patients with new-onset psychosis, hallucinations early in the course of parkinsonism, (within the first 12 months or even before dopaminergic drugs are introduced), may indicate DLB; [11] this "1-year rule" has been used to separate DLB from PDD [13]. This distinction has treatment implications as DLB patients may have marked neuroleptic sensitivity and, in rare cases, develop a neuroleptic malignant-like syndrome [70]. Psychosis in DLB patients also may respond to cholinesterase inhibitors [71].

For those PD patients with an acute exacerbation of chronic psychosis, in addition to excluding "medical" etiologies, medication changes, or medication interactions, several other points merit attention. Underlying sensory deficits (i.e., visual or hearing impairment), may contribute to psychosis. For example, visual impairment can lead to hallucinations; in the Charles Bonnet syndrome, elderly people with low visual acuity may experience benign visual hallucinations as "release" phenomena [14]. One should also inquire about primary psychiatric conditions such as depression, schizophrenia, schizoaffective disorder, or bipolar disorder. Depression in PD approaches 30–40% [72], and psychosis occasionally accompanies moderate-to-severe depression [73]. Previous studies, however, suggest that psychosis due to comorbid psychiatric conditions differs from PD psychosis; PD psychosis does not usually include thought broadcasting, delusions of grandeur, voices talking about the patient, mind reading, being controlled by foreign forces, or hyper-religiosity [14].

Regardless of whether a PD patient presents with first-time psychosis or an acute exacerbation of chronic psychosis, the psychosis may be a consequence of PD medications, especially when there is no "medical" cause or other explanation. The initial work-up for acute PD psychosis frequently occurs in the emergency department or outpatient clinic. From there, patients are usually admitted to the hospital for further evaluation and management, particularly when the psychosis cannot be managed effectively in an outpatient setting. Of all PD patient admissions to a community hospital during a 6-year period, 24% were due to psychosis, and drug-induced psychosis was the cause of repeated and prolonged admissions in 29% of patients [74]. The best setting for acutely psychotic PD patients is a well-controlled, calm environment where people are equipped to manage psychotic patients; this type of environment may be in a psychiatry unit but other settings also may be appropriate. Neurological consultation should be obtained early in the hospital course as there are often multiple considerations for hospitalized PD patients, such as the appropriate dose and timing of PD medications and the avoidance of medications that can worsen PD.

Treatment

In the setting of acute psychosis, patients may be very agitated. In this situation, low-dose benzodiazepines (intramuscular or oral) may be necessary to calm them [15]. Dopamine-blocking antipsychotics, including rapidly acting antipsychotics, are contraindicated in PD as they may exacerbate parkinsonism. If a specific etiology for the acute psychosis is determined, this should be addressed (e.g., antibiotics for an infection, correction of metabolic abnormalities, etc.) (Fig. 6.1).

Once the patient is no longer agitated, the next step is to reduce non-PD medications that may have psychoactive properties. Common medications in this category include anticholinergics for bladder hyperactivity, tricyclics for depression, benzodiazepines for anxiety or sleep, hypnotics for sleep, and opioids for pain. If there is no timely improvement, then PD medications should be gradually reduced. In reducing PD medications, the general consensus is to taper and stop the medications with the highest risk-to-benefit ratio first [75]. One proposed order of reduction or discontinuation includes the following: anticholinergics first, followed by amantadine, selegiline, dopamine agonists, COMT-inhibitors, and then levodopa [76]. The reduction or discontinuation of PD medications should be done under close observation by the neurologist as motor symptoms may worsen. A point, however, may be reached at which the PD medications cannot be reduced without compromising motor function. At this point, antipsychotic medications are frequently added [75].

Despite the high prevalence of psychosis in PD, there are few randomized, double-blind, placebo-controlled trials of the atypical antipsychotics in PD. Atypical antipsychotics include (in order of arrival in the United States) the following: clozapine, risperidone, olanzapine, quetiapine, ziprasidone, and aripiprazole [73]. The American Academy of Neurology (AAN) practice parameter on treatment of PD

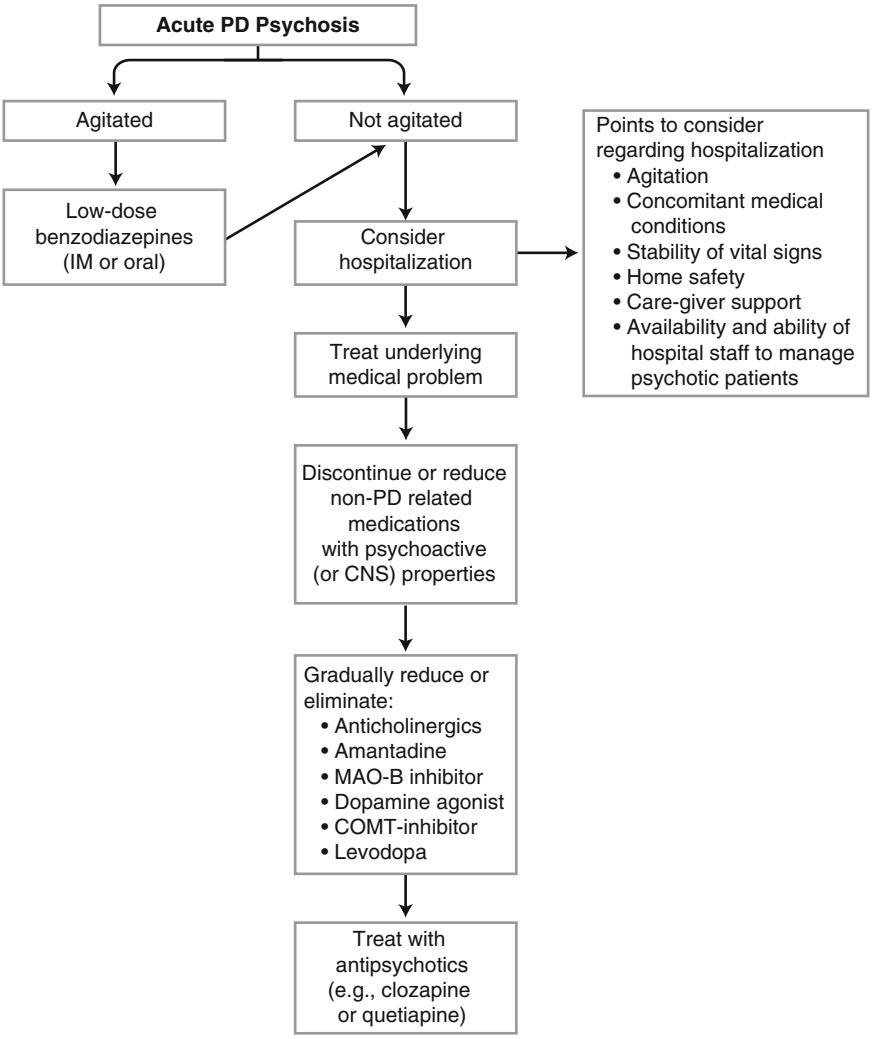

Fig. 6.1 Management of acute PD psychosis

psychosis (2006) considered only three atypical antipsychotics and recommended that clozapine should be considered (Level B), quetiapine may be considered (Level C), and olanzapine should not be considered (Level B) [77]. Once antipsychotic therapy is initiated, continued treatment may be necessary to maintain control and avoid exacerbation of psychosis.

The AAN practice parameter concluded that clozapine should be considered for treatment of PD psychosis based on one class I and one class II study. Clozapine remains the gold standard atypical antipsychotic for PD psychosis, and the majority of double-blind, placebo-controlled trials have shown improvement in psychosis

with negligible motor worsening [78–80]. In a double-blind study by Pollack, low dose clozapine (mean dose 35.8 mg/day) improved PD psychosis as early as a few days after initiation. Furthermore, more than one-third of patients were able to benefit from increased doses of levodopa or from the introduction of a dopaminergic agonist, without significant changes in clozapine dose and without recurrence of psychiatric symptoms [81]. In PD psychosis, the effective dose of clozapine is relatively low—6.25–50 mg daily compared with 300–900 mg daily in adult patients with schizophrenia [80, 81]. One commonly used regimen is to begin clozapine at 6.25 mg at bedtime and increase by the same amount every 4–7 days until psychosis remits or side effects occur [75]. The biggest drawback to its use is the risk of agranulocytosis, which is idiosyncratic rather than dose-dependent and requires close monitoring. The incidence of agranulocytosis was found to be 0.38% in a sample of 99,502 patients with schizophrenia [82]. White blood cell counts should be monitored weekly for the first 6 months. If the white blood cell counts are normal, the patient can be monitored every 2 weeks for an additional 6 months. Afterwards, the patient may qualify for every 4-week monitoring with physician authorization. Other side effects of clozapine include sedation, orthostatic hypotension, confusion, and sialorrhea [81].

Although open-label reports of quetiapine demonstrated improvements in PD psychosis, double-blind, placebo-controlled trials have failed to establish this. A review of several open-label reports of quetiapine revealed approximately 80% subjective improvement of psychosis in PD patients, all with doses less than 100 mg per day [83]. Two rater-blinded studies suggested efficacy, one by lack of inferiority to clozapine [84] and the other by showing that clozapine had greater efficacy in reducing the frequency of hallucinations and delusions [85]. Three double-blind trials, however, did not show efficacy for psychosis, [86–88] though all showed no change in motor function. Despite this, quetiapine is often used first in PD psychosis, due to its ease of use. Quetiapine doses used to treat PD psychosis are also relatively low, typically 12.5 mg at bedtime, then increasing by 12.5 mg every 4–7 days until on 25 mg twice a day or 50 mg at night [75], but many physicians use up to 100–200 mg per night. Drawbacks of quetiapine include some reports of mild motor worsening [89], particularly among demented patients [83], and side effects including excessive sedation, orthostasis, or confusion [89].

Other atypical antipsychotics have shown even less promising results for PD psychosis and increased motor side effects. Two open label studies using aripiprazole had discouraging results [90, 91], with one study demonstrating significant motor worsening. Data are scarce on ziprasidone, but two small case series have shown improvement in psychosis without motor compromise [92, 93]. In a series of four PD cases, one patient had an increase in off-periods and two patients developed pathological laughing [92]. In two double-blind, placebo-controlled studies, low dose olanzapine did not significantly improve psychosis but worsened motor function [94, 95]. One double-blind study of risperidone vs. clozapine showed similar improvement of psychosis to clozapine, but worsened motor function with risperidone [96]. Furthermore, treatment of PD psychosis is complicated by the recent

"black box" warning by the FDA regarding increased risk of death in elderly, demented patients treated with antipsychotics.

Other medications have been used to treat PD psychosis with variable success. Several reports suggest that cholinesterase inhibitors might improve neuropsychiatric features and behavioral problems associated with PDD and DLB [97–100]. Based on data from a double-blind, placebo-controlled study of rivastigmine in PDD, rivastigmine was found to be mildly more effective in PD hallucinators compared to non-hallucinators, but did not significantly reduce the visual hallucinations [14, 101]. While cholinesterase inhibitors may provide a treatment option for the management of psychosis in demented PD patients, these medications take longer to work and thus are not useful in acute psychosis, particularly in the emergency setting. At present, there is not enough evidence to suggest cholinesterase inhibitors for psychosis in non-demented PD patients. Newer drugs with greater affinity for serotonin have shown promise for attenuating psychosis, but benefit has yet to be demonstrated in double-blind, placebo-controlled trials. Pimavanserin which has greater affinity for 5-HT(2A) receptors did not worsen motor function in 60 PD patients with psychosis, but exhibited a nonsignificant trend toward improvement in a psychosis rating scale, the Scale for Assessment of Positive Symptoms [102]. Electroconvulsive therapy, a treatment used for refractory depression with or without psychosis, has been found to be helpful in case reports of PD psychosis [103]. Overall, these other therapies for PD psychosis require additional study and rigorous evaluation before they can be definitively included in treatment algorithms.

Follow-Up of Patient Vignettes

The patient in the first vignette was treated with ciprofloxacin for a presumed urinary tract infection. Within 24 hours, his delirium cleared but vivid hallucinations and paranoia persisted. His amitriptyline was also discontinued, and subsequently his entacapone doses were reduced and discontinued. His psychosis slowly improved, and he was discharged from the psychiatric unit after 10 days. In this case, the acute presentation of somnolence and confusion were indicative of a "medical" explanation (i.e., urinary tract infection). The exacerbation of his psychosis, however, occurred in the context of mild baseline hallucinations, advanced PD, and use of medications that could aggravate psychosis (i.e., amitriptyline, nighttime levodopa, and high doses of levodopa). Treatment of the underlying cause of his acute exacerbation of his psychosis and modifying his PD medication regimen led to a satisfactory outcome; in his case, antipsychotic medications were not needed, and his family was educated about recurrent urinary tract infections and psychosis exacerbations.

The second vignette illustrates a patient with delusions occurring in the context of long-standing PD with motor fluctuations. He did not exhibit features of delirium or dementia but had marked sleep fragmentation, which may have contributed to his psychosis. His psychosis had escalated to a dangerous point, and previous treatment

with quetiapine had not been effective. This patient required admission to the psychiatry unit where clozapine was started and his carbidopa/levodopa dose reduced. Although his motor function was somewhat compromised on the lower levodopa dose, he had less dyskinesia and improved psychosis, although mild delusions persisted. After several weeks of hospitalization and rehabilitation therapy, he was able to return home on a reduced dopaminergic medication regimen and a maintenance dose of clozapine.

Conclusion

Acute psychosis is one of the most common reasons for emergency department visits in PD patients. When evaluation is approached in a timely, stepwise fashion with close monitoring of the patient, psychosis in most PD patients can be effectively managed and major morbidity avoided.

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Chapter 7
Abductor Paresis in Shy–Drager Disease

Eiji Isozaki

This chapter contains video segments that can be found on the accompanying DVD.

Abstract Vocal cord abductor paralysis (VCAP) is one of the life-threatening complications in multiple system atrophy. We proposed the mechanism as a multifactorial process, involving paralytic, nonparalytic, and enhancing factors. VCAP is diagnosed by both clinical features, including nocturnal inspiratory stridor with severe oxygen desaturation, and laryngofiberscopic examination showing paradoxical vocal cord movement. While a tracheostomy has been exclusively applied for VCAP in the past, noninvasive positive pressure ventilation has recently been used with some effectiveness. Of clinical importance is that the upper airway obstructions caused by the supraglottic tissues such as floppy epiglottis and floppy arytenoid are unresponsive to noninvasive positive pressure ventilation.

Patient Vignettes

Patient 1

A 55-year-old woman was admitted to our hospital because of progressive parkinsonism. She was diagnosed with striatonigral degeneration. Because of nocturnal snoring, a fiberoptic laryngoscopy was performed during wakefulness, showing a mild abduction restriction of the vocal cords. Arterial blood gas analysis was normal. Over the next year, she developed inspiratory stridor during wakefulness,

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especially while talking. A second fiberoptic laryngoscopy during wakefulness showed a narrower glottic aperture as compared with the previous examination. Arterial blood gas analysis showed only mild hypoxemia: pH = 7.44, pCO_2 = 43 Torr, and PO_2 = 72 Torr. At this point, she had no dyspnea and could still speak and eat. Only 3 weeks after admission, she was found in a cardiopulmonary arrest in her bed at 8 PM, and only 15 min after she was heard snoring as usual. A diagnosis of multiple system atrophy (MSA) was confirmed on postmortem neuropathological examination. The posterior cricoarytenoid muscle—the laryngeal abductor—showed severe neurogenic atrophy. Neither pneumonia nor intratracheal secretions were present to explain her sudden death.

Patient 2

A 74-year-old man, who was diagnosed with MSA 9 years before, was readmitted to our hospital in 1999 because of pneumonia. A fiberoptic laryngoscopy showed no laryngeal abnormalities during wakefulness and diazepam-induced sleep (stage 0). In February 2000, he developed nocturnal snoring. On fiberoptic laryngoscopy, moderately severe vocal cord abductor paresis (VCAP) with abduction restriction during wakefulness and paradoxical movement during sleep was seen (stage 2). The posterior glottis could not be observed well. On an overnight recording of percutaneous arterial blood oxygen saturation (SpO_2), no desaturation less than 90 % was demonstrated. Arterial blood gas analysis on room air was normal. He was discharged on August 14, 2000, when he was still able to eat, and his nocturnal snoring was not so loud as to disturb other patients in the same room. Only 1 week later, he was readmitted to our hospital because of increasing snoring. Arterial blood gas analysis on oxygen inhalation with 2 l/m when awake showed pH = 7.39, pCO_2 = 51 Torr, and pO_2 = 88 Torr. On physical findings, his suprasternal recess became hollow during every inspiration. On August 23, 2000, a fiberoptic laryngoscopy during wakefulness demonstrated severe VCAP with slit-like aperture of the glottis (stage 3), requiring emergency intratracheal intubation. After tracheostomy was performed 10 days later, he could speak with a speech valve. Arterial blood gas analysis on room air became normal: pH = 7.46, pCO_2 = 45 Torr, and pO_2 = 82 Torr. No oxygen desaturation less than 90 % of SpO_2 was demonstrated on an overnight recording.

Introduction

In 1976, Holinger analyzed 389 patients with VCAP in various diseases including poliomyelitis, Parkinson's disease (PD), cerebrovascular accidents, Guillain–Barre syndrome, and multiple sclerosis [1]. Spinocerebellar degeneration was not included in his list, and the concept of MSA was not established at that time. Investigators reported that patients with MSA, including olivopontocerebellar atrophy, striatonigral

degeneration, and Shy–Drager syndrome, developed laryngeal complications such as velopharyngolaryngeal paralysis [2], upper airway obstruction [3], and vocal cord palsy [4]. In 1981, Bannister reported three necropsied MSA cases in which the posterior cricoarytenoid muscles showed neurogenic atrophy, whereas the nucleus ambiguous, innervating the abductor muscle, demonstrated no neuronal loss [5]. Selective neurogenic atrophy of the abductor muscle, among all the intrinsic laryngeal muscles, has been confirmed histologically [2, 5, 6] and electromyographically [7] in MSA. The myelinated nerve fibers of the recurrent laryngeal nerve, which innervates all the intrinsic laryngeal muscles, are decreased in number [8]. However, it is controversial whether the nucleus ambiguus is involved [2, 6] or not [5, 9]. Electromyographical studies support laryngeal dystonia [10, 11] or dyskinesia [12] as possible mechanisms of the nonparalytic type of VCAP described below.

Mechanism

Although the pathophysiology of VCAP in MSA has not been fully clarified, we propose the following hypothesis (Fig. 7.1): neurogenic atrophy of the posterior cricoarytenoid muscle, the sole abductor of the vocal cords, is caused by neuronal loss in the nucleus ambiguous [6]. In addition to weakening of the abductor, initiation of abduction (opening of the vocal glottis) becomes delayed. During normal inspiration, the laryngeal abductor muscles contract first, and then the diaphragm contracts to avoid upper airway collapse. However, in patients with MSA and VCAP, inspiratory negative pressure caused by diaphragm contraction occurs concurrent with or even before full opening of the vocal glottis, because of the delay in abductors. This results in laryngeal collapse [13]. Paradoxical movement of the vocal cords occurs, with inspiratory adduction and expiratory abduction [14]. Sleep enhances VCAP because it increases upper airway resistance [15]. In the early stage of VCAP, the stenotic breathing from obstruction in the upper airway is recognized as snoring occurring only during sleep. Then in the advanced stages, audible daytime inspiratory stridor occurs, often on talking. This daytime inspiratory stridor can be misdiagnosed as pseudo-steroid-resistant asthma [16].

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

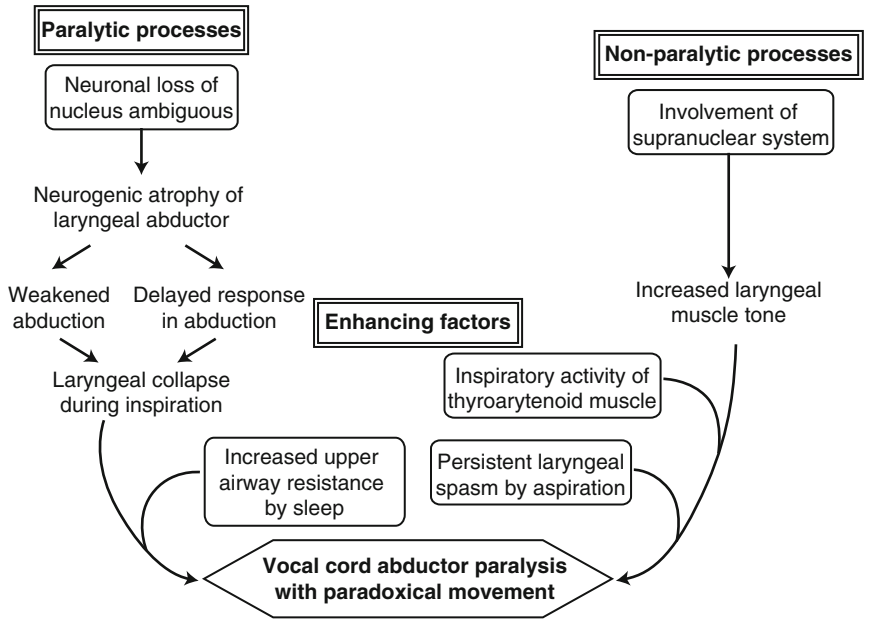

Fig. 7.1 Mechanism of vocal cord abductor paralysis in multiple system atrophy. Vocal cord abductor paralysis is caused by multifactorial mechanisms including paralytic processes, nonparalytic processes, and enhancing factors

Evaluation and Treatment

VCAP can appear at anytime in the course of MSA, even as an initial [20] or an isolated [21] symptom. From our study of 23 cases of MSA with VCAP, VCAP tends to appear around the time when urinary incontinence is noticed [22].

Symptoms suggestive of VCAP include loud nocturnal snoring, daytime inspiratory stridor, and inspiratory hollow at the suprasternal recess. On auscultation, snoring and daytime inspiratory stridor are louder in the neck than the chest. Snoring is loud and high-pitched with some limpidity [13, 22], often described as metallic, croup-like, or "donkey-braying" in quality [5]. Although respiration during sleep is often tachypneic in MSA patients presenting with VCAP [17], apnea or hypopnea may also occur [4]. Loud snoring may be the sole and most common symptom both in patients with VCAP and sleep apnea syndrome; however, these conditions are quite different in etiology, and should be distinguished as shown in Table 7.1.

A definite diagnosis of VCAP is made by fiberoptic laryngoscopy performed during both wakefulness and sleep. We classified the severity of VCAP into four stages from stage 0 (normal) to stage 3 (severe VCAP), according to the mobility of the vocal cords (Table 7.2) [14]. VCAP in MSA is characterized by paradoxical movement of the vocal cords and sleep-induced exacerbation (Fig. 7.2). The vocal glottis consists of two parts: the anterior glottis, mainly involved with voicing, and

Table 7.1 Difference between vocal cord abductor paralysis and sleep apnea syndrome

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

Table 7.2 Stage-classification of vocal cord abductor paralysis on a fiberoptic laryngoscopy

Stage	Awake	Asleep	Posterior glottal shape during sleep[a]
0 (normal)	Normal	Unchanged	
1 (mild)	Normal	Paradoxical	1a: triangular, 1b: slit-like
2 (moderately)	Abduction restriction	Paradoxical	2a: triangular, 2b: slit-like
3 (severe)	Midline fixation	Midline fixation	

[a]Posterior vocal glottis is still patent with a triangular shape (a) and almost closed with a slit-like shape (b). See Fig. 7.3

the posterior glottis, which is involved with respiration. The patency of the posterior glottis determines the severity of VCAP. Therefore, we further divided stages 1 and 2 into two types according to the patency, or shape of the posterior glottis [23]. Triangular shape with some airway space (a) and slit-like shape with marked respiratory difficulties (b) are shown in Fig. 7.3. Needless to say, type b (stages 1b and 2b) is more serious than type a (stages 1a and 2a). In some cases, stage 1b is more serious than stage 2a.

Figure 7.4 shows a flowchart for the diagnosis and evaluation of VCAP. In practice, when patients with MSA develop nocturnal snoring, a fiberoptic laryngoscopy is performed during both wakefulness and sleep induced by intravenous administration of diazepam, midazolam, or propofol in order to identify the source of the snoring. If the vocal cord is the culprit, stage classification of VCAP is determined according to the vocal cord movements shown in Table 7.2. In cases of stage 3 (and often severe stage 2b) VCAP, it will be needed to take more prompt action such as emergency tracheostomy or noninvasive positive pressure ventilation (NPPV). In less severe stages, including stages 1a, 2a, 1b, and mild 2b, an overnight recording of arterial blood oxygen saturation (SpO_2) is performed. This examination gives the value of "%90," the percentage of time spent at less than 90 % of SpO_2. If the value of %90 is less than 20 %, follow-up studies with fiberoptic laryngoscopy or overnight recording of SpO_2 are repeated. However, if it is more than 20 %, a tracheostomy or NPPV is often needed. After diazepam/midazolam-induced sleep laryngoscopy, we routinely administer flumazenil to awaken the patient fully. Otherwise, the patient may fall asleep again, resulting in an unexpected exacerbation of VCAP.

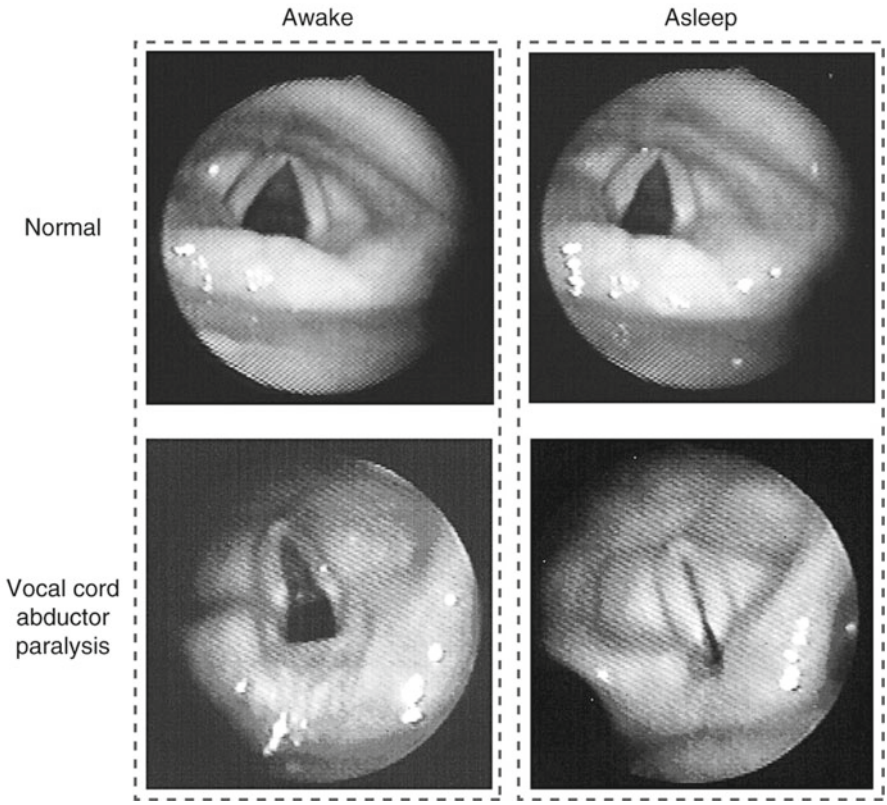

Fig. 7.2 Sleep-induced paradoxical movement of the vocal cords in MSA. Vocal cord movement is almost not changed between wakefulness and sleep in the normal subject. In the patients with MSA, vocal cords show some abduction restriction during wakefulness and adduct strongly with a slit-like glottis during sleep. Each fiberscopic photograph shows the inspiratory position of the vocal cords

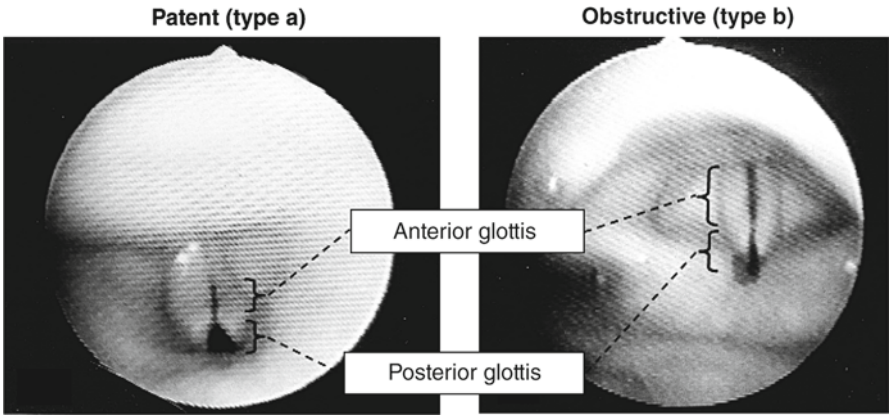

Fig. 7.3 Posterior glottis in the different two MSA patients with vocal cord abductor paralysis. Posterior glottis is still patent, indicating type a (*left*), while almost closed with a slit-like aperture, indicating type b (*right*)

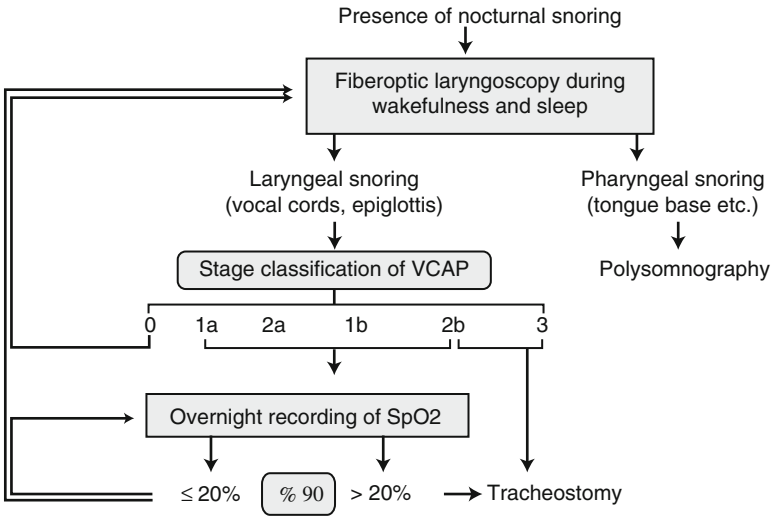

Fig. 7.4 A flowchart for diagnosis and evaluation of vocal cord abductor paralysis A fiberoptic laryngoscopy is performed during wakefulness and sleep to identify the obstructive site causing snoring and to classify the severity of vocal cord abductor paralysis. Application of a tracheostomy is decided by both findings of laryngoscopy and overnight recordings of SpO_2

There have been only a few reports on the acoustic analysis of nocturnal snoring [13, 24, 25]. Our previous study with a sound analyzer (Computerized Speech Lab, Model 4300, Kay Elemetrics Corp.) showed that the narrower the glottic aperture became, the higher the fundamental frequency of the vocal cord oscillation and the lower the voice turbulence index. Voice turbulence index is an acoustic parameter that shows the relative energy level of high-frequency noise. This index is thought to correlate with the turbulence caused by incomplete or loose adduction of the vocal cords [13].

VCAP usually takes two different courses: slowly progressive and rapidly progressive. In the former, VCAP worsens gradually over 1–3 years as a result of paralytic denervation of the abductor. Repeated measurements of the value of %90 may be useful in evaluating a gradual progression of oxygen desaturation. In the rapidly progressive type, an emergency tracheostomy or NPPV is often needed, even if the patient is already known to have VCAP. This type seems to be caused by nonparalytic mechanisms, based on increased laryngeal muscle tone. In rapid exacerbations, however, one should also consider mechanical obstruction by secretions in the upper airway, and severity of SpO_2 related to sleep depth in an overnight recording might be underestimated. If sleep depth is insufficient, VCAP may not be induced fully, resulting in seemingly "higher" SpO_2 values than actual values. Often a rapid exacerbation appears after a slowly progressive course.

Tracheostomy is believed to be the most reliable, yet most invasive, procedure for VCAP. Other therapeutic options include arytenoidectomy, cord lateralization, cordectomy [26], and botulinum toxin injection to the adductors [27]. Among these, only the first two have been attempted in patients with MSA [28, 29]. Recently,

NPPV, a pneumatic splint as an alternative to a tracheostomy, has been used with some efficacy in the patients with MSA [30, 31]. Although noninvasive and simple, the following problems have been reported: hypopharyngeal airway obstruction by a large and lax epiglottis in a patient with obstructive sleep apnea [32], continuous positive airway pressure-induced laryngospasm in the experimental study using dogs [33], and sudden death after bilevel positive airway pressure in a patient with primary pulmonary hypertension with central sleep apnea [34]. We have also seen an MSA patient with VCAP in whom bilevel positive airway pressure eliminated paradoxical vocal cord movements [35]. According to our experimental study with an artificial vocal cord, we clarified that in the therapy with NPPV there existed a threshold in setting up the optimal expiratory positive airway pressure to release the paradoxical vocal cord movement. It indicates clinically that an expiratory positive airway pressure-leading procedure seems to be preferable to an inspiratory positive airway pressure-leading procedure to dilate the narrow glottis in the management of the patients with MSA with a paralytic type of VCAP [36]. In addition to VCAP, we reported that other upper airway sites such as the epiglottis and the arytenoid regions can be also obstructed severely, and called those obstructive phenomena seen in MSA as floppy epiglottis and floppy arytenoid, respectively [35]. Of clinical importance in the treatments for them is the poor responsiveness to NPPV [35].

The most difficult decision after making a diagnosis of VCAP is determining when therapeutic procedures, such as a tracheostomy, should be performed. There are no generally acceptable guidelines on the appropriate time to intervene with tracheostomy—too early, and the patient's quality of life suffers; too late, and the patient may suffer sudden death. Patients 1 and 2 illustrate the difficult nature of this decision. Patient 1 could still eat and speak when the second fiberoptic laryngoscopy revealed an exacerbation of VCAP. Her arterial blood gas analysis on room air showed only mild hypoxemia. In this situation, can tracheostomy be recommended with confidence? Her sudden death only 3 weeks after admission without definite cause indicates that she probably succumbed to the advanced VCAP. Retrospectively, a tracheostomy should have been performed after the second fiberoptic laryngoscopy, as the rapid exacerbation of VCAP may have been related to the abnormally increased laryngeal muscle tone in addition to paresis of the abductor. Daytime inspiratory stridor is an ominous sign in advanced VCAP. A similar case has been reported [37]. Considering that her laryngeal complications were limited to respiration, NPPV including nasal continuous positive airway pressure may have been a reasonable option. In patient 2, the rapid progression of VCAP resembled that in patient 1. In February 2000, an overnight recording of SpO_2 was normal, although a fiberoptic laryngoscopy showed moderately severe VCAP (stage 2). What should have been done for such discrepant results? In retrospect, a repeat sleep laryngoscopy and overnight recording of SpO_2 would have been useful. Because the posterior glottis, which is important for airway integrity, is often difficult to observe fiberscopically, its patency should have been checked carefully. Another noteworthy point is to keep the influence of sleep depth on SpO_2 in mind. If sleep depth is insufficient (shallow sleep), VCAP can be "masked."

Table 7.3 Vocal cord abductor paralysis (VCAP) in multiple system atrophy

Clinical signs and symptoms
Loud and high-pitched snoring, often associated with tachypnea
Daytime inspiratory stridor during wakefulness in advanced stage
Inspiratory hollow of the suprasternal recess
Diagnosis and stage-classification
Restricted abduction and full adduction of the vocal cords
Paradoxical movement of the vocal cords showing inspiratory adduction and expiratory abduction
Sleep-induced exacerbation or manifestation of VCAP
Six stages in the severity of VCAP on a fiberoptic laryngoscopy (Stage 0, 1a, 1b, 2a, 2b, 3)
Pathophysiology
VCAP is caused by multifactorial mechanisms as described below:
Paralytic mechanism derived from denervation of the laryngeal abductor muscle
Nonparalytic mechanism derived from increased laryngeal muscle tone
Other mechanisms enhancing VCAP such as sleep and aspiration
Therapy
Tracheostomy: Time to perform tracheostomy is stage 2b on the laryngoscopic classification and nearly 20 % of %90 on an overnight recording of SpO_2
Local laryngosurgery including arytenoidectomy, cordectomy, cord lateralization, etc.
Airway splints: Continuous (CPAP)/Bilevel (BiPAP) positive airway pressure with a nasal mask
Botulinum toxin injection to the laryngeal adductor muscle

Therefore, when analyzing an overnight recording of SpO_2, it should be considered whether or not the patient slept well.

Table 7.3 shows a summary of the clinical findings, diagnosis, pathophysiology, and therapy of VCAP in MSA.

Future Questions

Which sedative is preferable in a sleep laryngoscopy to evaluate upper airway dynamics, including vocal cord movements? Diazepam, which we routinely use, is a muscle relaxant and a respiratory center suppressant. A recent study showed that the mechanism of respiratory insufficiency in nonintubated patients with drug-induced coma from benzodiazepines is an increase in upper airway resistance [38]. It is also unknown how sleep depth (both in drug-induced or natural sleep) influences the severity of VCAP. Because SpO_2 may depend in part on sleep depth, semiquantitative methods for evaluating sleep depth are needed to assess the overnight recording of SpO_2. The most pressing question is: Which therapy is most suitable for a given patient with MSA and VCAP: tracheostomy, laryngosurgery for glottal opening, NPPV, or botulinum toxin injection? In the future, we hope to choose appropriate treatments according to the features of VCAP in each patient.

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Chapter 8
Movement Disorder Emergencies of the Upper Aerodigestive Tract

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Abstract Movement disorder emergencies of the aerodigestive tract are dramatic and often life threatening. With appropriate, timely evaluation and intervention, most patients can be effectively managed and major morbidity avoided. This chapter provides a comprehensive review of both the causes and appropriate treatment of breathing disturbances secondary to primary disorders and iatrogenic causes, as well as swallowing emergencies. Additionally, basic physiology, anatomy, and various methods for assessment of the upper aerodigestive tract are provided for review. Specific disorders that are addressed include: spasmodic dysphonia, adductor laryngeal breathing dystonia, Shy–Drager abductor weakness, drug-induced tardive

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dystonia, oromandibulolingual dystonia, multiple system atrophy, multiple sclerosis, amyotrophic lateral sclerosis, Parkinson's disease, Huntington's disease, and palatal myoclonus.

Patient Vignette

A 52-year-old man was transferred to the emergency room of a major hospital from a referral facility because of recent slurred speech. He had been admitted to the referral facility the week before for treatment of alcohol abuse. Upon his arrival in the emergency room, the neurology resident was called to evaluate the patient after a normal computed tomography scan was obtained. Examination revealed normal comprehension and expression, slurring of speech, and an inability to fully open his jaw and protrude his tongue. There were no defects in visual field perception, power, or sensation. Review of the medical record from the referring institution revealed that the patient had been started on 5 mg of haloperidol four times daily on his admission to the referral facility as part of his treatment for alcohol abuse—he was unaware he was receiving the medication. An acute dystonic reaction was diagnosed, and 25 mg of intravenous diphenhydramine was administered, with resolution of the dysarthria and jaw restriction within 90 s of infusion. He was maintained on oral diphenhydramine (25 mg twice daily) for 1 week after discharge.

Introduction

Respiratory emergencies secondary to movement disorders are a rare but potentially life-threatening phenomenon. The clinician treating this patient population should be aware of the differential diagnosis and proper treatment to prevent adverse outcomes. The primary goal of intervention is to ensure a secure airway and to prevent respiratory embarrassment. Breathing disturbances of the larynx may be caused by primary movement disorders or may be iatrogenically induced, for example secondary to neuroleptic agents. In general, movement disorders of the upper aerodigestive tract lead to gradual respiratory compromise by diminishing the ability of the larynx to protect the lungs from aspiration. In this section we will focus on movement disorders that produce acute airway obstruction as a result of mechanical blockage by glottic dysfunction. Laryngeal anatomy and physiology, history and physical exam, differential diagnosis, and treatment of airway emergencies will also be discussed.

Laryngeal Anatomy and Physiology

The larynx serves as an organ for respiration, airway protection, and phonation. The larynx is lined by mucosa and is composed of cartilage, ligaments, membranes, and muscles. A detailed anatomic review is beyond the scope of this text;

instead we will concentrate on the function and innervation of the intrinsic laryngeal musculature.

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

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

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

Basic history with respect to the airway includes several key items. While dyspnea, shortness of breath, is often the focus, this symptom may occur late in the course of events and herald a true airway emergency. More subtle findings occur earlier and are critical to recognize. Stridor or "noisy breathing" suggests a disturbance of the normal laminar airflow pattern. It may be noted during inspiration, suggesting glottic or supraglottic origin; during expiration, suggesting a subglottic or tracheal origin; or it may be biphasic. This symptom may not necessarily be audible to the unaided ear and may require auscultation with a stethoscope over the trachea for early detection. Vocal quality, often described as dysphonia or hoarseness, is an important early finding. Questions about onset (acute vs. chronic), duration (continuous vs. episodic), and quality (harsh, raspy, breaks, breathy, fatigueable) give important information about airway stability.

The physical examination of the upper airway depends on accurate interpretation of findings on flexible fiberoptic laryngoscopy. Neurologic conditions present a particular challenge because there is often no anatomic distortion of laryngeal anatomy. Instead they often manifest as complex functional disturbances requiring

an experienced, trained observer. Failure of bilateral vocal fold abduction may warrant emergency intervention, cricothyroidotomy, or tracheotomy. As discussed above, early discoordination or generalized hypomobility may herald an impending emergency, requiring preventative action. The specific history and physical findings of each of the neurologic emergencies of the airway, including adductor breathing dystonia, Shy–Drager syndrome, and iatrogenic-related emergencies, will be discussed below.

Many neurologic airway emergencies will respond to medical intervention including high concentration humidified oxygen via a face tent, intravenous infusion of steroids, and continuous pulse oximetry monitoring (preferably in a critical care unit). These measures help stabilize the situation; either completely obviating the need for definitive airway management or at least allowing trained surgical staff to arrive for assistance with care. Great caution should be taken prior to attempted intubation in this patient group, as bilateral true vocal fold adduction may leave the vocal folds in a median or paramedian position making tube cannulation difficult or impossible even for experienced staff. Repeated attempts can further aggravate the situation by traumatizing the larynx and true vocal folds, causing bleeding and edema in an already compromised airway. Fiberoptic-guided intubation performed by highly trained staff with backup surgical staff on hand and tracheotomy equipment available at the bedside is far superior if time allows. If this option is not available or the situation too acute, cricothyroidotomy by incision into the cricothyroid membrane and insertion of a small endotracheal tube (e.g., #5.0 or #5.5) can be performed. This should be followed by conversion to tracheotomy as early as possible to prevent injury to the subglottis and potential further injury to the larynx and vocal folds.

Breathing Disturbances from Primary Disorders

Spasmodic Dysphonia

Dystonia is defined as involuntary sustained muscle contractions frequently causing twisting and repetitive movements or abnormal postures that may be sustained or intermittent. Spasmodic dysphonia (SD) is a clinical term used to describe focal laryngeal dystonia. The vocal apparatus usually functions normally during respiration, and laryngeal dystonia is triggered by speech. Most SD is idiopathic; however, it may occur secondary to neurological disorders (Wilson's disease, parkinsonism, Huntington's disease, ceroid lipofuscinosis), environmental factors (posttraumatic, postinfectious, vascular, neoplastic, toxic) and even psychogenic [1]. SD is generally categorized into an adductor (ADD) form, abductor (ABD) form, or mixed type.

In the ABD variant of SD, inappropriate contraction of the posterior cricoarytenoid muscles (the sole laryngeal abductors) results in hyper-abduction of the vocal folds. The voice quality is breathy and aphonic breaks occur during connected speech. In ADD SD, inappropriate hyper-adduction of the laryngeal adductors (primarily the

thyroarytenoids) results in a choked, strained voice quality with breaks in phonation. Laryngeal dystonias are task-specific (i.e., they occur only during speaking) and generally do not interfere with normal breathing, therefore respiratory compromise is not seen. Some studies have suggested that the sensation of dyspnea experienced by patients with laryngeal dystonia may be exacerbated by desynchronized contractions of the diaphragm [2]. The primary treatment of SD is with botulinum toxin injections to partially chemically denervate the specific laryngeal muscles responsible for the abnormal movements.

Adductor Laryngeal Breathing Dystonia

As mentioned earlier, focal laryngeal dystonias usually do not interfere with respiration; however, patients with adductor laryngeal breathing dystonia present with adductor spasms, which occur during inspiration. This usually presents as stridor of unknown etiology. Gerhardt first described this disorder, attributing it to paralysis of the abductor muscles. In 1992 Marion [3] studied three patients with Gerhardt's syndrome with laryngeal electromyography to show that adductor muscles were hyperactive. No weakness or denervation of the abductors was present, suggesting that the syndrome occurred as the result of ADD dystonia. In 1994, our group reported seven patients with stridor and paradoxical movement of the vocal folds [4]. They had normal abduction on coughing and laughing, but during inspiration they had closure of the vocal folds increasing airway resistance and producing stridor. Hyperactive adductor muscles were demonstrated on EMG, while normal activity was seen in the abductor muscles. None of these patients desaturated on pulse oximetry and none required tracheostomy or ventilatory assistance. Stridor disappeared during sleep, typical of dystonia, and reappeared on awakening. All of the patients improved with injections of botulinum toxin to weaken the adductor muscles. Adductor breathing dystonia has also been reported in association with Lubag syndrome [5] (X-linked dystonia-parkinsonism), with multiple system atrophy (MSA) [6] and with progressive supranuclear palsy [7] (both Parkinson-plus syndromes).

Shy–Drager Abductor Weakness

Shy–Drager syndrome, the autonomic variety of MSA, is a Parkinson-plus disorder characterized by orthostatic hypotension, loss of sweating, and urinary and/or rectal incontinence. Upper aerodigestive manifestations may include airway obstruction and/or swallowing difficulties that may lead to recurrent aspiration and pneumonia [8]. Airway obstruction is secondary to progressive vocal fold dysfunction, typically presenting as stridor that occurs first in sleep. In fact, nocturnal stridor portends a poor prognosis, with an increased risk of sudden death [9]. Deguchi studied

the relationship between urine storage dysfunction, abductor paralysis, and central sleep apnea in these patients, noting that a deterioration of the urine storage function might serve as a useful predictor of a parallel patient decline from abductor paralysis and central sleep apnea [10]. Vocal fold paresis and paralysis have been documented; however, the etiology of the vocal fold dysfunction is still elusive. Some authors have postulated that there is progressive weakness of the laryngeal abductors, while others suggest a dyskinesia or dystonia of the adductors leading to paradoxical vocal fold movement. Yoshihara noted a variety of stages of neurogenic degeneration of the muscle fibers and neuromuscular junctions of the posterior cricoarytenoid muscle, corresponding with abductor immobility in a patient with MSA [11]. Some authors have demonstrated adductor hyperfunctioning by laryngeal electromyography in patients with MSA, which responded to botulinum toxin injection to the thyroarytenoid muscles [6]. Flexible endoscopic evaluation usually reveals vocal fold adduction during inspiration. Earlier in the disease process, continuous positive airway pressure therapy has been proposed as a treatment for MSA-associated stridor, which often leads to excessive daytime sleepiness in these patients. CPAP can also serve as a tool for uncovering the possibility of central apnea in this population [12–14]. As the laryngeal dysfunction progresses, patients may require tracheotomy to protect the airway.

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

Iatrogenic Causes of Breathing Disturbances

Spasmodic Dysphonia: Airway Obstruction Secondary to Botulinum Toxin Treatment

The treatment of SD entails manipulation of the larynx in order to deliver botulinum toxin to the appropriate laryngeal muscles. Airway compromise may occur iatrogenically as the result of laryngospasm, excessive volume injection, or paralysis of the laryngeal abductors bilaterally. Laryngospasm is a sudden, sustained adduction of the vocal folds resulting in occlusion of the airway. This reflex is mediated via the vagus nerve and usually occurs in response to irritation of the vocal folds. It is thought to be a protective response that prevents irritants from reaching the lower airway. The treatment of ADD SD requires botulinum toxin injection under EMG guidance into the thyroarytenoid muscles. The needle is advanced through the cricothyroid membrane into the body of the thyroarytenoid muscle. In some individuals, the needle may stimulate laryngospasm resulting in acute airway obstruction. Initial treatment requires the patient to remain calm and to inhale nasally (“sniffing” maneuver) until the spasm breaks. This technique is often successful in breaking the

spasm. Failure of the spasm to break with conservative measures may require securing the airway via intubation, cricothyroidotomy, or tracheotomy. In the operating room, laryngospasm may be arrested with positive pressure ventilation, or with paralytic agents followed by endotracheal intubation.

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

The treatment of ABD spasmodic dysphonia requires botulinum toxin injection under EMG guidance into the posterior cricoarytenoid muscles. Because these are the only intrinsic laryngeal muscles responsible for abducting the vocal folds, bilateral paralysis can result in acute laryngeal obstruction. To prevent this from occurring we inject only one side per clinical visit. Approximately 2 weeks later, after the peak effect of the botulinum toxin has passed, flexible nasolaryngoscopy is performed to evaluate the abductor capability of the injected vocal fold. If there is satisfactory motion of the treated vocal fold, the contralateral posterior cricoarytenoid muscle is treated. Precise unilateral injection is mandatory to prevent inadvertent bilateral posterior cricoarytenoid muscle paralysis by direct injection or local diffusion.

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

Drug-Induced Tardive Dystonia

Typical neuroleptics and antipsychotics may trigger tardive dyskinesia or tardive dystonia, which can cause acute respiratory compromise if the larynx is involved. The extra-pyramidal side effects of neuroleptic and antipsychotic medications have been extensively reviewed in the literature [15–17]. We will focus on tardive dystonia, as laryngeal involvement may precipitate acute respiratory embarrassment and sudden death if not properly diagnosed and treated. Tardive dyskinesia typically presents as involuntary choreic movements of oral, buccal, and lingual areas whereas tardive dystonia produces involuntary spasmodic movements of the head, neck, tongue, and mouth. When the dystonia involves the laryngeal musculature, respiratory compromise may ensue as a result of vocal fold spasms. The diagnosis of tardive dystonia of the larynx should always be suspected in patients with a history of neuroleptic use. Patients may present with acute stridor without obvious precipitating cause. The diagnosis is based on history and clinical examination including endoscopy to rule out other causes of airway obstruction [18]. Primary medical management of tardive dystonia is with anticholinergics such as diphenhydramine, which should be administered parenterally in the acute setting. Once the patient is stabilized, pharmaceutical treatment should be continued orally as an

outpatient for 3–5 days. Patients with laryngeal dystonia may require resuscitative treatment, i.e., intubation, cricothyroidotomy, or tracheotomy while antidotal therapy is rendered [19]. Fortunately, tardive dystonias respond promptly when properly diagnosed and treated.

Swallowing Emergencies

Deglutition is a complex act of the laryngopharynx, requiring the successful passage of a food bolus into the upper esophagus and simultaneous protection of the laryngotracheal airway. This act relies upon the complex interrelationship of neuromuscular coordination of the oral cavity, oropharynx, hypopharynx, and larynx. Breakdown in the neuromuscular coordination of deglutition causes dysphagia (difficulty swallowing) or aspiration (food bolus passing into the airway distal to the level of the true vocal folds). Emergencies of swallowing can be categorized into those related to dysmotility and those related to aspiration; in the first, the patient is unable to maintain nutritional sustenance via oral intake, and in the second, the patient is unsafe to maintain an oral diet due to airway protection. These emergencies of swallowing rarely require immediate attention but often benefit from urgent intervention to allow adequate nutritional intake and to prevent aspiration pneumonia.

Swallowing Physiology

Deglutition describes the mechanical passing of a food bolus from the oral cavity into the esophagus and stomach. This can be divided into three phases: oral, pharyngeal, and esophageal. Deglutition begins with the introduction of food into the oral cavity. The oral preparatory phase (mastication) mechanically breaks down the food particles into a manageable bolus while mixing the food with salivary secretions to provide lubrication and early enzymatic digestion. The voluntary oral phase then propels the bolus into the pharynx by elevation of the tongue to the palate. Once the bolus stimulates afferents at the base of tongue and the faucial arches the pharyngeal phase of deglutition is initiated [20]. This is associated with closure of the velopharyngeal port, glottic, supraglottic, and epiglottic closure and elevation of the larynx. The pharyngeal phase is involuntary and involves the peristaltic contraction of the pharyngeal constrictors followed by the relaxation of the cricopharyngeus muscle, allowing the bolus to pass into the cervical esophagus. The third phase of swallowing is then initiated and proceeds with involuntary repetitive peristaltic contractions of the esophagus. The involuntary pharyngeal phase of swallowing lasts approximately 1 s. The temporal coordination of this phase is crucial for successful passage of the bolus into the esophagus and concomitant protection of the laryngotracheal airway [20].

The neurologic control of swallowing is a complicated interaction of both voluntary and involuntary efferent and afferent impulses. Centers in both the pons and the medulla have been implicated in the swallowing mechanism. There are two regions at the level of the pons which, when stimulated, evoke the swallowing process [20]. The reticular formation lies immediately dorsal to the trigeminal motor nucleus and transmits sensory input to the thalamus. The descending cortical-subcortical pathway is ventral to the motor trigeminal nucleus. Stimulation in this region induces mastication and swallowing. These two regions in the pons, however, do not comprise the core pathways of motor control in deglutition. The core pathway interneurons are situated in the medulla. Similar to the pons, there are two regions in the medulla which, when stimulated can evoke swallowing. A dorsal region of the reticular formation, which includes part of the nucleus tractus solitarius, and a ventral portion of the reticular formation in proximity to the nucleus ambiguus comprise the medullary swallowing centers. Peripheral afferents involved with initiating the involuntary swallow include the maxillary division of the trigeminal nerve, pharyngeal branches of the glossopharyngeal nerve, and sensory branches of the SLNs and RLNs [20].

Swallowing Evaluation

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

Objective methods of evaluating swallowing function include modified barium swallow and fiberoptic endoscopic evaluation of swallowing (FEES). The modified barium swallow (MBS) [21] involves videofluoroscopic evaluation in both anteroposterior and lateral views of swallowing while the patient is given barium coated foods of different consistencies (thin and thick liquid, puree and solid). The examiner assesses for dysfunction in either structural or mechanical dysmotility during swallowing in the oral, pharyngeal and upper esophageal phases. In order to evaluate the entire esophagus a barium esophagram is performed which involves the patient swallowing liquid barium. Views are taken before, during and after the barium is administered. If a difficulty is identified, feeding position and strategy can be tested using the barium to evaluate the efficacy of the compensatory maneuvers. FEES allows direct visualization of swallowing with a flexible laryngoscope in place during deglutition [22, 23]. The patient is offered food boluses of different consistencies with the addition of food coloring. The swallow is observed through the flexible videolaryngoscope. Many aspects of the swallow can be assessed in this manner except during velopharyngeal closure when the view is

transiently obstructed. FEES can be performed at the bedside or in the office. MBS and FEES, when performed by experienced examiners, have similar specificity and sensitivity [24].

Laryngeal sensory testing is a method of evaluating the afferents of the laryngopharynx [23]. This is done at the same time as the FEES and evaluates the laryngeal adductor reflex. When present, the reflex implies that sensory input to the larynx is intact. A calibrated air puff stimulus is applied to the aryepiglottic fold mucosa while watching for the adductor reflex. Sensory deficits have been shown to contribute to aspiration [25]; however, the role of sensation in dysphagia associated with movement disorders requires further investigation.

Esophageal function can also be evaluated with manometry. This technique measures the sequential muscular function of the esophagus and can thus confirm dysmotility disorders of the esophagus [26]. This technique may be combined with videoflouroscopy, which adds information regarding bolus location [27].

Treatment of Swallowing Disorders

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

Aspiration of a food or liquid bolus can result in aspiration pneumonia, which is associated with significant morbidity in patients with degenerative movement disorders. Behavioral modifications through speech and swallowing therapy are first implemented. If vocal fold immobility (VFI) is contributing to aspiration, then medialization laryngoplasty may help the patient to swallow safely [28]. Gastric tube feeding bypasses the upper aerodigestive tract and may decrease the frequency of aspiration. Tube feeding, however, does not prevent the aspiration of oral secretions, and patients may develop aspiration pneumonia even with a PEG. Patients who continue to aspirate oral secretions despite the presence of a gastric feeding tube may benefit from surgical airway protection. This includes glottic closure, epiglottic closure, laryngotracheal separation, and total laryngectomy [29, 30]. Tracheotomy does not prevent aspiration, and it may actually increase the risk of aspiration. This is due to the tethering effect of the trachea, which may inhibit laryngeal elevation, along with the inability to create adequate subglottic pressure during the swallow. Tracheotomy, however, does improve pulmonary toilet.

Specific Disorders Related to Swallowing Emergencies

Oromandibulolingual Dystonia

Oromandibulolingual dystonia [31, 32] (OMD) is a form of focal dystonia involving the masticatory, lower facial, and tongue musculature, producing spasms and often jaw deviation. In the early sixteenth century, Brueghel often painted faces with open mouths and contracted facial muscles, perhaps due to OMD [33]. In 1899 Gowers [34] described conditions producing tonic and clonic jaw contractions. The differential diagnosis of tonic jaw spasms includes dystonia, tetanus, trauma, hysteria, brainstem lesions, and hypothermia. Just after the turn of the century, Meige [35] reported a syndrome of spasms of the eyelids in addition to contractions of the pharyngeal, jaw, and tongue muscles. These spasms were often provoked by voluntary action (talking and/or eating) and lessened by humming, singing, yawning, or voluntarily opening the mouth. Some patients with Meige's syndrome developed other signs of dystonia, including torticollis, spasmodic dysphonia, or writer's cramp. In 1976, Marsden [36] realized that blepharospasm and oromandibular dystonia were both forms of adult-onset focal dystonia, a view supported by others [37–47]. In the most severe cases of OMD, dysphagia and/or airway obstruction can occur. One such case was published in a patient who sustained hypoxic brain injury, presenting several years later with intermittent respiratory distress requiring tracheostomy [48].

The etiology and differential diagnosis of OMD is similar to other forms of focal dystonia [49]. Misdiagnosis is common. Sustained or repetitive muscle contractions associated with bruxism typically occur in sleep and OMD disappears in sleep. Many patients are initially diagnosed as having temporomandibular disorders (TMD) and are treated with a variety of appliances [50]. Dental appliances may be useful, as sensory tricks help orofacial dyskinesias and OMD. On the basis of clinical exam, patients can be classified as having predominantly jaw-closing, jaw-opening, or jaw-deviation dystonia. Drug therapy is the mainstay of treatment; anticholinergics, benzodiazepines, and baclofen have proven to be most effective [51, 52]. We and others have reported success in managing OMD with local injections of botulinum toxin [53, 54]. There have been reports of successful management of the jaw spasms using anesthetics and alcohol, suggesting an important role for modulating afferents in OMD [55]. Side effects and complications of botulinum toxin injection of OMD are uncommon. In our initial report, there were 14 instances of dysphagia, mostly of the jaw-opening dystonia variety, where the anterior digastric muscles were injected. This injection can cause weakness of the suprahyoid muscle causing poor elevation of the larynx on swallowing and also changing the effectiveness of the tongue base on swallowing. One patient had severe dysphagia requiring a change of diet. One patient with jaw-closing dystonia had marked weakness of jaw closing and required an elastic bandage wrapped around his jaw to assist with chewing. Injection of the external pterygoid muscles occasionally caused rhinolalia or nasal regurgitation when drinking liquids. One patient with severe jaw-opening

dystonia was treated too aggressively and developed antibodies to BTX-A [56]. We initially treated a number of patients with severe lingual dystonia that caused posturing of the tongue or even prevented jaw-closing. However this approach converts a hyperfunctional tongue to a hypofunctional tongue. In most cases, we found the disability from the treatment worse than the disease. We recommend not treating the tongue, particularly the tongue base, since this worsens both speech and swallowing. In our initial series, six patients experienced such severe dysphagia that they required a temporary nasogastric tube for alimentation from 3 to 8 weeks. Two patients with severe lingual dystonia (tongue remained postured out of their mouths most of the time) were treated successfully because they already had a tracheostomy and a gastrostomy tube. In these cases, a hypofunctional tongue was a clinical improvement. [57, 58]. Some authors report benefit with low dose injections of lingual musculature [59]. Lyons recently reported on deep brain stimulation as an effective and safe treatment for patients with medically refractory Meige syndrome [60].

Multiple System Atrophy

The main laryngopharyngeal deficit in patients with MSA is VFI, which may be related to abductor paresis [6]. Persistent activity of the cricopharyngeus muscle during swallowing has also been noted in EMG studies [6]. Clinically, patients with advanced stages of MSA are more likely to have VFI. This, along with dysfunction of the cricopharyngeus muscle, contributes to dysphagia. There is an increase in bolus stasis at the level of the piriform sinuses and the cricopharyngeus [61]. The presence of VFI has been associated with increased risk of aspiration in patients with MSA, and therefore increased risk of aspiration pneumonia [61]. Patients with laryngopharyngeal deficits related to MSA often require a tracheotomy to maintain the airway as the disease advances. At this point there is often the need for gastric tube feeding to maintain adequate nutrition in these patients.

Multiple Sclerosis

Dysphagia is a secondary symptom of multiple sclerosis (MS), and a leading cause of morbidity and mortality in patients with MS [62]. Difficulty swallowing can lead to dehydration, malnutrition and aspiration pneumonia. Dysphagia may be present in up to 43 % of patients with MS, and the severity of the disease does not correlate with the degree of dysphagia. Dysphagia is caused by dysmotility at the level of the pharyngeal constrictors. This can result in penetration of the food bolus into the laryngeal vestibule. Slowing of the laryngopharyngeal phase of swallowing results in pharyngeal dysmotility [62]. Since there is no specific correlation between the disease state and the degree of dysphagia in MS, any complaint of swallowing

dysfunction should be evaluated and treated regardless of the patient's overall disability. Speech and swallowing therapy may be beneficial to help compensate for the laryngopharyngeal dysfunction [63]. Patients at risk for aspiration or who are unable to maintain oral intake may require tube feeding for maintenance of nutrition.

Amyotrophic Lateral Sclerosis

Dysphagia in amyotrophic lateral sclerosis (ALS) usually manifests several months after the onset of the disease [64]. Dysphagia in these patients may progress to aspiration pneumonia, poor nutrition, and dehydration. Dysphagia in ALS is related to dysfunction at various phases of swallowing. There is generalized weakness of the perioral, submental, suprahyoid muscles, and the tongue. This affects the oral preparatory and oral phases of swallowing and can result in difficulty controlling liquids and purees [64]. There is a delay in triggering the pharyngeal phase of swallowing in patients with early, moderate dysphagia. In addition there is a delay in laryngeal elevation in ALS patients with dysphagia. These patients also exhibit decreased tonic pause duration of the cricopharyngeus muscle with laryngeal elevation resulting in shorter periods of upper esophageal sphincter opening [65]. ALS patients with dysphagia have weakness of laryngeal and respiratory muscles. They also exhibit brisk mandibular and gag reflexes. In advanced stages, patients can lose all voluntary control of the swallow resulting in a spontaneous reflex swallow [65]. Using a mouse model, Lever suggest that pharyngeal dysphagia in ALS may be attributed to both motor and sensory pathologies [66].

Speech and swallowing therapy may provide compensatory techniques for early and moderate dysphagia. As the disease progresses and dysphagia becomes debilitating, gastric tube feedings are required. Spataro showed that PEG placement improves survival in dysphagic ALS patients, with few side effects [67]. Some patients with severe aspiration of secretions may benefit from surgical airway protection via glottal closure, laryngotracheal separation or total laryngectomy.

Parkinson's Disease

Swallowing dysfunction is present in 30–52 % of patients with Parkinson's disease (PD); in fact, gastrointestinal symptoms (including dysphagia) are among the most common nonmotor manifestations of PD [68–70]. Dysphagia and aspiration in the setting of respiratory insufficiency are a major cause of death in patients with PD [71]. In patients with PD there is a positive correlation between dysphagia and both disease duration and severity [72]. Potulska [68] compared swallowing function in PD patients with normal subjects using EMG and pharyngoesophageal scintigraphy. PD patients exhibited either subclinical dysphagia or overt dysphagia. Overall pharyngeal transit times, laryngeal movement times and esophageal transit times

were prolonged in PD patients with overt dysphagia. As the dysphagia progressed, the pharyngeal phase of swallowing became more disrupted. Furthermore, the dysphagia limit (maximum bolus volume safely swallowed) was significantly less in patients with overt dysphagia compared to patients with subclinical dysphagia [68]. EMG studies showed prolonged triggering of the swallowing reflex and prolonged duration of the pharyngeal reflex time without disturbance in the function of the cricopharyngeus muscle [65]. In the early stages of PD, patients have been shown to have manometric abnormalities even before clinical manifestations of dysphagia [73]. In a recent meta-analysis performed by Menezes and Melo, levodopa intake was shown not to be associated with an improvement in swallowing function in patients with Parkinson's disease [74]. PD patients with dysphagia may benefit from speech and swallowing therapy to compensate for the impaired swallowing mechanism. Expiratory muscle strength training may improve swallow safety, as recently illustrated by Troch [75]. If the dysphagia progresses such that oral nutrition is either inadequate or unsafe, then tube feeding should be implemented.

Huntington's Disease

Huntington's disease (HD) is a neurodegenerative disorder of the basal ganglia resulting in choreic movements, dementia, and neuropsychiatric features. These patients have impaired motor control of nearly all voluntary muscles, with many patients suffering from dysphagia [76]. In a review of the Nationwide Inpatient Sample database from 1996 to 2002, the most common HD-associated reason for hospital admission was pneumonia, of which aspiration pneumonia represented 22 % of cases [77]. Death occurs within 20 years in most patients and is often due to aspiration pneumonia. HD-related dysphagia is classified as hyperkinetic or bradykinetic [78]. The hyperkinetic variant is more prevalent of the two. This type is associated with uncoordinated, hyperactive movements of the tongue, mandible, and soft palate. There is also reduced activity of the suprahyoid, cricopharyngeus, and extrinsic muscles of the larynx [78]. In addition there are abrupt swallowing and involuntary respiratory maneuvers associated with the hyperkinetic variant [79]. Tachyphagia, or rapid swallowing maneuvers, is a unique characteristic of HD-related dysphagia. The bradykinetic variant of HD manifests with reduced motor function, range of motion, and coordination of the lips, mandible, tongue, and extrinsic laryngeal musculature [78]. Lingual sensory deficits may be present in both hyperkinetic and bradykinetic variants of HD. Kagel and Leopold [78] reviewed patients with HD over a 16-year period and found 28 of 29 patients had severe oral phase dysphagia by videoflouroscopic swallowing study, 17 of 29 patients had severe pharyngeal phase dysphagia, yet only 2 of 29 patients penetrated or aspirated. It should be noted that these swallow studies were performed with the patients in specially designed chairs to facilitate safe swallowing via postural fixation and spinal extension. Over one half of the patients studied exhibited uncoordinated and

asynchronous vocal fold function. This laryngeal chorea resulted in almost one-third of the patients with a potentially unprotected tracheal airway [78].

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

Palatal Myoclonus

Palatal myoclonus is a form of focal myoclonus, which manifests as repetitive contractions of the soft palate and uvula. It may affect only one side, although bilateral symmetric involvement is more common. Continuous, synchronous contractions of the uvula and soft palate occur at a frequency of 100–150 beats per minute [80]. The myoclonic activity persists during sleep. There may be associated focal myoclonic involvement of the larynx, extraocular muscles, neck, diaphragm, tongue, and face [80]. Palatal myoclonus is classified as symptomatic or essential. Symptomatic myoclonus occurs secondary to an underlying central nervous system disturbance, most commonly a brainstem stroke [81]. Other causes of symptomatic myoclonus include trauma, brainstem tumors or lesions, multiple sclerosis, encephalitis, progressive bulbar palsy, syringobulbia, obstructive hydrocephalus, and infectious causes (syphilis, malaria) [80–82]. There may be a latency period between the brainstem insult and onset of myoclonus of 3 weeks to 3 years [80]. Essential myoclonus, which is much less common, has no identifiable etiology [82]. The essential variant is associated with earlier onset (30–40 years), equal incidence in men and women, and often presents with the sole complaint of ear clicking. Symptomatic palatal myoclonus usually occurs in older males with less frequent subjective complaints [81]. There are occasional reports of palatal myoclonus contributing to dysphagia, dysarthria, and aspiration [82].

Treatment regimens for palatal myoclonus may include medical therapy with or without speech and swallowing therapy. Unfortunately palatal myoclonus is often refractory to systemic medications. Occasionally successful medications include anticholinergics and clonazepam. Botulinum toxin has been used for treatment with successful results as well [80]. Swallowing therapy can also benefit patients with significant dysphagia and aspiration related to the palatal myoclonus. Behavioral techniques such as the supraglottic swallow can allow safe oral feeding [82].

Conclusion

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

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Chapter 9
Dystonic Storm

Melissa J. Nirenberg and Blair Ford

This chapter contains video segments that can be found on the accompanying DVD.

Abstract In rare cases, generalized dystonia can rapidly progress to cause severe, continuous forceful contractions. This phenomenon—referred to as "dystonic storm" or "status dystonicus"—is a severe, life-threatening crisis that requires urgent evaluation and treatment. Dystonic storm can occur in idiopathic dystonia, or in symptomatic dystonia due to trauma, encephalitis, static encephalopathy, acute neuroleptic exposure, or neurodegenerative disorders. The differential diagnosis of dystonic storm includes bacterial meningitis, neuroleptic malignant syndrome, serotonin syndrome, malignant hyperthermia, and intrathecal baclofen withdrawal. Treatments for dystonic storm are empiric, and can be divided into three categories: supportive care, temporizing measures, and dystonia-specific treatments. Supportive care includes admission to an intensive care unit, mechanical ventilation, treatment with intravenous fluids and antipyretics, and monitoring of creatine phosphokinase, renal function, and urine output. Potential triggers (such as infection or medications) should also be identified and treated. Temporizing measures include the use of sedative-hypnotics, general anesthetics, or non-depolarizing paralytic agents. Dystonia-specific therapies should begin with catecholamine-depleting agents, anticholinergics, and/or dopamine receptor blocking agents. Other medications that may be effective include baclofen and benzodiazepines. If oral dystonia therapies are ineffective, then interventions such as an intrathecal baclofen pump or deep brain stimulation of the globus pallidus interna should be considered.

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Patient Vignettes

Patient 1

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

When he was 16 years old, he developed severe, relentless dystonic spasms over a period of 5 days, with no clear precipitant. He was febrile to 40°C, with a creatine phosphokinase (CPK) level of 1,032 U/ml. He had severe dystonia of the face and all four extremities and opisthotonic posturing. *Supportive care* was initiated, including admission to the pediatric intensive care unit, intravenous hydration, and administration of antipyretics (acetaminophen). An intravenous lorazepam drip (and later a midazolam drip) was used as a *temporizing measure*, to sedate the patient, suppress the dystonic spasms, and reduce the risk of medical complications (such as rhabdomyolysis), while other treatments were initiated. *Dystonia-specific therapy* consisted of increased doses of his outpatient medications (baclofen, trihexyphenidyl, and clonazepam), and the gradual addition of gabapentin, clonazepam, and dantrolene. Repeated attempts to wean him from intravenous benzodiazepines were unsuccessful, however, due to recurrent dystonic spasms.

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

Eight months later, when tolerance to the intrathecal baclofen developed, a bilateral pallidotomy was performed. There was an immediate improvement in his dystonia, with no associated neurosurgical complications. After 15 months, he required a repeat right pallidotomy, for persistent left arm dystonia. Because of ongoing severe dystonia, he subsequently underwent bilateral deep brain stimulation (DBS) of the globus pallidus interna at the age of 20. Although there were no surgical complications, there was minimal additional benefit; he continues to suffer from intractable generalized dystonia.

Patient 2

A 17-year-old boy developed dystonia involving his lower cranial muscles, affecting phonation and swallowing. A diagnosis of Wilson's disease was made based on

the presence of Kayser–Fleischer rings and a reduced serum ceruloplasmin. During chelation therapy with trientine, his dystonia markedly increased, causing generalized sustained dystonic spasms. His craniofacial dystonia became so severe that he developed stridor, requiring intubation and admission to the Pediatric Intensive Care Unit. Additional *supportive measures* included cardiopulmonary monitoring, intravenous hydration, and parenteral nutrition. Treatment with *dystonia-specific agents* consisted of baclofen, up to 60 mg/day, lorazepam up to 40 mg/day, trihexyphenidyl up to 50 mg/day, clonidine 0.2 mg/day, and carbidopa/levodopa 10/100 mg, two tablets three times daily without benefit. He underwent a prolonged ICU course of 3 months, during which time he was sedated on a pentobarbital drip and propofol. He was unable to be weaned from his ventilator, and required a tracheostomy. Ultimately, he underwent bilateral implantation of globus pallidus interna (GPi) stimulators. Over the next several weeks, as the stimulation was adjusted, it became possible to wean him from the intravenous sedatives and ventilator. His continuous dystonic spasms resolved, but his residual dystonia remained substantial. His speech was severely dysarthic and dysphonic, but he was able to swallow. He regained the use of his arms but required a wheelchair for ambulation. After 3 years, his dystonia remained disabling.

Introduction

Dystonia is defined as a syndrome of sustained muscular contractions, frequently causing twisting and repetitive movements or abnormal postures. It may be restricted to specific part(s) of the body, or generalized in distribution [1, 2]. When generalized dystonia "rapidly escalate(s) from its baseline to a presentation of extreme, forceful, continuous generalized contractions," it has the potential to precipitate a severe, life-threatening crisis that requires urgent evaluation and treatment. Importantly, dystonic storm represents an exacerbation of dystonia from a preexisting baseline, and is not a de novo presentation of dystonia. This phenomenon was first reported by Jankovic and Penn in 1982; they described a patient with "severe dystonia and myoglobinuria," in whom hyperpyrexia and rhabdomyolysis resulted from powerful and sustained dystonic spasms [3]. In 1984, Marsden and his colleagues reported two similar cases of severe, refractory generalized dystonia, which they referred to as "desperate dystonia" [4]. More recently, the terms "status dystonicus" [5, 6] and "dystonic storm" [7–9] have been used to describe such episodes of severe, relentless, and life-threatening generalized dystonia. These terms are valuable in that they convey the serious nature of this neurological emergency.

Clinical Features and Differential Diagnosis

The risk of dystonic storm appears to correlate with the severity of dystonia [3], and most commonly occurs in patients in whom there is poorly controlled generalized dystonia at baseline. The etiology of the underlying dystonia varies widely. Dystonic

Fig. 9.1 Table listing the differential diagnosis of dystonic storm

Differential Diagnosis of Dystonic Storm
• Bacterial meningitis
• Neuroleptic malignant syndrome
• Serotonin syndrome
• Malignant hyperthermia
• Intrathecal baclofen withdrawal
• Paraneoplastic encephalitis

storm occurs in idiopathic torsion dystonia with or without a DYT1 mutation [5, 7, 8, 10, 11]. It has also been reported in secondary dystonia due to trauma [5], encephalitis [5], static encephalopathy [5, 11–15], or acute neuroleptic exposure [16, 17]. Several neurodegenerative disorders in which dystonia is prominent have also presented with dystonic storm. These include Wilson's Disease [6, 11], infantile striatal necrosis [5], neuroacanthocytosis [5], pantothenate kinase-associated neurodegeneration [9, 15, 18, 19], and Batten's disease [20].

Dystonic storm often occurs after a triggering event, such as fever [9, 11], intercurrent infection [5, 15], stress [11], general anesthesia [21], or medication changes. Drugs that have been implicated include dopamine receptor blocking agents [16, 17]; metoclopramide [21], penicillamine [6, 22], zinc [11], and possibly clonazepam [5, 23]. Abrupt tapering or discontinuation of tetrabenazine, lithium, or anticholinergic medications may also precipitate dystonic storm [3, 5]. In many cases, however, no inciting factors can be identified [5, 8–10, 15].

The clinical presentation of dystonic storm is characterized by severe generalized muscle stiffness (due to dystonia), pain, hyperpyrexia, and even rhabdomyolysis [3–10, 14]. Other features may include aphagia and anarthria [4–7, 9]. Patients may require endotracheal intubation and mechanical ventilation because of bulbar dysfunction, decreased ventilatory capacity, muscular fatigue, or exhaustion [5, 7, 9]. Secondary complications may include tongue biting with lingual swelling [10, 17], dehydration, inanition [9], cardiac dysfunction [4, 5], gastrointestinal hemorrhage [4, 9], hypotension [6], aspiration pneumonia, and nosocomial infection [5]. When rhabdomyolysis occurs, there is a high risk of associated acute renal failure and metabolic acidosis [5, 6, 16, 17].

When a patient with dystonic storm is brought to medical attention, it is important to exclude other disorders that may present with extreme muscular contraction and abnormal movements (Fig. 9.1). The differential diagnosis of dystonic storm includes neuroleptic malignant syndrome, malignant hyperthermia, serotonin syndrome, acute withdrawal from intrathecal baclofen, paraneoplastic encephalitis, generalized tetanus, acute stiff person syndrome, and bacterial meningitis [5, 8, 13, 24, 25]. Because dystonic storm represents an exacerbation of preexisting dystonia, the diagnosis is usually evident as the dystonic spasms and generalized torsional movements escalate. However, in the setting of generalized spasms, abnormal movements, altered mental status, fever, or headache, it is

important to exclude the possibility of meningitis by lumbar puncture. Similarly, it is critical to identify a drug-induced encephalopathy, such as serotonin syndrome or neuroleptic malignant syndrome. The paraneoplastic NMDA-receptor encephalitis presents as progressive psychosis, encephalopathy, generalized rigidity and abnormal movements, usually in the craniofacial distribution. Intrathecal baclofen withdrawal can cause a rebound in dystonia or spasticity, depending on the underlying condition that may be life-threatening. Moreover, patients with intrathecal baclofen pumps are at an increased risk for bacterial meningitis [26].

Management

Once the diagnosis of dystonic storm has been established, prompt and aggressive treatment is indicated. Dystonic storm is a rare, life-threatening, fluctuating disorder. There are unfortunately no evidence-based management guidelines. The approach is therefore empiric, based on a compilation of effective treatments derived from case reports in the literature [9]. We subdivide management into three major components: supportive care, temporizing measures, and dystonia-specific therapy. An algorithm is shown in Fig. 9.2.

1. *Supportive care* is directed at minimizing the systemic complications of severe dystonia. Most patients are admitted to an intensive care unit where cardiopulmonary monitoring is available [5, 8, 9]. Airway and respiratory status should be rapidly evaluated and closely observed; endotracheal intubation and mechanical ventilation should be performed when clinically indicated [3–5, 7, 9, 12]. Hyperpyrexia should be treated with cooling blankets and antipyretics [3, 7, 8]. Pain is nearly universal [3–5, 9]; analgesic medications such as fentanyl or morphine are therefore indicated until dystonia-specific therapy takes effect [5, 8].

   Intravenous hydration is critical in all cases [3, 8–10, 17]. The serum CPK, creatinine, and urine output should be followed closely, given the high risk of rhabdomyolysis [5]. Alkalinization of the urine is indicated if rhabdomyolysis occurs [10, 17]; if rhabdomyolysis progresses to acute renal failure, then dialysis may be needed [16]. If the dystonia cannot be controlled quickly, then tube feedings or parenteral nutrition should be initiated to prevent inanition [9, 16].

   Potential triggers for the development of dystonic storm should also be identified and treated. If there is suspicion of an underlying bacterial infection, then broad-spectrum antibiotic therapy should be administered [5]. When dystonic storm has been precipitated by a specific medication, discontinuation of the offending agent is prudent, but unlikely to abort the crisis [6].
2. *Temporizing measures* consist of sedative-hypnotic agents that provide relief of intractable muscle spasms and pain until dystonia-specific medications can be substituted. A continuous midazolam drip is a good initial choice, because it is a direct muscle relaxant, has a relatively short half-life, and has little effect on cardiovascular function [5, 8]. The dose can be titrated to the degree of dystonic spasms, with the goal of optimizing the level of alertness while

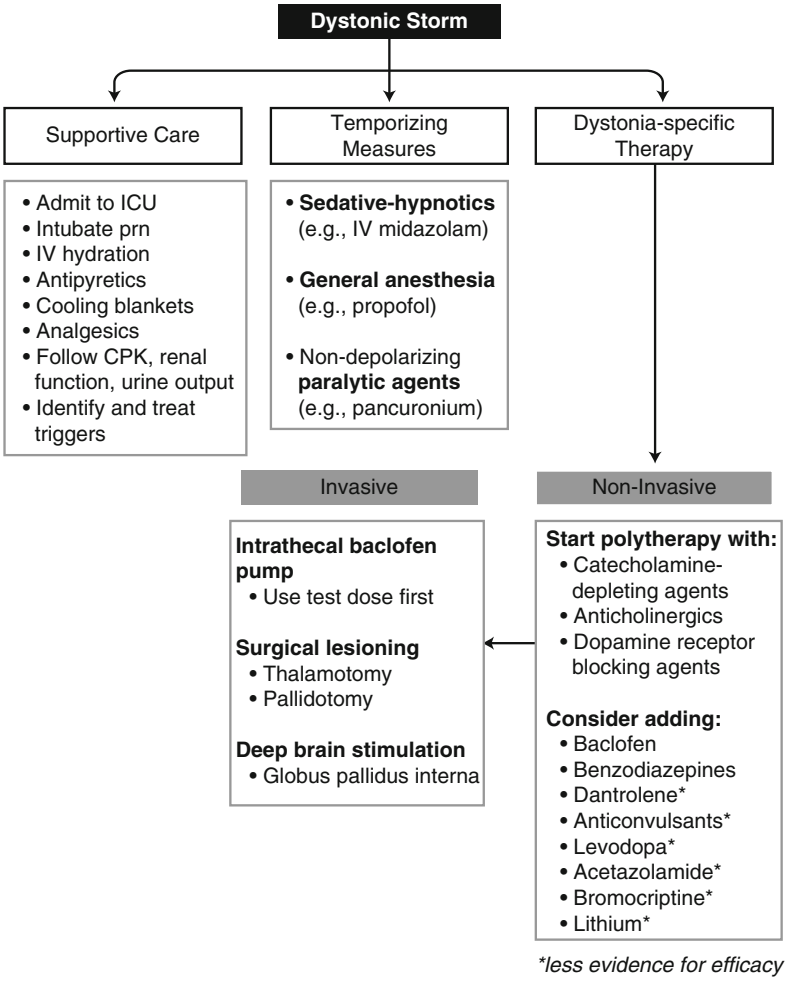

Fig. 9.2 Suggested algorithm for the treatment of dystonic storm. *CPK* creatine phosphokinase, *ICU* intensive care unit

minimizing respiratory depression. In refractory cases, general anesthesia, often in combination with paralytic agents, may be necessary to control overwhelming dystonic spasms. A variety of general anesthetics have been used for this purpose [4, 5, 9, 10]. Of these, propofol is probably the best choice, because of its short half-life. Various paralytic agents have also been used for dystonic storm [3, 5, 9, 12]; non-depolarizing agents such as pancuronium are preferable, since depolarizing agents may precipitate or exacerbate rhabdomyolysis.

Intravenous sedative-hypnotic agents are highly effective in controlling the symptoms of dystonic storm. Unfortunately, these interventions do not affect the underlying dystonic symptoms, which may recur as soon as the agent(s) are withdrawn [8, 9]. As a result, it may take weeks or months to wean individuals with severe, prolonged dystonic spasms unless a more definitive intervention can be made. Some individuals with dystonic storm face a prolonged intensive care unit course, during which the placement of a tracheostomy and gastrostomy tube may be necessary, in addition to intensive supportive care and treatment of ongoing medical complications to which these patients are vulnerable.

3. *Dystonia-specific therapy* represents interventions that have traditionally been employed in the treatment of dystonia, and are considered more specifically targeted to the basal ganglia than generalized anesthesia. The goal of treatment with a combination of high-dose anti-dystonia agents is to abort the dystonic crisis, and reduce the abnormal movements to their previous baseline. Marsden and his colleagues reported success with a combination of drugs (the "Marsden cocktail"), consisting of a fixed dose of tetrabenazine (75 mg/day), to which a dopamine receptor blocking agent, and then an anticholinergic medication were gradually added as tolerated [4]. Mani advocated use of the same medications with a different titration schedule [5] The regimen began with a trial of levodopa therapy in all patients (to exclude the possibility of dopa-responsive dystonia); when that was unsuccessful, anticholinergic medications, followed by tetrabenazine, and then a dopamine receptor-blocking agent such as pimozide were used. Each agent was started slowly, and titrated gradually to minimize side effects [4, 27]. Even so, serious medication side effects required discontinuation of the offending agent in several cases. Pimozide in particular precipitated a superimposed acute dystonic reaction in one case [4], and cardiotoxicity in several others [5]. Reversible, dose-dependent side effects of these dystonia-specific medications also occur frequently, including drug-induced parkinsonism, akathisia, depression, drowsiness, cognitive impairment, and urinary retention [4, 5, 9]. While these side effects are a major concern in an outpatient setting, they are more easily managed in the intensive care unit.

   The approach to dystonic storm is not based on clinical trials or standardized evidence but has evolved from clinical practice. In addition to high-dose anticholinergics, catecholamine-depleting agents, and dopamine receptor blockers, additional medications that may help in the treatment of dystonic storm include combinations of dantrolene, benzodiazepines (e.g., clonazepam or diazepam), baclofen, anticonvulsants (e.g., carbamazepine, valproic acid, primidone, phenytoin), lithium, bromocriptine, levodopa, acetazolamide, and gabapentin, with variable results [3, 5, 7–10, 22]. Dantrolene is especially helpful in the setting of rhabdomyolysis, and is non-sedating. Unfortunately, even with aggressive polytherapy, dystonia often remains staunchly unresponsive to oral medications [5, 6, 9]. *Moreover*, because the patients are virtually always treated concurrently with several different medications, it is often unclear which one(s) may be responsible for clinical improvement.

When oral medications fail, more invasive approaches are warranted. Intrathecal baclofen therapy, well established in the treatment of severe spasticity [28, 29], has been used with variable success in the chronic management of generalized dystonia [24, 30–34]. Intrathecal baclofen was first reported to provide benefit in a case of refractory dystonic storm in 1992 [12], and has been used in subsequent cases [8, 35]. Major advantages include the potential to relieve pain from muscular spasms [24, 36, 37], to prevent the need for general anesthesia [8], and to provide long-term therapy for the underlying dystonia after the acute crisis has resolved. Potential disadvantages include the generally disappointing long-term effect of intrathecal baclofen in dystonia, the developmental of tolerance, and the high rate of complications, especially skin breakdown, malfunction and infection. Potentially serious complications include cerebrospinal fluid leak, meningitis, seizures, mechanical failure (which may precipitate a life-threatening withdrawal syndrome), and overdose (which may result in bradycardia, hypotension, respiratory depression, or coma) [18, 24, 26, 28, 38]. The role of intrathecal baclofen in the treatment of dystonic storm is therefore uncertain [24]. Until there are better data regarding the safety and efficacy of this approach, it should probably be reserved as a temporizing measure only for medically refractory cases.

Over the past 20 years, thalamotomy, pallidotomy, and deep brain stimulation [DBS] of the globus pallidus interna, have played an increasingly important role in the management of medically refractory dystonia [19–21, 39–49]. DBS has largely supplanted the lesion-based approaches to dystonia and other movement disorders because it offers the ability to revise the therapy by reprogramming if tolerance develops. Although neurosurgical approaches offer the potential of providing long-term control of the underlying dystonia, their safety and efficacy in the management of dystonic storm remain unclear. Surgical intervention is relatively contraindicated in the acute setting, where renal failure and other organ system dysfunction may increase surgical morbidity and mortality [8]. Moreover, even in stable patients, up to 9% may have serious complications, including stroke, cognitive symptoms, visual field deficits, dysarthria, dysphagia, hypophonia, and infection [50–54]. These procedures, particularly DBS, also have a delayed onset to maximal benefit that may limit their utility in the acute setting [40, 43, 51]. Nonetheless, several reports have illustrated the safe and effective use of thalamotomy, pallidotomy, or pallidal DBS in the management of dystonic storm [3, 5, 8, 19, 55]. Thus, neurosurgical intervention should be considered in patients who fail to respond to more conservative therapy.

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

Conclusion

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

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Chapter 10
Pseudodystonic Emergencies

Jong-Min Kim and Beom S. Jeon

This chapter contains video segments that can be found on the accompanying DVD.

Abstract Dystonia is a syndrome of sustained muscle contractions, causing abnormal postures, twisting, and repetitive movements. Dystonic appearance may be mimicked by other neurological diseases in which sustained abnormal postures may be present, but which are not considered a true dystonia, and hence are called pseudodystonia. Some forms of pseudodystonia are neurological emergencies, requiring urgent evaluation and treatment. Atlanto-axial subluxation, infectious torticollis, and tetanus all require appropriate measures; otherwise they will result in medical disasters. In this chapter, we discuss causes, evaluation, and management of pseudodystonic emergencies.

Clinical Vignettes

Patient 1

A 6-year-old boy presented to the outpatient department for head tilt. Since the age of 2, head tilt to the right side had been noted. When he was 4 years old, cervical spine imaging was done. Congenital laminar fusion on the right at C2–3 vertebrae was found (Fig. 10.1). At age 6, posterior in situ fusion of C2–3 vertebrae with iliac bone graft was performed. However, head tilt was not relieved. The patient was

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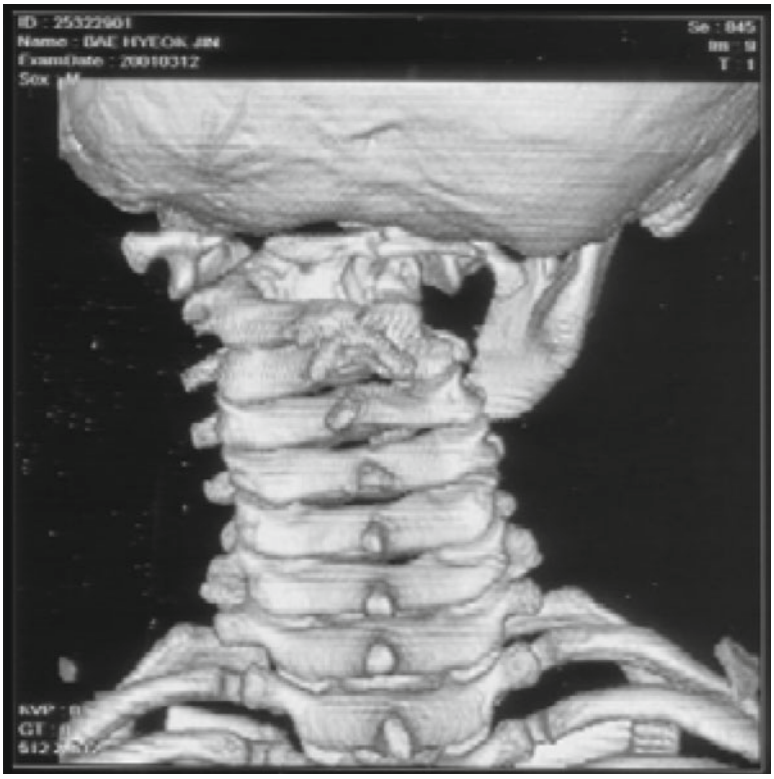

Fig. 10.1 Radiographic findings from Patient 1. Three-dimensional reconstructed CT image demonstrates fusion of the right laminae at C2–3 vertebrae (posterolateral aspect of cervical spine)

referred to a neurologist. He had head tilt to the right side with painful contraction of the neck muscles. Manual rotation of the neck to either side and straightening of the neck caused severe pain. The images checked before and after operation were reviewed. There was an enhancing lesion anterior to the atlas, axis, and C3 vertebra. It appeared to be an inflammatory lesion, whose exact etiology was not clear. Anti-inflammatory drugs and muscle relaxant were started. Painful contractions of neck muscles were somewhat reduced resulting in mild improvement in head tilt. Still, future management remains a challenge.

Patient 2

A 54-year-old woman came to the emergency room with severe muscle spasms of the neck and inability to speak or swallow. She had been healthy until progressive muscle spasms developed about a week prior to the visit. She had retrocollic posture

with inability to move the neck in any directions. She had difficulty in opening her mouth due to trismus. She recalled that she had a minor scratch on the left shoulder about a week before developing her symptoms. Continuous trains of muscle firing were seen on EMG. She was diagnosed with localized tetanus. High doses of diazepam relieved much of the pain and spasm. She improved gradually over the next 3 months.

The Concept of Pseudodystonia

Dystonia is a syndrome of sustained muscle contractions, causing abnormal postures, twisting, and repetitive movements [1]. The etiologic classification divides the causes of dystonia into four major categories: primary (or idiopathic), dystonia-plus syndromes, secondary (or symptomatic), and heredodegenerative diseases in which dystonia is a prominent feature [2]. However, there are other neurological diseases in which sustained abnormal postures may be present, but are not considered a true dystonia, and hence are called pseudodystonia.

Pseudodystonia includes stiff-person syndrome, Isaacs' syndrome, Sandifer's syndrome, juvenile rheumatoid arthritis, tetanus, torticollis associated with pharyngitis, torticollis due to spinal cord astrocytoma, congenital muscular torticollis, ocular muscular torticollis (compensatory act for strabismus and diplopia), and other numerous conditions [3] (Table 10.1). Musculoskeletal abnormality of the spine (Satoyoshi syndrome, atlanto-axial subluxation in Down syndrome, congenital laminar fusion, ligament absence, laxity, damage, congenital Klippel–Feil syndrome), syringomyelia, and Arnold–Chiari malformation can induce torticollis, and are other examples of pseudodystonic conditions [4].

Table 10.1 Pseudodystonia

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

Pseudodystonic Emergencies

Some pseudodystonic disorders may present as emergencies. Atlanto-axial subluxation, tetanus, neoplastic torticollis, and infectious torticollis are pseudodystonic conditions requiring emergent workup and treatment (Table 10.2). Atlanto-axial subluxation is a serious cause of torticollis in childhood. Children are liable to this condition due to the degree of freedom of the atlas and axis and the laxity of spinal ligaments. The trauma needed to produce atlanto-axial subluxation can be trivial, and the condition may occur spontaneously without trauma [5]. The typical manifestations of atlanto-axial subluxation are head tilt, contralateral head rotation, and mild neck flexion. The neck muscles appear loose. The spinous process of the axis may be palpable in the same direction as the head rotation. The patient may be unable to rotate the neck past midline.

The consequence of missed atlanto-axial subluxation in children can be devastating. Early diagnosis can, however, produce complete recovery. Axial traction combined with rotation to the neutral position is the treatment of choice. If the diagnosis is delayed for more than 1 month, axial traction is not helpful and an operation for atlanto-axial fusion is necessary, with the consequence of limitation in range of motion of the neck.

Tetanus may affect a limb, the neck (localized), or the face (cephalic) or it may be generalized. Generalized tetanus presents with pain or stiffness over the back or the neck, usually followed by trismus and autonomic disturbances. Cephalic or localized tetanus may be misdiagnosed as focal dystonia. Trismus mimics jaw dystonia. Fiorillo reported a 10-year-old boy who developed continuous painful spasm of the foot after an injury [6]. Initially, the diagnosis was delayed. He was eventually treated with tetanus immune globulin and antibiotics, although foot spasms continued for 4 months.

Spinal cord tumor may rarely present as torticollis. Shafrir reported a tragedy in an infant with congenital torticollis due to spinal cord astrocytoma [7]. Chiropractic manipulation prior to the correct diagnosis triggered a respiratory arrest and quadriplegia due to tumor necrosis. The authors suggest that all children with torticollis, even those with congenital torticollis, should have a radiologic evaluation before any physical therapy is started.

The most common cause of an emergency presentation of torticollis is an infectious or inflammatory process of the head or the neck. Torticollis may follow nonspecific pharyngitis, tonsillitis or adenoiditis, retropharyngeal or tonsillar abscess, parotitis, mastoiditis or otitis media, acute rheumatic fever, or influenza [8]. All children presenting with acute nontraumatic torticollis should be assumed to have an inflammatory process of the head or the neck. Initial management must include cervical immobilization. CT or MRI imaging is necessary to delineate the atlanto-axial joint, and plain radiographs are insufficient. All patients with acute or persistent torticollis must be assumed to harbor an atlanto-axial subluxation until proven otherwise.

Table 10.2 Pseudodystonic emergencies

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

Evaluation and Treatment of Pseudodystonic Emergencies

All patients presenting with acute torticollis should be assumed to have a traumatic or inflammatory head and neck process. Initial management should include cervical immobilization. All children with torticollis, even those with congenital torticollis, must have a neurologic and radiologic evaluation before any physical mobilization. CT or MRI imaging is necessary to delineate the atlanto-axial joint, and to identify space-occupying lesions in the head and neck. All patients with persistent torticollis must be assumed to harbor an atlanto-axial subluxation until proven otherwise. By following these guidelines, and maintaining a high level of suspicion, patients presenting with pseudodystonia can be safely and effectively managed.

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Chapter 11
Tardive and Neuroleptic-Induced Emergencies

Paul E. Greene and Steven J. Frucht

This chapter contains video segments that can be found on the accompanying DVD.

Abstract Tardive and neuroleptic-induced movement disorders can be among the most dramatic conditions affecting patients. One has only to witness a patient with severe acute jaw dystonia from haloperidol, or watch a patient develop neuroleptic-induced oculogyric crisis to appreciate how sudden and devastating these disorders can be. Fortunately, prompt recognition and treatment are usually effective and, occasionally, lifesaving. This chapter reviews tardive and neuroleptic-induced movement disorder emergencies, and their diagnosis and management.

Patient Vignettes

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

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

Introduction

Exposure to most centrally acting dopamine receptor-blocking agents (DRBAs) can cause a variety of movement disorders. Neurologists characterize the movement disorders according to their natural history when the causative agent is stopped; they can be self-limited and have short duration, or they can be long lasting. The self-limited movement disorders usually appear shortly after exposure to the DRBA and resolve quickly after the agent is stopped. The most common short duration disorders are acute dystonic reactions, including oculogyric crises and acute akathisia. The long duration movement disorders usually appear after chronic exposure to the DRBA and may last a lifetime or for many years after the DRBA is stopped. The long-duration disorders usually consist of dyskinesias, dystonia, or akathisia. Occasionally, other movement disorder symptoms, such as myoclonus, tics, or tremors have been attributed to DRBA exposure.

Despite the usefulness of the distinction between acute and tardive drug-induced movement disorders, the line between the two is sometimes blurred, especially in the older literature. There have been reports of recurrent acute dystonic reactions [1], and tardive movements that typically appear after prolonged exposure may appear after as little as 1 week of neuroleptic exposure. Whenever possible, we try to distinguish between acute and tardive symptoms. In addition, many patients with tardive syndromes have a combination of symptoms, and it can be difficult to separate the effects of dystonia, dyskinesias, and akathisia. It is also important to remember that other centrally acting dopamine receptor blockers besides neuroleptics may cause tardive syndromes, including antinausea agents such as prochlorperazine [2] and metoclopramide [3], calcium channel blockers such as flunarizine and cinnarizine [4], and that these disorders may occur in childhood and even infancy [5].

Tardive symptoms may be mild and barely bothersome to the sufferer (as is frequently the case with oral-buccal dyskinesias), or they may cause severe discomfort (as is often the case with DRBA-induced dystonia and akathisia). Occasionally,

these movement disorders present as emergencies, sometimes as life-threatening events, and hence their inclusion as movement disorder emergencies.

Tardive Respiratory Phenomena

Respiratory compromise rarely occurs with idiopathic dystonia; rather, it generally occurs in the setting of a severe exacerbation of symptoms called dystonic storm [6]. Respiratory compromise probably occurs more commonly with DRBA-associated dystonia than with idiopathic dystonia. The majority of reported cases seem to be associated with acute dystonic reactions [7]. Several of these cases have been associated with stridor, and presumably most occur because of dystonia of the larynx and or pharynx [7]. However, in several cases, respiratory compromise with hypoxia occurred in the setting of chronic neuroleptic use, and tardive dystonia was the probable underlying condition [8, 9]. Respiratory compromise may also occur from aspiration in the setting of dysphagia.

The prevalence of respiratory irregularity in patients with tardive syndromes was estimated at 7.4% [10]. Patients may have a variety of findings: irregular respiration, grunting, sighing, humming, gasping, and choking [10]. At the time of that study, dystonia was not widely recognized as a tardive symptom, so the exact underlying tardive symptoms cannot be known for certain. We have seen patients with respiratory irregularities that have had exclusively oral-buccal dyskinesias. However, idiopathic cranial dystonia (Meige syndrome) is accompanied by respiratory irregularity in as many as 5% of patients [11], so it is likely that patients with tardive dystonia may also have this problem. Patients may have irregular respirations and grunting. The irregularity appears to be asymptomatic in many cases, but it can also present emergently as shortness of breath [12]. Although some patients with symptomatic respiratory dysrhythmia may have normal blood gases [12], some apparently develop hypoxia cyanosis [13]. Although many of the reported cases involve chronic respiratory dysrhythmia, in some of these cases doses of neuroleptics were changed shortly before the acute episode [14], and respiratory involvement may have been related to an acute dystonic reaction [13].

Other Tardive Complications

Dysphagia in varying degrees of severity has been reported in conjunction with tardive syndromes. Tardive dystonia of the pharynx has been the presumptive diagnosis in some of these patients [15–19] but some may have just had oral-buccal dyskinesias [10]. In some patients, drug-induced parkinsonism has been hypothesized to exacerbate dysphagia, or possibly be the sole cause [16]. Choking, regurgitation of food, and weight loss are the usual symptoms. In some cases, these symptoms are accompanied by aspiration and recurrent pneumonia [10].

Since the early 1980s, there have been a series of case reports ascribing suicidal ideation, suicide attempts, or completed suicide in akathisia [20]. Some of these cases appear to occur in the setting of acute akathisia, whereas the akathisia in other cases persists for so long that tardive akathisia is probably the underlying condition [20]. Many of these patients have underlying psychiatric disorders, such as depression and schizophrenia that may also be associated with suicidal ideation. Some authors have questioned the association between suicide and akathisia [21]. However, there are reports of suicidal ideation in patients with no psychiatric history who developed akathisia from gastrointestinal DRBAs [22, 23].

Tardive dystonia can be severe and interfere with functions normally performed by the affected body parts. Severe jaw-closing dystonia can make it difficult or impossible for patients to take oral food. Severe jaw-opening dystonia can make chewing impossible, limiting patients to liquid nutrition. One patient with severe tardive jaw-opening dystonia improved dramatically with bilateral pallidotomy [24]. Severe lingual dystonia can make it impossible for patients to pass the bolus of food to the posterior pharynx where swallowing can be initiated [25, 26]. These patients may be unable to eat solid food even when swallowing itself is normal. Dystonia or dyskinesias may make walking difficult and lead to falls and fractures, as has been reported several times [27, 28]. The risk of fractures may be higher in the presence of osteoporosis. When severe, truncal dystonia can make sitting and lying difficult, which quickly leads to an emergency presentation. There is at least one report of a patient who developed myoglobinuria associated with severe tardive dystonia [29]. There are also rare patients who develop intractable vomiting as a result of air swallowing, presumably related to pharyngeal dystonia [9].

Oculogyric Crisis

The phenomenon of oculogyric crisis was first described in patients with encephalitis lethargica. A form of acute dystonia, it takes its name from the tendency of the eyes to deviate, although eye movements are only part of the syndrome. Sacks [30] elegantly summarized the panoply of disturbances in postencephalitic crises: “among the common accompanying symptoms we have observed in oculogyric crises are the following: opisthotonus and generalized rigidity, intense terror or rage, thalamic pain and anguish, multiple autonomic symptoms (sometimes accompanied by conspicuous tachycardia and hypertension), hypervigilance, extreme motor urge, akathisia, complex reiterative movements and ticking, forced gasping and gagging, loud phonation, tachyphemia and tachypraxis, pallilalia and verbigeration, obsessional and sometimes delusional remuneration, and—in all cases to some degree, and in the worst crises a profound degree, of catalepsy and/or block”.

Oculogyric crises are most commonly seen following exposure to neuroleptics and crises may occur as acute or tardive phenomena [1, 12]. The incidence of oculogyric crises in patients treated with chronic neuroleptics may be as high as 10% [12], and in one report of 24 children accidentally exposed to haloperidol, 14 developed

oculogyric crises [31]. Tetrabenazine [32], gabapentin [33], domperidone [34], carbamazepine [35], lamotrigine [36], cetirizine [37], imipramine [38], and lithium carbonate [39] have all been reported to trigger oculogyric crises. Sacks [30] reported that levodopa initially suppressed crises in postencephalitic patients, although it later enhanced their severity and intensity. Oculogyric crisis may occur in patients with dopa-responsive dystonia, and in one such patient, treatment with levodopa eliminated both dystonia and crises [40]. There are also credible reports of oculogyric crises associated with structural brain lesions, such as bilateral paramedian thalamic infarction [41], midbrain lesion [42], herpes encephalitis, cystic glioma of the posterior third ventricle [43], and as the initial manifestation of Wilson's disease [44]. Oculogyric crises may recur despite withdrawal of dopamine-blocking agents, even if the original exposure was brief [45].

Treatment

The treatment of acute dystonic reactions is usually easy. Anticholinergics or antihistamines generally abort the dystonia within minutes when given by the intravenous route. Regardless of their cause, acute oculogyric crises can be terminated with injection of intravenous anticholinergics or diphenhydramine. 25 or 50 mg of intravenous diphenhydramine is readily available in hospital emergency rooms and is probably the treatment of choice for this condition. Oral clonazepam may be effective for patients with chronic neuroleptic-induced oculogyric crises that are resistant to anticholinergics [46].

Acute akathisia can also usually be controlled with propranolol or benzodiazepines until it resolves. It is much more difficult to treat tardive syndromes. Discontinuation of the DRBA, when possible, is sometimes—but not always—effective. When persistent, or when the DRBA cannot be stopped, treatment of tardive syndromes is difficult and beyond the scope of this review. Atypical neuroleptics, such as clozapine, may allow symptoms to abate with continued therapy. Botulinum toxin injection, performed carefully, may benefit select patients [47]. Dopamine depletors, such as reserpine or tetrabenazine, are probably the most effective agents, but they can cause depression, hypotension, and drug-induced parkinsonism [48–50].

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Chapter 12
Hemiballism–Hemichorea

Ronald B. Postuma and Anthony E. Lang

This chapter contains video segments that can be found on the accompanying DVD.

Abstract Hemiballism is an uncommon movement disorder that presents with unilateral flinging movements of the limbs. It varies considerably in intensity and severity—often in its acute phase it can be of sufficient severity to present as a true emergency. It is most classically associated with ischemic lesions to the subthalamic nucleus (STN), although the majority of cases involve basal ganglia structures outside the STN. An important recently described association is with diabetes, during crises of severe non-ketotic hyperosmolar hyperglycemia. Pathophysiology is related to abnormal firing patterns in the globus pallidus interna, with intermittent firing bursts followed by pauses during which movements occur. The key treatment is anti-dopaminergic therapy, either with dopamine blockers such as neuroleptics or with dopamine depleters such as tetrabenazine. In extreme cases, functional neurosurgery can be performed; either lesioning or deep brain stimulation of the globus pallidus can be considered the treatments of choice. Most patients respond well to medical treatment and spontaneous resolution is common.

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Patient Vignettes

Patient 1

A 69-year-old man was followed at the Toronto Western Hospital with a 7-year history of Parkinson's disease. Other past medical history included diabetes, coronary artery disease, and a previous stroke involving the right frontal lobe. Two weeks before presentation he noticed the acute onset of involuntary movements of the left side, predominantly affecting the arm but also involving the leg and face. They tended to worsen soon after taking his levodopa. Clinical examination showed choreic movements of the left arm. Interestingly, the bradykinesia and rigidity were significantly ameliorated on the left side. MRI examination demonstrated an infarction of the posterior putamen and globus pallidus, extending upwards into the periventricular white matter (see Fig. 12.1). Dopaminergic medications were decreased, resulting in improvement of his symptoms. During his admission, he began to have spontaneous improvement in symptoms, and did not require therapy.

This case illustrates several points. The first is that although stroke is the commonest single cause of hemiballism, lesions are often outside of the subthalamic nucleus. The second is that prognosis is often benign. The third is that dopaminergic medications (in this case levodopa) worsen hemiballism, just as dopamine antagonists treat it. Finally we note the fortuitous effect of his stroke upon his Parkinson's disease, perhaps due to infarction of the motor GPi.

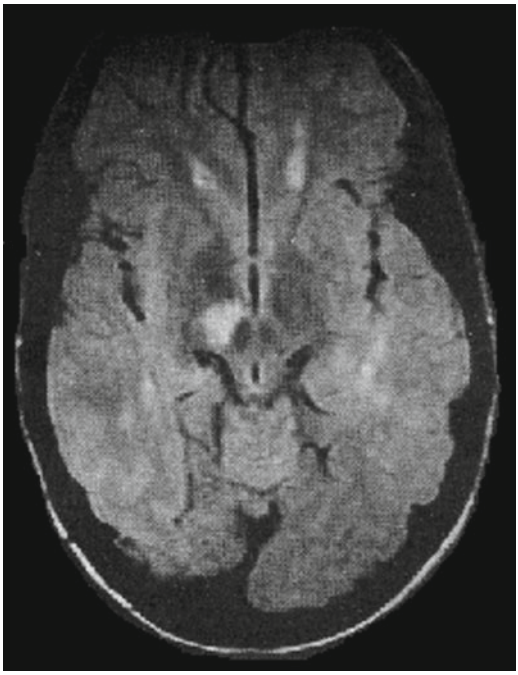

Fig. 12.1 Axial FLAIR and high resolution coronal T2-weighted (reprinted with permission [33])

Patient 2

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

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

Clinical Description and Epidemiology

Hemiballism is one of the most dramatic disorders in neurology. Because of its acute onset, it is frequently seen in the emergency room. Typically the patient presents with an acute or subacute onset of flinging movements of one side of the body. These tend to occur both in the arm and leg, with variable involvement of the face. Movements often have a rotatory component and usually predominantly affect proximal muscles. They can be severe enough to cause the patient to strike walls and bedrails, causing bruising and lacerations of the limb. Movements increase with action and stress, and are only rarely suppressible for more than a few seconds. They generally disappear in sleep. Hemichorea refers to movements that are similar in character but lower in amplitude, affecting both the distal and proximal limb. There is probably little pathophysiologic difference between the two movement disorders, as they share common etiologies, prognosis and treatment. In fact, they can often be present in the same patient, with hemiballism more prominent early and the lower-amplitude hemichorea emerging as the disorder resolves. Therefore, for the purposes of this chapter, we will consider them to be the same disorder, and will use the terms interchangeably. Bilateral ballistic movement (“bi-ballism,” or “paraballism” if lower limbs are predominantly involved) is very uncommon and occurs with bilateral CNS lesions.

Hemiballism is an uncommon disorder, and most general neurologists would not expect to see more than a handful of cases in their career. Dewey and Jankovic reported 21 patients with hemiballism out of 3,084 patients evaluated in a specialty movement disorder clinic [1]. Of 2,000 strokes in the Lausanne stroke registry, 550 involved basal ganglia structures but only 11 caused hemiballism [2]. A population-based study in

Serbia found an incidence of vascular hemiballism of 0.45 per 100,000 [3]. In most series the mean age of onset is between 55 and 75, although many series are derived from subspecialty clinics, which may be biased towards seeing younger, more atypical patients. There is no clear gender predominance.

Etiology

Historically, hemiballism has been classically considered one of the most localizable symptoms in neurology, pathognomonic of a lesion of the subthalamic nucleus (STN). This thinking has been based on the earliest pathological studies and on animal lesion studies, which suggested that hemiballism was reliably evoked by ablation of at least 20% of the subthalamic nucleus (see below). However, review of the more recent literature, particularly stroke literature, suggests that the subthalamic nucleus is not the site of the lesion in the majority of cases. Stroke is without question the single most common cause of hemiballism. It has become clear that hemiballism can be caused by infarcts or hemorrhages in a variety of locations both inside and outside the basal ganglia. Stroke causing hemiballism was localized to the subthalamic nucleus in only 4 of 27 cases with neuroimaging reported by Ristic, 4 of 27 reported by Chung, 4 of 22 reported by Vidakovic, 4 of 21 reported by Dewey and Jankovic, 4 of 11 in the Lausanne stroke registry, and 2 of 15 in our series at the Toronto Western Hospital [1, 2, 4–7]. However, since only CT imaging was performed in some, STN lesions could have been missed. There is some evidence that hemiballism is more severe and persistent when due to subthalamic nucleus lesions [5], which may have skewed early pathologic studies. Therefore, while stroke is the commonest cause of hemiballism, the minority of these infarcts involves the STN directly.

More recently attention has been drawn to hemiballism associated with non-ketotic hyperglycemia. With approximately 100 reported cases, it may be the second most common cause worldwide. The condition has been described most commonly in Asian populations. A typical patient is elderly, female, presenting with hemiballism and severe non-ketotic hyperosmolar hyperglycemia [8]. As the blood glucose is corrected the disorder usually resolves in days to weeks, although in 20% of patients milder symptoms persist for more than 3 months. Neuroimaging findings in these patients are striking. In all reported cases high signal is seen on T1-weighted images in the putamen, with similar signal occasionally found in the globus pallidus and remainder of the striatum [8]. Two thirds of patients also have high signal abnormalities on T2-weighted sequences, and some have corresponding abnormalities on diffusion-weighted imaging [8, 9]. PET scanning has demonstrated decreased glucose uptake, suggestive of metabolic failure/infarction [10]. Pathologic studies in two patients several months after symptoms resolved demonstrated significant gliosis, with microglial activation and presence of gemistocytic astrocytes [11, 12]. This might represent a reaction to microinfarction or incomplete infarction, although no blood vessel abnormalities were visualized. Two other

Table 12.1 Causes of hemiballism

Common
Stroke (ischemic or hemorrhagic) in basal ganglia structures
Non-ketotic hyperglycemia
Uncommon or single case reports
Focal lesions in basal ganglia
Neoplastic
Metastases
Other primary CNS tumors
Infectious
Cryptococcal granuloma
Toxoplasmosis
Tuberculoma
Vascular
Cavernous angioma
Postsurgical complications
Inflammatory
Multiple sclerosis
Iatrogenic
Subthalmotomy
Thalamotomy
Other mass lesions
Cerebellar metastases
Strokes in non-basal ganglia areas
Subcortical white matter
Middle cerebral artery territory
Immunologic disorders/Vasculitis
SLE—often with anticardiolipin antibodies
Scleroderma
Bechet's disease
Hypoglycemia
Meningitis/encephalitis
Cryptococcal
Tuberculous
Sydenham's chorea
Head injury
Medications (usually if superimposed on pre-existing basal ganglia lesion)
Anticonvulsants
Oral contraceptives
Levodopa
Ibuprofen

pathological cases have revealed more classic signs of infarction, and isolated activation of microglia in the subthalamic nucleus with no other signs of infarction [13, 14]. Therefore, the cause of this striking condition remains uncertain.

Numerous other causes of hemiballism have been reported, summarized in Table 12.1. These include mass lesions involving the basal ganglia or STN (often in

association with HIV infection), medications, and medical diseases that predispose to infarction or hemorrhage. A recent report of resolution of hemichorea in three patients with carotid endarterectomy for severe stenosis, suggests hypoperfusion can cause hemichorea [15].

Pathophysiology

Much of our understanding of the pathophysiology of hemiballism derives from classic animal models of lesions of the subthalamic nucleus. The original experiments were carried out by Whittier, Mettler, and Carpenter in 1949 and 1950 [16], in which lesions of the basal ganglia were created in primates and their behavioral effects monitored. Contralateral hemiballism could be reliably produced only by lesions that destroyed more than 20% of the STN. Lesions in some areas of the globus pallidus occasionally caused hemiballism, and it was postulated that these were due to disruption of connections to the STN. A second lesion to some areas of the globus pallidus interna (GPi) could abolish the movements. Crossman injected GABA antagonists, which affect neuronal cell bodies but not axons, into basal ganglia locations in alert monkeys, and again, only STN injections reliably caused hemiballism [17]. This confirms that the effects are due to lesions of neuronal cell bodies and not to passing white matter tracts. Injections in the lateral globus pallidus occasionally caused slower hemichoreic/hemiathetoid movements. This may be analagous to hyperglycemic hemichorea, in which the areas predominantly affected are the putamen and GPi, and movements tend to be slower than those after a lesion of the STN. It has been postulated that STN lesions interrupt the excitatory connections to the GPi, resulting in hypoactivity of the GPi. This disinhibits the motor thalamus, which in turn drives the motor cortex, resulting in excessive movement [18]. This simple model, which is based predominantly on neuronal firing rates, does not explain the mechanism of hemiballism caused by lesions outside of the STN, why movements are ballistic and intermittent, and why lesioning of the apparently hypoactive GPi is capable of abolishing hemiballism, nor does it adequately explain why dopamine antagonists, which target the striatum, are especially effective in treating hemiballism (see Sect. 6). Finally, it does not explain why subthalamotomy and subthalamic nucleus stimulation for Parkinson's disease are only very uncommonly complicated by hemiballism [19].

Some additional recent insights have come from electrophysiologic studies of three patients undergoing pallidotomy for hemiballism, in which microrecording of individual GPi neurons was obtained. All three had stroke, two localized to the STN and one with a much more extensive infarct [20–22]. The two cases with STN lesions had firing rates of GPi neurons that were lower than expected normal values, whereas the third had a rate within the normal range. However, all three demonstrated an altered firing *pattern*, with intermittent bursts followed by pauses. EMG examination demonstrated that for some individual GPi neurons, ballistic movements correlated with pauses in firing. This suggests that the temporal pattern of GPi neuronal activity

rather than the overall rate of firing is important in hemiballism, and that brief pauses in GPi firing may be responsible for the generation of ballistic movements.

Prognosis

In the early literature, hemiballism was thought to carry a grave prognosis. Exhaustion and self-injury could cause significant morbidity, and at a time when medical therapy was unavailable, measures as extreme as limb amputation were sometimes considered. However, it has become clear that the natural history of hemiballism is much more benign than previously thought, and numerous effective treatments are now available. Since most cases are treated medically, the natural history of hemiballism is unknown. Most cases will resolve spontaneously, usually in a few months to a year. Hyland and Foreman presented 14 patients with hemiballism, 12 of whom had spontaneous resolution within 3 months [23]. Similarly, 15 of 16 patients reported by Vidakovic had successful withdrawal of medication without recurrence [7], and in a series by Klawans, only 3 of 11 patients required long term perphenazine therapy [24]. As mentioned above, hemiballism associated with hyperglycemia usually improves over days. The tendency for hemiballism to spontaneously improve should be considered when planning treatment and when interpreting reports of responses to treatment in the literature.

Management

An algorithm for treating hemiballism is presented in Fig. 12.2. The first priority in the management of hemiballism is to look for reversible causes. Hyperglycemia, infectious and neoplastic lesions of the basal ganglia should be excluded. Treatment of the underlying cause may reverse the hemiballism, although severely affected patients may still require concomitant pharmacologic therapy. If stroke is the cause, standard stroke management such as anti-platelet therapy and secondary preventive measures such as blood pressure control and normalization of blood sugar must be implemented. The next step is to decide whether hemiballism is severe enough to warrant therapy. As mentioned previously, many cases will be mild and the majority of these will improve spontaneously. If therapy is required, non-pharmacologic therapy, such as padding of the affected limb should be considered. In severe cases, attention should be paid to systemic complications such as exhaustion, dehydration, and rhabdomyolysis. In the very rare case of extremely severe hemiballism causing dangerous complications, patients may require sedation or even intubation with neuromuscular blockade as a temporary bridge until effective pharmacologic therapy is instituted.

Anti-dopaminergic therapy is the mainstay of treatment for hemiballism. The best-studied medications are typical neuroleptics such as haloperidol, perphenazine, pimozide, and chlorpromazine [24, 25]. However, dopamine-depleting drugs,

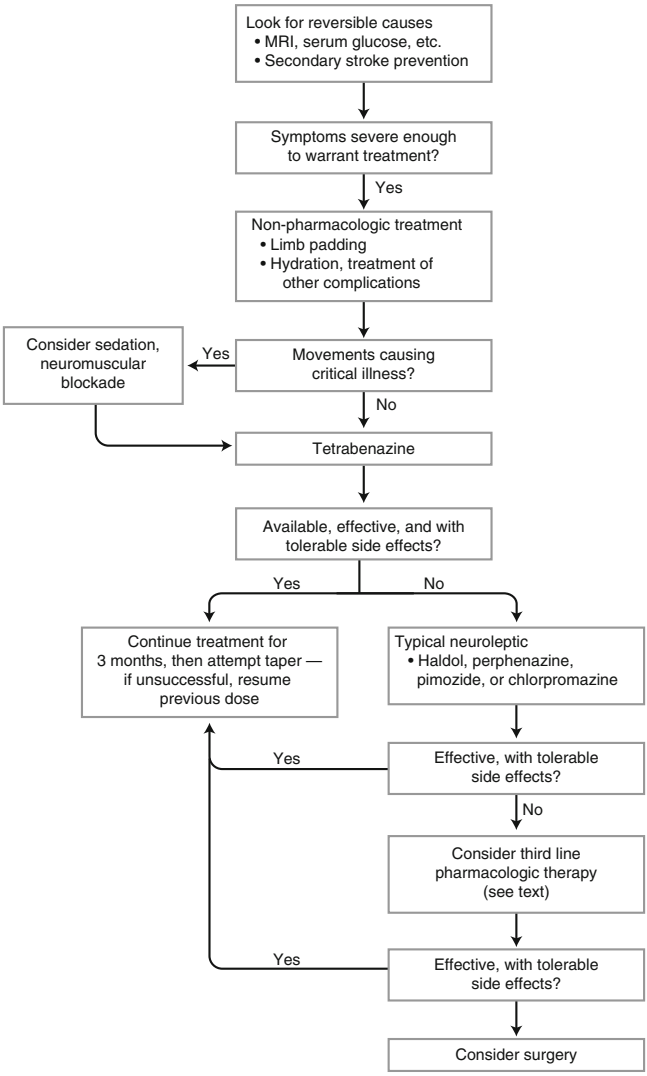

Fig. 12.2 Treatment algorithm (reprinted with permission [33])

particularly tetrabenazine, can also produce marked benefit similar to that obtained with neuroleptics [6, 26]. Given the minimal risk of tardive dyskinesia or acute dystonic reactions associated with its use, tetrabenazine is our preferred treatment for patients with persistent hemiballism who require ongoing dopaminergic blockade. Dosage can start at 12.5 mg TID and be titrated upwards to a maximum of approximately 150–200 mg per day. The speed of the titration and the maximum dose depends on the severity of symptoms and the initial response to therapy. Clinicians should remain vigilant for the side effects of depression, orthostatic

hypotension, parkinsonism, and akathisia. Blood pressure reduction may be a dose-limiting side effect if rapid titration is required for severe hemiballism.

If tetrabenazine is unavailable, ineffective, it causes severe side effects, or if the patient has a history of severe depression, typical neuroleptics should be tried. Although there are a wide variety of neuroleptics that may work, we favor haloperidol, starting at a dose of 0.5–1 mg BID, and titrating upwards as needed. In emergency situations, this can be given as an intramuscular dose of 1 mg, and if ineffective, 2 mg can be given 4 h later. If there is still no improvement, 4 mg q4 h or even higher doses can be used, with subsequent attempts at downward titration if movements are successfully suppressed [27]. In urgent situations, tetrabenazine and haloperidol can be given together, to take advantage of their different mechanisms of action. The side effects of typical neuroleptics are well known, and will not be elaborated on further. However, one somewhat unique problem encountered with dopamine antagonists in hemiballism, especially in the elderly, is the development of drug-induced parkinsonism on the non-hemiballistic side. When this problem occurs before substantial benefit to the hyperkinetic movements, one may see an impressive combination of persistent hemiballism and contralateral parkinsonism, both causing disability.

Response rates to dopamine-antagonist drugs are on the order of 90%, with quite dramatic reductions often achieved [2, 24, 25]. If typical neuroleptics fail, it is unlikely that other medications will have a dramatic effect. However, positive results have also been obtained with atypical neuroleptics such as risperidone, olanzapine and clozapine, and with other presynaptic dopamine-depletors such as reserpine [6]. In addition, there have been reports of effective treatment with clonazepam, valproic acid, levetiracetam, topirimate, gabapentin, trihexyphenidyl, and amitriptilline [6, 28–31]. Although use of amantadine has not been documented in hemiballism, its utility in chorea associated with Huntington's disease and levodopa-induced dyskinesia suggest that it may be helpful. As noted above, carotid endarterectomy may be effective for hemichorea in some cases of severe carotid stenosis [15].

If effective, treatment should be maintained for a period of approximately 3 months after which the medication should be gradually withdrawn. It is likely that the majority of patients will not have a significant recurrence. If pharmacologic therapy is ineffective and patients have severe unremitting hemiballism for at least 3 months (or shorter, if symptoms have life-threatening consequences), surgical intervention may be appropriate. The procedure with the greatest reported experience is ventrolateral nucleus thalamotomy, with just under 30 patients reported. Here the lesion is placed in the VA/VL thalamus (the region that receives basal ganglia (GPi, SNr) outflow) in contrast to the ViM thalamotomy used for tremor (which is directed more posteriorly to areas that receive cerebellar input). Krauss and Mundinger have reported the largest series, with 13 patients followed more than 3 years [32]. Eleven of these thirteen patients had significant improvement in their hemiballism. Side effects were few, with one patient suffering a transient hemiparesis, and two with mild persistent dystonia. Another good option is GPi pallidotomy, with numerous case reports of successful treatment [20, 22, 32]. No large-scale series exist to thoroughly evaluate the efficacy of this approach. Finally, with the

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

Conclusion

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

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Chapter 13
Sydenham's Chorea, PANDAS, and Other Post-streptococcal Neurological Disorders

Roser Pons

This chapter contains video segments that can be found on the accompanying DVD.

Abstract Sydenham's chorea is a post-streptoccocal movement disorder and one of the major criteria for the diagnosis of rheumatic fever. The likely pathophysiological mechanism involves induction, as a response to the infection, of antibodies that cross-react with the basal ganglia. Anti-basal ganglia antibodies are found in 45–100% of patients with Sydenham's chorea, and their levels correlate with disease activity.

Further post-streptococcal non-rheumatic neurologic disorders include the contested condition PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection) and other diseases such as disseminated encephalomyelitis with basal ganglia lesions; acute myoclonus; isolated striatal necrosis; paroxysmal dystonic choreoathetosis; acute parkinsonism; and the opsoclonus-myoclonus syndrome. In many of these conditions, antineuronal antibodies are detected raising the hypothesis of a common autoimmune pathophysiological mechanism.

The symptoms of Sydenham's chorea, PANDAS, and other post-streptococcal CNS disorders can evolve rapidly, often requiring prompt intervention. Management of post-streptococcal CNS disorders includes symptomatic treatment of the acute movement disorder and/or psychiatric problem; antibiotic therapy; and immunotherapy.

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Patient Vignette

Patient 1

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

Introduction

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

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

Recent reports have suggested that the spectrum of post-streptococcal central nervous system (CNS) disease is broad, including a number of hyperkinetic movements and behavioral abnormalities. A subgroup of patients with acute disseminated encephalomyelitis with basal ganglia lesions, dystonia, and emotional lability associated with streptococcal infection was identified [6]. Other reports of post-streptococcal CNS disorders include acute myoclonus [7], dystonia with isolated striatal necrosis [8], paroxysmal dystonic choreoathetosis [9], acute parkinsonism [10], and opsoclonus myoclonus [11]. These reports, together with the finding of antineuronal antibodies in many of these diseases, have raised the hypothesis of a common autoimmune pathophysiological mechanism [12].

Clinical Features and Diagnosis

Sydenham's Chorea

Sydenham's chorea is the neurological manifestation of RF. A major criterion for the diagnosis of acute RF, chorea alone is sufficient to make this diagnosis [2]. Up to a quarter of acute rheumatic fever cases develop Sydenham's chorea, though this proportion varies according to temporal and geographic factors [13–15]. Usually Sydenham's chorea begins after a prolonged latent period following group A streptococcal infection. Generally, patients develop chorea 4–8 weeks after an episode of streptococcal pharyngitis [16], but a delay of several months has also been described [17]. Chorea may begin acutely or subacutely. The age of presentation ranges from 5 to 15 years, and there is a female preponderance [13–19] (Table 13.1). The main features of Sydenham's chorea are involuntary, random, purposeless, nonrhythmic, sudden, brief movements. They flow from one body part to another, and patients often appear restless. Chorea spreads rapidly, although in 20–30% of cases it remains unilateral [13, 16, 18, 19]. Chorea is often severe enough to be disabling, and in rare cases may prevent the patient from walking [13, 18]. Patients display motor impersistence, noticeable during tongue protrusion or when sustaining muscle contraction. Muscle tone is usually decreased. In rare cases, symptoms are so severe that the patient becomes bedridden (so-called paralytic chorea).

Other neurological features include dysarthria, weakness, clumsy gait, hypometric saccades, and hung-up reflexes [13, 17]. Motor and vocal tics can also occur, and oculogyric crises have been reported [13].

Psychiatric symptoms are common in Sydenham's chorea. These include obsessive-compulsive symptoms, attention deficit hyperactivity disorder (ADHD), major depressive disorder, and separation anxiety [3, 20, 21]. Clinical features of RF accompanying chorea, such as cardiac involvement, have been reported in 10–84% of patients [13, 14]. Arthritis is seen in up to 30% [13]. Sydenham's chorea is a self-limited condition, usually spontaneously remitting after 2–6 months [17, 18]. In some patients it may last up to 2 years, and in rare cases it persists [14, 22]. Chorea may recur, and the incidence of recurrences may be as high as 20–60% [14–18] (Table 13.1). Recurrences may be induced by reinfection with *Streptococcus*, birth control pills, and pregnancy ("chorea gravidarum").

Diagnosis relies on clinical findings of acute chorea with a history of prior *Streptococcus* infection. Because chorea is generally a late manifestation of RF, it is unusual to find clinical evidence of acute streptococcal infection [2]. Elevated acute-phase reactants and antistreptococcal antibodies (antistreptolysin O, antiDNAse-B antibodies) may be absent in patients with isolated chorea [15, 18]. The electroencephalogram may show nonspecific abnormalities [19], and brain magnetic resonance imaging (MRI) is usually normal, although reversible hyperintensities in the basal ganglia have been reported [23, 24] (Table 13.1).

Table 13.1 Clinical spectrum of post-streptococcal movement disorders

	Sydenham's chorea	PANDAS	Post-streptococcal acute disseminated encephalomyelitis [6]	Post-streptococcal myoclonus [7]	Post-streptococcal isolated bilateral striatal necrosis [8]	Post-streptococcal paroxysmal dystonic choreoathetosis [9]	Post-streptococcal parkinsonism [10]	Post-streptococcal opsoclonus myoclonus syndrome [11]
Age	5–15 years	3–8 years	3–14 years	5–12 years	1–4 years	8 years	17 years	10–16 years
Gender	F>M	M>F	M>F	M	M	M	M	F
Onset	Acute/subacute	Acute	Acute	Acute	Acute	Acute paroxysmal	Acute	Acute
Movement disorders	Chorea	Tics	Dystonia	Myoclonus	Dystonia	Chorea	Akinetic-rigid syndrome	Opsoclonus
	Tics	Choreiform movements	Tremor		Rigidity	Dystonia	Tremor	Myoclonus
			Rigidity		Tremor			Ataxia
			Paroxysmal dystonia		Chorea			
Psychiatric disorders	OCD, anxiety, major depression, ADHD	OCD, anxiety, major depression, ADHD	Emotional lability, disinhibition, perseverations, inattention, separation anxiety, confusion	Aggression, hyperactivity	Emotional lability	Immature behavior, separation anxiety, depression	NR	Insomnia, auditory hallucinations, disinhibition, anxiety, low mood
↓Level of consciousness	–	–	50%	–	50%	–	–	–
Exacerbations/ recurrences	20–60%	100%	20%	33%	–	+	–	–
Heart involvement	+(up to 48%)	–	–	–	–	–	–	–
↑ASO	±	+	+	+	+	+	+	+
Antineuronal antibodies	+	+	+	NR	+	+	+	+
Brain MRI	Normal	Normal	Basal ganglia demyelinating lesions	Normal	Striatal abnormalities	Normal	Increased BG signal	Normal
	Increased BG signal	Enlarged BG						
	Enlarged BG							

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

PANDAS

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

In 1998, Swedo [5] reported clinical features of the first 50 patients diagnosed with PANDAS. The age of presentation ranged from 3 to 10 years, with a male preponderance. Forty-eight percent of the patients presented with acute obsessive-compulsive symptoms, and fifty-two percent presented primarily with motor and vocal tics. The severity of obsessive-compulsive symptoms and tics was moderate on average, and comorbid psychiatric symptoms were common. Patients typically presented abruptly, with significant distress. The most prevalent psychiatric diagnoses were ADHD, affective disorders, and anxiety disorders. Choreiform movements described as small, jerky movements occurring irregularly and arrhythmically in different muscles were noted in half of the patients. No child had overt chorea [5]. The clinical course was episodic, characterized by a waxing and waning course and abrupt onset of symptoms. Symptom onset and exacerbations were temporally related to preceding streptococcal infection. Such infection was not always proven, although each child had at least one symptom exacerbation that was preceded by a documented streptococcal infection within the prior 6 weeks [5] (Table 13.1).

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

Post-streptococcal Acute Disseminated Encephalomyelitis

Acute disseminated encephalomyelitis is a postinfectious or postvaccination inflammatory disease of the CNS. The pathological hallmark is scattered foci of demyelination throughout the brain and spinal cord. Various viral and bacterial pathogens have been associated with this condition [25]. A subgroup of patients with acute disseminated encephalomyelitis associated with streptococcal infections had been reported [6]. Recently, Dale [6] presented ten patients with post-streptococcal acute disseminated encephalomyelitis. Extrapyramidal manifestations were present in 50% of the patients: four had dystonia, three had axial and limb rigidity, and two had resting tremor. Behavioral problems were seen in seven patients. Streptococcal serologies were significantly elevated in all patients, and 80% showed basal ganglia lesions on neuroimaging. Thalamus, subthalamus, and substantia nigra were also involved in 60, 30, and 50% of the cases, respectively (Table 13.1).

Post-streptococcal Acute Myoclonus

In 1998, three patients with acute-onset myoclonus following streptococcal infection were reported [7]. Myoclonus was generalized in two patients and segmental in another. In one patient, myoclonus was associated with behavioral change, including aggression and hyperactivity. Streptococcal serologies were elevated in all patients (Table 13.1).

Post-streptococcal Autoimmune Dystonia with Isolated Striatal Necrosis

Bilateral striatal necrosis is an acute-onset extrapyramidal disorder that may occur following a variety of infections. Neuroimaging shows symmetric lesions in the striatum [26]. Two patients with isolated striatal necrosis occurring shortly after a streptococcal pharyngitis were reported [8]. One patient presented with an acute neurological illness, with weakness, ataxia, and dystonic posturing followed by rigidity and tremor, oropharyngeal incoordination, and generalized chorea. The second patient presented with lethargy, episodic dystonic posturing, ataxia, and emotional lability. Cerebrospinal fluid protein concentration was elevated in both patients. Brain MRI showed selective striatal abnormalities. Streptococcal serologies were elevated and convalescent serology showed a reduction in titers (Table 13.1).

Post-streptococcal Paroxysmal Dystonic Choreoathetosis

There is one reported case of paroxysmal dystonic choreoathetosis occurring 1 week after a streptococcal pharyngitis [9]. This patient presented with acute onset of paroxysmal episodes of dystonic posturing, choreoathetosis, visual hallucinations, and immature behavior lasting minutes to hours. The episodes occurred several times per day, and symptoms fluctuated, lasting 6 months. Streptococcal serologies were elevated, and convalescent serologies showed a reduction in titers (Table 13.1).

Post-streptococcal Parkinsonism

There is a recent report of a young man who presented with a severe acute akinetic-rigid disorder 2 weeks after an episode of pharyngitis. Magnetic resonance imaging showed abnormalities localized to the basal ganglia. There was serological evidence of recent streptococcal infection and presence of anti-basal ganglia antibodies in the serum [10] (Table 13.1).

Post-streptococcal Opsoclonus-Myoclonus Syndrome

Two case of post-streptococcal opsoclonus-myoclonus syndrome have also been recently described [11]. Both patients experienced a prodromal upper respiratory tract illness with elevated ASO. In addition to the opsoclonus-myoclonus syndrome they both presented with psychiatric disturbances. Brain MRI was normal and neither had evidence of an underlying tumor. They both had evidence of anti-neuroleukin antibodies [11] (Table 13.1).

Pathophysiology

The basal ganglia are believed to be the source of the problem in Sydenham's chorea and other post-streptoccocal movement disorders. This is supported by the known role of the basal ganglia in motor and behavior control, and by postmortem and neuroimaging studies in patients with Sydenham's chorea. Early pathological reports of Sydenham's chorea showed inflammatory changes involving the basal ganglia and, to a lesser extent, the cortex [1]. MRI has shown signal abnormalities in the striatum in some patients with Sydenham's chorea [23, 24]. Abnormal striatal spectra consistent with neuronal damage have been reported in one patient with Sydenham's chorea [24]. Volumetric studies have demonstrated enlargement of the caudate, putamen, and pallidum in patients with Sydenham's chorea and PANDAS [23, 27]. Furthermore, patients with post-streptococcal acute disseminated encephalomyelitis showed basal ganglia lesions in 80% of the cases [6] and bilateral striatal lesions were noted in the patients with post-streptococcal autoimmune dystonia with isolated striatal necrosis [8], and in the patient with acute parkinsonism [10]. Single-photon emission computed tomography studies have also revealed hyperperfusion of the basal ganglia in some patients with Sydenham's chorea [28].

Particular serotypes of the group A β-hemolytic *Streptococcus* are involved in RF and post-streptococcal disorders. The likely mechanism involves induction of antibodies to the infection that cross-react with the basal ganglia. This is supported by the induction of such antibodies when rats are immunized with the major virulence factor of group A *Streptococci* (surface M protein) [12]. Anti-basal ganglia antibodies have been found in 45–100% of patients with Sydenham's chorea, and their levels correlate with disease activity [29, 30]. A recent study showed that these antibodies possessed specific immunoglobulin binding sites for large striatal neurons, and that the binding was confined to tracts of neurons in the caudate head [31]. Anti-basal ganglia antibodies have also been reported in other post-streptococcal disorders, including PANDAS, acute disseminated encephalomyelitis, paroxysmal dyskinesias, striatal necrosis, and acute parkinsonism [6, 8–10, 32].

Recently, a study of monoclonal antibodies derived from a Sydenham's chorea patient and selected for cross-reactivity with group A streptococci, allowed the identification of specific neuronal target antigens in Sydenham's chorea [33].

These neuronal targets corresponded to the intracellular brain protein tubulin and extracellular lysoganglioside. Interestingly, chorea antibodies lead to the specific induction of calcium/calmodulin-dependent protein kinase II thus providing new evidence implicating antibody-mediated neuronal cell signaling in the immunopathogenesis of Sydenham's chorea [33].

Given the fact that RF and Sydenham's chorea are more common in first-degree relatives of affected patients [12], and the fact that obsessive-compulsive disorder and tics are more common in family members of PANDAS patients [34], an underlying genetic predisposition has been proposed. The B-lymphocyte marker D8/D17 has been detected in high levels in patients with RF, Sydenham's chorea, and PANDAS supporting this concept [35, 36]. The biological function of this marker remains undefined. In fact, it is fair to say that the relationship of streptococcal infection with post-streptococcal CNS syndromes other than Sydenham's is controversial. Evidence of current or recent streptococcal infection in school children in winter is common, and symptom exacerbations related to streptococcal or other infections may represent a nonspecific response to stress [37]. In addition, unlike Sydenham's chorea, no correlation between the production of autoantibodies and severity of symptoms has been demonstrated, and no features of RF have been reported to date.

Treatment

The symptoms of Sydenham's chorea, PANDAS, and other post-streptococcal CNS disorders can evolve rapidly, often requiring prompt intervention. Management of post-streptococcal CNS disorders is discussed in these settings (Table 13.2): (1) symptomatic treatment of the acute movement disorder and/or psychiatric problem, (2) antibiotic therapy, and (3) immunotherapy.

Sydenham's Chorea

Symptomatic Treatment

Sedatives, anticonvulsants, and neuroleptics have been used in the symptomatic management of Sydenham's chorea. Valproic acid is the anticonvulsant most widely used for the treatment of Sydenham's chorea. Several reports have shown that valproic acid is effective for the treatment of Sydenham's chorea, at doses of 10–25 mg/kg/day [19, 38, 39]. Patients who respond to valproic acid may show a marked reduction of involuntary movements within 1 week of treatment, although slower onset of action has also been reported [38]. Treatment is usually given for 4–8 weeks, although in cases where symptoms recur, patients may need to be treated for a longer period [38]. Carbamazepine has also been reported as a successful treatment for

Table 13.2 Treatment options reported in post-streptococcal movement disorders[a]

	Sydenham's chorea	PANDAS	Post-streptococcal acute disseminated encephalomyelitis [6]	Post-streptococcal myoclonus [7]	Post-streptococcal isolated bilateral striatal necrosis [8]	Post-streptococcal paroxysmal dystonic choreoathetosis [9]	Post-streptococcal parkinsonism [10]	Post-streptococcal opsoclonus myoclonus syndrome [11]
Symptomatic treatment	First line: Valproic acid Carbamazepine Second line: Pimozide Haloperidol	Serotonin reuptake inhibitors Clonidine Neuroleptics	NR	NR	NR	Carbamazepine	None	None
Antibiotic therapy for streptococcal acute infection		Penicillin Cephalosporin		+	+		Erythromycin	Penicillin
Antibiotic therapy for prophylaxis	B Penicillin Penicillin V Sulfadiazine	Penicillin	Penicillin	–	+	+	–	–
Immunotherapy	Steroids Immunoglobulin	Plasma exchange Immunoglobulin	Steroids	NR	Steroids	NR	Steroids Immunoglobulin	Steroids

NR nor reported, + antibiotic treatment was not specified in these reports, *PANDAS* pediatric autoimmune neuropsychiatric disorder associated with streptococcal infections

[a]Except for antibiotic prophylaxis in Sydenham's chorea, there are not routine treatment guidelines for the management of poststreptococcal movement disorders

Sydenham's chorea [40]. A non-controlled study of low-dose carbamazepine (4–10 mg/kg/day) showed improvement of chorea in 2–14 days. Treatment was continued for 1–15 months [41]. Recently, two prospective studies suggested that valproic acid and carbamazepine have similar efficacy and safety in this patient population [19, 39].

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

Antibiotic Treatment

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

Immunotherapy

Immunomodulatory treatment is not routinely used in patients with Sydenham's chorea. However, corticosteroids have been successfully used in severe cases [38, 45]. One uncontrolled prospective study showed marked improvement of chorea within a few days of treatment. The duration of treatment ranged from a few days to 1 month. One patient experienced a recurrence of chorea after discontinuation of treatment, requiring a total of 3 months of steroid therapy [45]. Although there are no guidelines for immunotherapy in Sydenham's chorea, it is considered reasonable to try a short course of steroids in severe cases in which symptoms fail to respond to conventional treatment.

The role of intravenous immunoglobulin for the treatment of Sydenham's chorea has been recently investigated. A randomized controlled study was designed to determine if intravenous immunoglobulin or plasma exchange would be superior to prednisone in decreasing the severity of chorea. Although the differences between groups were not statistically significant, due to small patient numbers, clinical improvements were more rapid and robust in the intravenous immunoglobulin and

plasma exchange groups than in the prednisone group. So, although further studies are needed, it appears that intravenous immunoglobulin may become an alternative to steroids in the treatment of severe Sydenham's chorea [46].

PANDAS

Symptomatic Treatment

The neuropsychiatric symptoms of PANDAS at onset or during acute exacerbations may be severe [47]. Symptomatic treatments include serotonin-specific reuptake inhibitors for obsessive-compulsive symptoms, and clonidine and neuroleptics for tics. However, often patients are refractory to treatment with standard agents [48].

Antibiotic Treatment

A recent, prospective study of patients with new-onset PANDAS and documented Streptococcal infection (using penicillins or cephalosporins) produced improvement of the neuropsychiatric symptoms within 5–21 days [45]. A double-blind crossover study comparing penicillin prophylaxis to placebo in patients with PANDAS failed, however, to show any change in symptom severity. The authors raised the possibility that failure to achieve acceptable antibiotic prophylaxis may have explained the negative results [49].

Immunotherapy

A double blind, randomized, placebo-controlled study compared either plasma exchange or intravenous immunoglobulins with placebo in a group of 30 patients with severe neuropsychiatric symptoms meeting criteria for PANDAS [48]. One month after treatment, patients who received plasma exchange or intravenous immunoglobulins showed significant improvement in obsessive-compulsive symptoms and psychosocial functioning. The plasma exchange group showed significant improvements in tic severity, whereas the intravenous immunoglobulin group did not. The beneficial effect was noted at the end of the first week in patients who received plasma exchange and at 3 weeks in the patients receiving intravenous immunoglobulins. Benefits of treatment were maintained at 1 year in both groups. Based on this single study, it appears that immunotherapy may be beneficial in select cases. The authors were careful to stress that their study did not provide support for generalized routine use. The decision to use immunomodulatory therapy in children must be balanced with the potential immediate and long-term risks of treatment.

Post-streptococcal Acute Disseminated Encephalomyelitis

Of the ten reported patients with post-streptococcal acute disseminated encephalomyelitis, nine were treated with intravenous methylprednisolone for 3 days [6]. This was followed by rapid clinical improvement in all treated patients, and subsequent relapse in two patients several months after presentation. Patients who relapsed were given penicillin prophylaxis to minimize the occurrence of further relapses [6].

Post-streptococcal Acute Myoclonus

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

Post-streptococcal Autoimmune Dystonia with Isolated Striatal Necrosis

Of the two reported patients with post-streptococcal striatal necrosis, one was treated with antibiotic prophylaxis and oral prednisolone with significant improvement over several weeks. The second patient was treated with antibiotics, with improvement of symptoms within a few days [8].

Post-streptococcal Paroxysmal Dystonic Choreoathetosis

In the reported patient with paroxysmal dystonic choreoathetosis associated with streptococcal infection, there was no response to antibiotic prophylaxis. Chlorpromazine also failed, whereas carbamazepine decreased the number of attacks [9].

Post-streptococcal Parkinsonism

The reported case of post-streptococcal parkinsonism was treated with high doses of intravenous steroids and immunoglobulins. He improved steadily over the following weeks and had a full recovery [10].

Post-streptococcal Opsoclonus-Myoclonus Syndrome

The two reported cases of post-streptococcal opsoclonus-myoclonus syndrome were treated with steroids. One case improved steadily while the other was resistant to the initial treatment and required prolonged steroid treatment [11].

Conclusion

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

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Chapter 14
Emergencies in Huntington's Disease

Kathleen M. Shannon

Abstract Huntington's disease is a rare, dominantly inherited degenerative disease of the central nervous system characterized by gradually progressive motor and cognitive impairment and a panoply of psychiatric manifestations. Emergencies in HD generally relate to complications of immobility (respiratory disorders and injuries due to falls), or to acute psychiatric morbidity or complications of psychiatric treatment. Clinicians must remain vigilant to acute changes in HD, since clinical changes may be wrongly attributed to the underlying disease, and patients themselves may have reduced awareness of their symptoms or their complications. Emergencies in HD may cause premature death or contribute to poor quality of life in this population.

Patient Vignette

A 53-year-old man with a 4-year history of symptomatic Huntington's disease was evaluated in clinic in the company of his daughter. Divorced and retired, he lived alone and took care of all of his activities of daily living, including balancing his checkbook, shopping, cooking, and cleaning. At his office visit, his daughter reported that he was doing well, and he had no new complaints. He was not currently taking any medications.

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The covering physician received a panicked call from the daughter the morning of New Year's Day. She reported that she had visited her father at his apartment the night before, and that he became argumentative and violent without provocation. He proceeded to turn over chairs and the kitchen table, made threatening remarks to her, and even gesticulated as if he were going to hit her. She became fearful for her safety and called the police. While waiting for them to arrive, her father proceeded to straighten up his apartment, so that no evidence of a disturbance was present when the police arrived. When interviewed by the police, he appeared calm and cooperative, and his daughter decided not to press charges. The following morning, she called the covering physician, confused and distressed about what had happened.

The covering physician called the patient at his home, and convinced him to come to the hospital emergency room, where he was evaluated by the neurology and psychiatry services. When directly questioned, he admitted to episodes of impulsive anger, and also to feelings that his family was trying to harm him, or to "take his money and put him away." He was admitted to the hospital, and olanzapine was begun, with marked improvement in these feelings. Follow-up care with visiting nurse services and support for his daughter allowed him to return home to independent living.

Introduction

Huntington's disease (HD) is a dominantly inherited neurodegenerative disease with progressive disabilities in three spheres of function: movement, cognition and behavior. The disease prevalence is 4–7 per 100,000 in most nations, though it is less frequent in Africa and Japan [1]. Disease onset is usually in the fourth to fifth decades, but onset across the lifespan even in infancy or old age has been observed [2–4]. Following a period of clinical normalcy, patients progress through a 10–20 year period of gradual decline that is not clinically perceptible but can be demonstrated using sensitive experimental measures of brain volume, motor function, cognition, and psychiatric function [5–7]. Subtle but definite motor, behavioral, and cognitive signs emerge from this transitional period, and include clumsiness, mild chorea, difficulty with complex cognitive tasks and affective or personality changes. Although predominantly behavioral or cognitive presentations of HD are well recognized, current criteria for clinically manifest disease are anchored in the presence of a clinically typical extrapyramidal motor syndrome.

The motor illness changes in appearance across the spectrum of progression. Chorea may be very subtle at first, but increases over the course of the illness, often reaching a plateau in mid-stage disease. Chorea severity may actually decline in later stage disease. However, with disease progression, rigidity, bradykinesia, and dystonia assume increasing importance, and in many patients these movement disorders come to predominate over time [8]. The motor picture in end-stage disease includes severe dysarthria and dysphagia, very slow and poorly coordinated movement, severe postural abnormality even when seated, and inability to stand or walk [8].

The cognitive disorder reflects subcortical pathology, with deficits in attention and concentration, processing speed, multitasking, planning and organization, problem solving, and visuoperceptual abnormalities [9, 10]. Cognitive changes lead to loss of work and driving and contribute to loss of function and poor quality of life in HD. The cognitive disorder progresses to a global dementia in late-stage disease [11]. It is well recognized that HD patients have decreased awareness of all aspects of their clinical state.

Behavioral and psychiatric changes include abnormal affect (especially depression), personality change, irritability or aggression, anxiety, apathy, and rarely psychosis [12]. Behavioral changes may begin very early in the illness, often before clinically manifest motor changes. Unlike the motor and cognitive changes in HD, behavioral changes do not progress in a linear fashion. Thus, aberrant behaviors can arise suddenly and unexpectedly, and may respond to drugs or other therapies [13, 14].

When HD begins before the age of 21 (juvenile HD), a relatively rare phenomenon, the motor phenotype is characterized by bradykinesia, rigidity, dystonia, myoclonus, and often seizures [4].

Eventually every patient with HD requires 24 hour supervision and assistance with all daily tasks. For many, this level of care is possible only in an institutional setting. Nursing home placement is predicted by more severe motor impairment (especially gait abnormality and bradykinesia), and is usually permanent [15, 16]. Disease duration at death averages about 17 years [17].

Emergencies in HD

Given its chronic progressive nature, there is little published literature on a glimpse into the types of emergencies encountered in HD care. In one study of 3,612 hospitalizations in HD patients, 22% were related to respiratory illness, 10% to urinary tract infection or sepsis, and 6% to trauma. Twenty-one percent were related to psychiatric diagnoses [18]. Death certificate studies in HD reveal that important causes of death are pneumonia and choking, nutritional deficiency, chronic skin ulcer and debility, and mental disorders [19, 20]. These studies suggest that emergencies in HD generally result from (1) complications of the movement disorder, or (2) psychiatric and behavioral changes or sequelae of their management.

Complications of the Movement Disorder

Important complications of the movement disorder include consequences of disordered swallowing, such as aspiration and choking, and traumatic injuries, mainly related to falls.

Pneumonia and Aspiration Pneumonitis

Pneumonia and aspiration pneumonitis are important complications of HD, together accounting for almost 20% of hospitalizations and 42% of deaths in HD [18, 20]. The in-hospital mortality of respiratory disease in HD is about 7% and more than half of the survivors who had previously lived at home enter institutional care after discharge [18].

The importance of respiratory disease in HD relates to the prominence of dysphagia in the illness. While there are no published data on the prevalence of dysphagia by illness stage or on the progression of dysphagia, the literature is clear that dysphagia is universal in middle to late-stage HD. Descriptive series suggest dysphagia in HD reflects both hyperkinetic (chorea, repetitive swallow, inability to stop respirations) and hypokinetic (mandibular rigidity, slow lingual movements, coughing and choking) features [21]. The combination of hyperkinetic and hypokinetic motor abnormalities, cognitive decline and behavioral changes causes complex disorders of eating and feeding. Abnormalities have been noted in almost every aspect of eating and swallowing. These abnormalities include features related to eating (poor posture, rapid and impulsive feeding and poor tongue control), and oral (poor coordination, repetitive swallow, oral residue) and pharyngeal (coughing, choking, and aspiration) functions [22].

Pneumonia and pneumonitis may require intravenous antibiotics and respiratory therapy. The development of this illness should also prompt a speech therapy assessment for swallowing, and often requires a formal swallowing study. It is thought that aspiration risk can be reduced by supervised or assisted feeding and by swallowing therapy, but there is a scant evidence base to support these contentions [21]. Pneumonia risk coupled with malnutrition in late stage disease prompts the consideration of percutaneous feeding tube insertion for most patients in later stage HD. Published indications for a feeding tube include weight loss greater than 10% over 1 month, dehydration, repeated aspiration and severe dysphagia [23]. The frequency of feeding tube uptake in the HD community is unknown, but it is far from universal, and there are many factors to consider before making a decision including the patient's expressed wishes regarding artificial feeding.

In addition to the risk of aspiration pneumonitis, there is a risk of asphyxiation from acute choking. The combination of a healthy appetite, impulsivity, cognitive impairment, and deranged swallowing can precipitate an acute choking emergency. Attention to the size and consistency of food, and supervised or assisted feeding reduce the risk of this calamity. Caregivers are well advised to seek training in acute first aid including an approach to choking.

Trauma

Trauma accounts for about 5% of HD hospital admissions, and is associated with 2% in-hospital mortality, and high likelihood of discharge to a long term care facility [18].

Falls are an important cause of these injuries in HD. One study of 45 early- to mid-stage HD patients showed 75% had fallen at least once in the preceding year, and 40% had one or more falls over the subsequent 3 months. HD causes a complex gait disorder that includes progressive slowing, shortening of stride length and reduced cadence with increased double-support time and base of support. There is significant and progressively increasing variability in all these measures as well [24]. Impulsivity and poor judgment contribute to fall risk, and HD falls are associated with poorer motor function, more aggression and worse cognition [25]. The most important sequelae of trauma in HD are intracranial injuries and fractures, but open wounds, dislocations and crushing wounds are also seen.

Intracranial injuries prompt nearly half of acute hospitalizations for HD [18]. Many of these admissions were likely for subdural hematoma (SDH). SDH refers to a neurosurgical condition in which blood accumulates in the potential space between the arachnoid membranes and dura mater. It is a somewhat common neurosurgical condition that is usually caused by tearing of the veins that carry blood from the cortical surface to the dural sinuses or by rupture of small cortical arteries [26, 27]. Acute SDH usually present within a few days of a significant head injury, while chronic SDH generally present more than 3 weeks from the ictus and tend to be associated with more minor head injury. Age, male gender, alcoholism, cerebral atrophy, and use of anticoagulants are risk factors for SDH.

Cerebral atrophy coupled with a tendency to fall in HD predisposes these patients to the development of SDH (see Fig. 14.1). In one center, nearly 7% of 58 cases of subdural hematoma surgeries occurred in patients with HD. About 2.5% of their chronic HD population developed SDH [20, 28]. SDH may leave a patient with substantial disability or may be fatal. It typically occurs in a moderately affected HD patient who is still walking without assistance but with significant postural instability, and typically presents in a chronic state. Of the 4 HD subjects with SDH in the aforementioned study, age ranged from 44 to 62 years, and disease duration ranged from 3 to 11 years. None had major head trauma, though 3 had one or more minor head traumas 2–3 months prior to SDH. In one case the diagnosis was incidental. Symptoms in the other three cases included headaches, gait disturbance, hemiparesis, anisocoria, and coma. One patient had bilateral hematomas. In all, there was evidence of mass effect with shift. All patients were managed with surgical evacuation although reoperation was required in 2/4 [28].

The most common acute traumatic injuries in a large hospitalization cohort were hip fracture (25%), and limb or other fractures (25%). Soft tissue trauma, crushing injuries, and open wounds were also reported [18]. It is important to note that HD patients often are poorly aware of their physical deficits [29] including pain, so families and physicians must be alert to changes that might reflect the patient having sustained a traumatic injury.

Falls in HD can be predicted by performance on measures of gait and balance, such as the Berg Balance Scale, Timed Up and Go test and the Tinetti Mobility Test [30–32]. Fall prevention is critical in HD and requires judicious use of physical therapy. Walkers and other aids often prove difficult to use by HD patients. A gait belt may be useful to the caregiver. A patient with repeated falls should be encouraged to

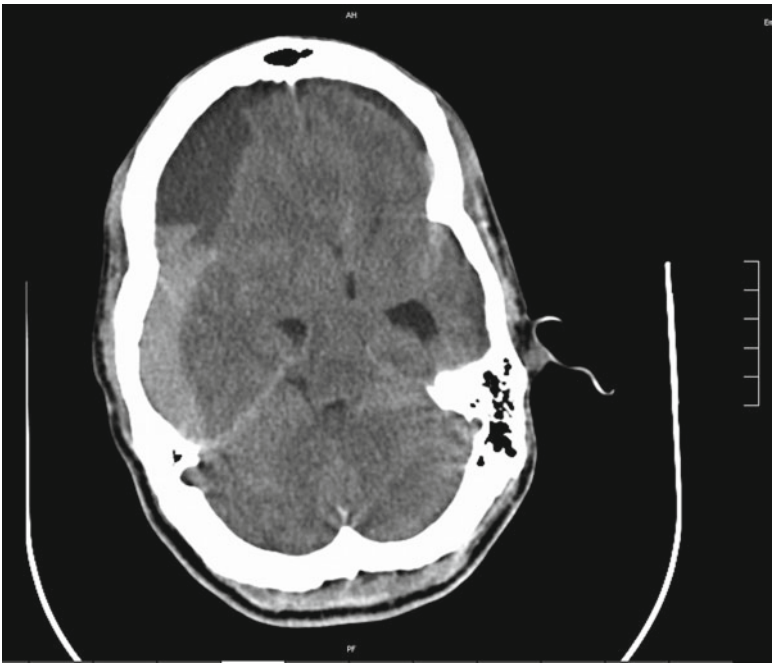

Fig. 14.1 CT brain scan in a patient with late stage HD and multiple falls. There is a chronic subdural hematoma over the right side of the brain with mass effect and midline shift. This hematoma required multiple surgeries and was ultimately fatal

wear a safety helmet. Passive restraints are often the easy solution to the falling patient, but this approach exposes the patient to the risk of injury or death. Restraint-related deaths in the general population tends to occur in nursing homes and are associated with cognitive impairment, impulsivity and involuntary movements, suggesting HD patients may be at particular risk [33]. While restraint related injury and even death are reported in the HD literature [16], the frequency of these events is unknown. Given these factors, restraints should be avoided in HD patients in favor of other measures to reduce falls.

Psychiatric Emergencies in HD

Psychiatric symptoms are nearly universal in HD, and span the spectrum from personality changes through affective disorders and psychosis [13]. Psychiatric syndromes precipitate about 20% of acute HD hospitalizations. Dementia and affective disturbances are the most frequent psychiatric causes of hospitalization, but are rarely associated with in-hospital mortality [18].

Depression occurs commonly in HD. First-degree relatives of HD patients report that sadness and depression are among the earliest symptoms of the disorder [34]. A study in HD subjects in the Huntington Study Group database showed nearly half of all subject endorsed anxiety or depression and 25% had low self-esteem. Patients in stage 2 were more likely to endorse symptoms of sadness and depression than were patients in other stages of the illness [35].

George Huntington himself observed a connection between HD and suicide, writing "(t)he tendency to insanity, and sometimes that form of insanity which leads to suicide, is marked" [36]. An increase in suicidality in HD patients compared to the general population is widely accepted, though estimates of the magnitude of this increase vary [37–39]. Suicidal ideation and suicide have been reported in clinically manifest disease, pre-manifest gene carriers, and even in family members not known to carry the mutation [37]. In a large study of the Huntington Study Group dataset, including 4,171 subjects (1,483 "at risk" and 2,688 with clinically manifest HD), suicidal ideation was endorsed by 17.5% of these subjects and was "moderate" or "severe with intent and plan" in about 10% of subjects. This study identified two critical periods of increased risk: at the time of development of soft neurological signs early in the "zone of onset" of clinical signs, and later when clinical signs begin to impair occupational or financial functions. A cross-sectional study of 2,835 HD subjects in the Huntington Study Group database found 10% had a prior suicide attempt [35]. Large studies suggest suicide is the cause of death in 0.1–14% of HD cases [37, 40, 41].

Continued surveillance for depressed mood and suicidal ideation is critical if suicide is to be prevented. HD families should be counseled to recognize suicidality, remove potential means of suicide from the home, and when and how to handle acute suicidality. The importance of vigilance in the care of HD patients is underscored by the report that a participant in a controlled clinical trial of the catecholamine depletor tetrabenazine committed suicide just 2 weeks following a study visit at which neither the subject nor caregiver expressed depressed mood or suicidal ideation, and at which the Hamilton rating scale did not suggest the presence of depression [42].

Other psychiatric syndromes that result in a significant number of HD hospitalizations include dementia-related symptoms (7% of admissions), and psychotic symptoms (4% of admissions). Admissions also occur for ethanol and substance abuse, anxiety and personality disorders, medication toxicity and others [18].

There are no published high-quality controlled clinical trials of any therapy for psychiatric disorders in HD. An evidence-based review suggested that amitriptyline and mirtazepine were possibly useful for the treatment of depression, that risperidone was possibly useful for psychosis, and that haloperidol, olanzapine, propranolol, and buspirone were possibly useful for behavioral disorder [43].

Neuroleptic malignant syndrome (NMS) was first described in 1960. It is a dramatic iatrogenic disorder resulting from the use of drugs with dopamine-receptor blocking activity. Diagnostic criteria for NMS include hyperthermia, autonomic instability, rigidity, altered consciousness, elevated creatine kinase, and leukocytosis [44]. Onset of symptoms is often within 1 week of initiation or escalation of dose

of the causative agent. Once the offending agent has been discontinued, recovery can be slow and complications are common. These include aspiration, rhabdomyolysis, or renal failure. Most often reported with first generation antipsychotics, NMS has been reported with second-generation antipsychotics and with other agents that block dopamine receptors, including antiemetics. Young and middle-aged men seem to have a higher risk of NMS. [45] Among patients treated with these agents, the incidence of NMS is low (about 0.2%) [45].

Isolated cases of NMS in HD have been reported. Implicated drugs included tetrabenazine [46, 47], and aripiprazole [48]. There is no reliable evidence base for treatment of NMS in HD. Prudence dictates discontinuation of the offending dopamine-receptor blocking agent, or dose reduction as appropriate. Further management should be guided by the usual principles of NMS care in a psychiatric population.

Conclusions

HD is a chronic progressive neurodegenerative disease with a predictable downhill course. Emergencies in HD generally comprise life threatening or morbid complications of deranged movement such as trauma and pneumonia, and these cause death and disability in many patients. Unlike progressive motor and cognitive deficits, psychiatric changes may be sudden and severe, and frequently require hospitalization. Pitfalls in the identification of emergencies in HD include a tendency to attribute changes in cognition and mobility to the disease rather than a complication, and a lack of awareness of pain or other changes in bodily function on the part of the patient. Appropriate identification and treatment of complications can make substantive improvements in the quality of life for HD patients and their families.

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Chapter 15
Acute Spinal Rigidity

P.D. Thompson

Abstract In each section of this chapter, relevant case histories from the literature illustrating structural, inflammatory or paraneoplastic causes of spinal rigidity are discussed to highlight the presenting and diagnostic features. Such cases are rare, and the importance of imaging cannot be overemphasised in cases of segmental rigidity where a spinal origin is suspected. Modern imaging techniques permit detailed anatomical examination of the spinal cord, making such diagnoses much simpler than in the past.

Patient Vignettes

Case 1

A 69-year-old woman presented with a 1-year history of low back and leg pain accompanied by progressive difficulty walking. Lumbar surgery was undertaken for spondylolisthesis and canal stenosis. Postoperatively the pain improved but her walking continued to deteriorate. She then developed spasms of the back and right leg causing flexion of the trunk, hip and knee. Her mobility deteriorated further. Examination at this time revealed a rigid right leg with palpable muscle activity in all muscle groups, brisk tendon reflexes and an extensor plantar response. There was no truncal rigidity. There was no sensory loss but sensory stimulation elicited a brisk flexion withdrawal movement of the whole leg. Similar flexion spasms of the

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leg and hip were evident while walking and severely restricted her gait. Further imaging of the whole spinal cord was normal. A glucose tolerance test was abnormal, but antiGAD antibodies were not detected. Baclofen was prescribed with some improvement in the rigidity and mobility. One year later her mobility declined again. Examination on this occasion revealed abdominal wall and lumbar paraspinal rigidity along with bilateral leg rigidity. The clinical picture was now that of the Stiff Person syndrome though antiGAD antibodies remained negative.

This case illustrates the focal onset of rigidity in one leg and subsequent evolution of the Stiff Person syndrome. Although the Stiff Person syndrome is a rare condition, it is a more common cause of segmental rigidity than spinal lesions. The clinical picture was now that of the Stiff Person syndrome though antiGAD antibodies remained negative until 10 years after the initial presentation, at which time a low titre was detected.

Case 2

A 68 year old woman presented with a 2 month history of progressive difficulty walking associated with leg pain, spasm, falls and pins and needle sensations in the distal legs. Upper limbs and sphincter function were normal. Examination revealed rigid extension of both legs and plantar flexion of the feet that could not be bent by passive manipulation. Voluntary leg movement was not possible because of the rigidity. Tendon taps and cutaneous stimulation elicited vigorous prolonged jerking of the legs with prominent crossed reflex responses. Plantar responses were spontaneously extensor. Magnetic resonance imaging of the spinal cord was normal. Magnetic brain stimulation produced normal responses in leg muscles (indicating intact corticospinal pathways). Peripheral nerve stimulation elicited bursts of muscle activity followed by prolonged tonic activity consistent with exaggerated cutaneomuscular (exteroceptive) reflexes. Multiple investigations were normal or negative, including anti-GAD antibodies. The cerebrospinal fluid contained 6 monocytes and borderline IgG elevation but no oligoclonal bands. She then developed a right facial sensory disturbance, a left sixth nerve and then a left conjugate gaze palsy. Intravenous methyl prednisolone and oral prednisolone improved her rigidity and gaze palsy. Three weeks later rigidity had subsided, she was able to walk unaided, and tendon reflexes were normal. There has been no recurrence of symptoms over 5 years of follow-up.

This patient's presentation illustrates leg rigidity as a presenting feature of progressive encephalomyelitis with rigidity. Leg rigidity was severe enough to mimic paraplegia but electrophysiological testing confirmed that corticospinal tracts were intact. The subsequent dramatic response to corticosteroids was consistent with an inflammatory, presumably immune-mediated aetiology.

In each section of this chapter, relevant case histories from the literature illustrating structural, inflammatory or paraneoplastic causes of spinal rigidity are discussed to highlight the presenting and diagnostic features. Such cases are rare, and the

importance of imaging cannot be overemphasised in cases of segmental rigidity where a spinal origin is suspected. Modern imaging techniques permit detailed anatomical examination of the spinal cord, making such diagnoses much simpler than in the past.

The Differential Diagnosis of Rigidity

Rigidity and Basal Ganglia Disease

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

Increased Tone in Spasticity and the Upper Motor Neuron Syndrome

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

Frontal Lobe Rigidity

The distinguishing characteristic of frontal rigidity is a progressive increase in muscle tone or resistance to movement during limb manipulation. As the examiner

applies increasing force to move the limb, the amount of resistance encountered increases. The examiner may suspect the patient is not fully relaxed or is voluntarily opposing the movement (gegenhalten). Frontal lobe signs, including grasp reflexes, are useful adjuncts to recognising frontal rigidity.

Muscle Stiffness and Peripheral Nerve Hyperexcitability

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

Primary Muscle Disease and Muscle Stiffness

Myotonia and delayed muscle relaxation in primary muscle disease may present with complaints of muscle stiffness during voluntary movement, although muscle tone and resistance to passive movement are normal. Some congenital myopathies, muscular dystrophies and inflammatory myopathies are associated with muscle contractures, limiting the range of limb movement, which may be misinterpreted as rigidity.

The Clinical Features of Spinal Rigidity

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

In most examples of spinal rigidity in man, other signs of spinal cord disease are present. These include segmental muscle wasting and weakness, absent tendon reflexes at the level of the spinal lesion, brisk reflexes below the lesion and extensor plantar responses. Segmental radicular and tract sensory disturbances complete the clinical picture of a myelopathy. Spinal rigidity and spasms have been described in

a variety of diseases of the spinal cord including traumatic spinal injury, tumours, multiple sclerosis, paraneoplastic myelopathy, arteriovenous malformations, ischaemia and syringomyelia. The common pathological feature in these conditions is predominant and selective involvement of the central spinal cord affecting spinal interneurons within the spinal grey matter.

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

Accordingly, spinal or "alpha-" rigidity is attributed to the unrestrained discharge of alpha motor neurones isolated from normal inhibitory interneuron control [1–3]. The rigidity is caused by continuous muscle activity in antagonist muscle groups that co-contract because of the loss of interneuronal mediated reciprocal inhibition. The motor activity is barely influenced by voluntary effort or stimulation of reflex pathways, indicating isolation of the spinal motoneurons from segmental reflex and descending supraspinal influences. Some modification of the pattern of discharge may be evident by an increase in spasms during traction or passive limb manipulation.

Disorders of Spinal Rigidity in Man

Structural Lesions of the Spinal Cord

Rushworth [3] reported a patient in whom a cervical intramedullary astrocytoma infiltrated the central grey matter throughout the cervical cord between C2 and C6. The patient presented with neck pain, a wasted left arm and a Brown-Sequard syndrome. Over the following months both arms became weak, areflexic, rigid, adducted and extended. Spontaneous electromyographic (EMG) activity was recorded in deltoid, pectoralis major, biceps and triceps. Muscle stretch evoked an increase in EMG activity in these and the antagonist muscles. Reciprocal innervation during voluntary shoulder abduction was impaired but was preserved between biceps and triceps. The authors concluded that this "alpha rigidity" was due to

spontaneous discharge of motoneurones isolated from interneuronal inhibitory control, and therefore insensitive to reflex or voluntary inputs.

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

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

Necrotizing Myelopathy

Penry [2] described a patient with "subacute necrotizing myelopathy" and extensive gliosis with destruction of the posterolateral central grey and white matter in the posterolateral regions of the spinal cord between C3 and T8. The initial clinical presentation was of a cervical myelopathy evolving over weeks, with flaccid weakness of the left arm and an asymmetric quadriplegia. Five months later, rigidity and spasms developed in the left arm. The arm was held in a posture of shoulder abduction and internal rotation, elbow flexion, dorsiflexion of the wrists and finger flexion. Intense EMG discharges in muscles of the left arm were not influenced by muscle stretch or tendon taps. A curious and distinctive finding was the inability to activate voluntarily the muscles in spasm.

Tetanus and Strychnine

The rigidity accompanying tetanus may be localised to the site of infection but there is often facial (risus sardonicus) and jaw spasm (trismus or lock jaw). Spasms occur

spontaneously or in response to stimulation by sound and touch, spreading throughout the body, producing abdominal rigidity and opisthotonic spasms. Spasms and rigidity may be dramatic, building in a crescendo fashion over several seconds, lasting for minutes and spreading from one site to another. Profound autonomic features including hypertension, tachycardia and sweating frequently accompany the spasms. Myoclonus and tremor may also occur [7]. Similar spasms occur in strychnine poisoning [8]. Tendon reflexes are brisk. An encephalopathy with decreased consciousness may accompany the spasms of strychnine poisoning. Both tetanus and strychnine disrupt inhibitory glycinergic and GABA release, blocking interneuronal inhibition of motoneurons in the spinal cord, brainstem and possibly cortex. Prolonged rigidity and spasm can lead to fever, rhabdomyolysis and acute renal failure.

Spinal Segmental Rigidity and Myoclonus

The capacity of the isolated spinal cord to produce a range of rhythmic activities was documented in traumatic spinal injuries during the First World War [9]. These included jerks and spasms with phasic and tonic elements that resulted in multisegmental movements of the abdomen, pelvis and legs, and coordinated locomotor-like activities of the legs [9, 10]. Similar rhythmic activities arising from an isolated segment of the spinal cord have been described in traumatic paraplegia [11], spina bifida [12] and experimental encephalomyelitis [13]. Varying combinations of spontaneous motor activities including rigidity and myoclonic or tremulous movements have been described in “spinal myoclonus”.

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

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

myelopathy [16]. Spasms, rigidity and continuous motor unit activity have been described following an inflammatory myelopathy suggesting a disorder of spinal interneurons in addition to the usual signs of a spinal cord lesion [17, 18].

Rigidity in the Stiff Person Syndrome

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

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

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

Progressive Encephalomyelitis with Rigidity and Myoclonus

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

encephalomyelitis with rigidity and myoclonus [19]. The relationship of these cases to apparently isolated inflammatory myelopathies with rigidity [17] is uncertain.

Rigidity in Spinal Interneuronitis and the Stiff Leg Syndrome

Isolated rigidity and spasms affecting one leg (the "stiff leg syndrome") has been attributed to segmental motoneuronal disinhibition caused by a localised form of chronic spinal interneuronitis [24]. Segmental or focal leg rigidity due to continuous motor unit activity is a common initial sign of the stiff person syndrome and of progressive encephalomyelitis with rigidity with progression to generalised distribution of rigidity occurring after a variable interval [19]. The onset of upper limb rigidity in a female should prompt a search for breast malignancy [25]. Follow-up examinations are important in these situations.

Management

The management of acute spinal rigidity and associated movement disorders relies on the recognition of the spinal origin and identification of the underlying cause. This will usually require appropriate imaging of the spinal cord. In the case of identifiable structural or inflammatory disease of the spinal cord, treatment revolves around management of the underlying cause. Serological studies for anti-GAD antibodies and electrophysiological testing for enhanced cutaneo-muscular reflexes may be helpful when the stiff person syndrome is suspected. Immunological therapies such as intravenous immunoglobulin are increasingly used as disease modifying strategies in the stiff person syndrome [26].

Drugs such as baclofen, tizanidine, and diazepam are useful in the treatment of spinal rigidity and spasms (Table 15.1). Large doses are often needed and intrathecal baclofen may provide a more effective method of delivery. Abrupt cessation of these drugs must be avoided as this may precipitate a severe exacerbation of rigidity accompanied by acute autonomic failure [20].

Table 15.1 Drugs that may be useful in treatment of spinal rigidity and spasms

Benzodiazepines: Diazepam, Clonazepam
GABA analogue: Baclofen
Centrally acting anti-adrenergic: Tizanidine, Clonidine
Anticonvulsants (valproate, carbamazepine, gabapentin)
Botulinum toxin injections (for focal rigidity, spasm)

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Chapter 16
Tic Emergencies

Vanessa K. Hinson and Christopher G. Goetz

This chapter contains video segments that can be found on the accompanying DVD.

Abstract Tics are sudden involuntary stereotypic movements or sounds that emerge out of a normal background. The majority of patients with tic disorders either do not require pharmacological intervention or have a benign course of the tic disorder with appropriate treatment. In rare instances, tics are severe enough to cause a neurologic emergency. First, intense exacerbations may occur in the normal context of the waxing and waning course of tic disorders, sometimes exacerbated by medication or stress. Second, tics can cause secondary neurological impairment that may result in new disability, such as a case described here of sciatic nerve damage due to marked leg tics. Third, sudden and unusual tics can emerge in the context of acute neurological disorders other than Tourette Syndrome, and finally, the pharmacological treatment of tics can cause sudden adverse events in the form of tardive dyskinesia or akathisia. In this chapter, each of these tic emergencies is discussed, and the diagnosis and treatment are reviewed.

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Patient Vignettes

Patient 1 (Video 16.1)

Natural exacerbation of fluctuations in chronic tics with emergence of falls and near falls from tics. An adult woman with a 20-year history of tics had been under recent stress and her tics became severe enough for her to seek additional care. Whereas her usual tics involved eye and neck movements, over 3 months their severity increased to include flailing arm jerks and truncal movements that caused her to stumble and in some instances fall to the ground. She became cautious about taking public transportation and standing on train platforms because of fears she would stumble and fall onto the train tracks.

Patient 2 (Video 16.2)

Compressive neuropathy from tics. An adult with over 40 years of tics was concerned about muscle wasting and numbness in one leg. He had an array of fluctuating tics that included loud vocalizations, bruxism, and nasal and facial movements that waxed and waned. Over the last year, he developed leg tics that involved knee banging and unusual rotational movements of one leg. When he performed these leg tics, he had a tingling sensation in one leg that was uncomfortable but "strangely satisfying." On examination, tics were observed, but also wasting of muscles supplied by the sciatic nerve. Electromyography confirmed a sciatic neuropathy at the level of the sciatic notch.

Patient 3

Sydenham's disease with chorea and tics (no video). A 9-year-old girl with no prior history of tics presented with a 3-week history of facial grimacing, abdominal flexion, and finger curling. She described a sensation in her abdomen preceding the involuntary movements, and she was able to temporarily suppress the facial and abdominal movements. Simultaneously, she developed mild confusion and headaches. Laboratory workup through the pediatrician's office revealed a positive strep throat culture and elevated anti-streptolysin O titer. On examination, there were fine, random choreic movements of hands and fingers but in addition, there were distinct, repetitive eye blinks, stereotypic neck jerks, and abdominal thrusting tics.

Patient 4 (Video 16.3)

Neuroleptic-induced akathisia, initially diagnosed as a new tic. A patient with a 10-year history of GTS presented with a complaint of worsening leg and truncal tics. He had been started on pimozide 3 weeks prior because of facial and neck tics. His family physician further increased the pimozide because of his complaint of new leg movements and truncal rocking 1 week later. On examination by a neurologist, multifocal motor tics affecting eyes, face, neck, and shoulder were present, as well as complex phonic tics. In addition, marked rhythmic leg movements and rocking motions were accompanied by a subjective sense of inner restlessness and an inability to sit still. When asked if the leg and truncal movements seemed different than his familiar tics, he affirmed that they were. Whereas he could suppress his eye, face, and neck movements for several minutes, he could not keep his legs or trunk still for even a few seconds.

Introduction

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

In rare instances, tics are severe enough to cause a neurologic emergency, and these fall into several categories (Table 16.1). First, intense exacerbations may occur in the normal context of waxing and waning. On occasion, these fluctuations are exacerbated by medication or stress (Patient Vignette 1 with video), and can frighten patients and their families and limit social or academic integration. Second, tics can cause secondary neurological impairment that may result in new disability, as seen in Patient Vignette 2 (with video) with sciatic nerve damage due to marked leg tics. Third, sudden and unusual tics can emerge in the context of acute neurological disorders other than GTS (such as Sydenham's disease, Patient Vignette 3), and therapies aimed at the primary disorder need to be started promptly. Finally, the pharmacological treatment of tics can cause sudden adverse events, as seen in

Table 16.1 Tic emergencies

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

Patient Vignette 4 whose emerging akathisia caused by neuroleptic therapy for tics markedly increased when the leg discomfort was misinterpreted as increasing motor tics. In this chapter, each of these tic emergencies is discussed, and the diagnosis and treatment are reviewed.

Tic Exacerbations

The natural history of chronic childhood-onset tic disorders is well described. Typically symptoms start at around 5 or 6 years of age, often with simple motor tics such as frequent eye blinking. Tics tend to peak in severity between 7 and 15 years of age, followed by a steady decline [1, 2]. Tics wax and wane in frequency and severity, and the tic repertoire varies. Simple motor tics (only affecting one muscle group) may migrate or become more complex (coordinated, sequenced movements). Complex tics often resemble normal movements or gestures, but they occur at an inappropriate time or with exaggerated intensity. Gestures may be obscene or provocative and are often socially embarrassing. Phonic tics might appear in the form of simple noises (e.g., throat clearing, sniffing, humming), or complex words or phrases. Complex phonic tics containing profanities are referred to as *coprolalia*, repetitions of someone else's words *echolalia*, and repetitions of the subject's own words *palilalia*. Tics are temporarily suppressible, often preceded by a premonitory sensation or urge to perform them, and usually produce a sense of relief. Tics can persist in adulthood [2], but are usually mild or well suppressed and do not cause disability.

Because tics occur in bouts, and the course of chronic tic disorders waxes and wanes, exacerbations are common. Factors that influence tic severity and may trigger exacerbations can be divided into *internal* and *external* factors (Table 16.2). An individual's susceptibility to these factors varies greatly. Internal factors include fatigue, hormone status, and levels of perceived stress. Children commonly experience exacerbations of tics at the beginning of the school year and at the time of return from school holidays. Tics also may increase during relaxation after a period of stress. Lack of sleep has been well documented to cause tic exacerbations [3]. Late or night-shift work may not be advisable in a professional with problematic tics. Hormonal fluctuations during teenage years have been implicated in worsening tics. Some patients also report fluctuations with their monthly menstrual cycles [4].

External factors that may exacerbate tics are diet, drugs, and concurrent infections. Even though there is no proven link between dietary products and tic severity, some

Table 16.2 Tics: Exacerbating factors

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

Table 16.3 Drugs implicated in tic exacerbations

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

patients report symptom exacerbations associated with the consumption of certain foods. Numerous drugs have been reported to exacerbate tics (Table 16.3). The most commonly encountered scenario occurs with stimulant drugs for the treatment of comorbid ADHD [5, 6] or performance-enhancing stimulants used by some students during exam time. Over-the-counter drugs for common colds [7], anticonvulsants [8], tricyclic antidepressants [9], selective serotonin reuptake inhibitors [10], and certain illicit drugs [11] have also been reported to exacerbate tics. A patient suffering from a concurrent infection may experience a tic exacerbation related either to the drugs used to treat the infection or to compromised general health.

During these periods, tics may become disabling, requiring urgent management, as illustrated with Patient Vignette 1. In the case of an external provoking factor, the elimination of the latter (e.g., discontinuation of the offending drug) may solve the problem. If there is no reversible causative agent, drugs for tic suppression may be warranted (Table 16.4). At present, the only agents approved for treatment of tics by the US Food and Drug Administration are haloperidol and pimozide. There is evidence that pimozide is more effective and better tolerated than haloperidol [12].

Table 16.4 Selected drugs to treat tics

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

Pimozide is our first choice for the treatment of acute, disabling tics. Because of the potential side effects of typical neuroleptics (extrapyramidal symptoms, sedation, weight gain, cardiac arrhythmias), the lowest possible dose should be used, and the need for treatment needs to be critically reviewed on a regular basis. Other neuroleptics commonly used to treat tics are fluphenazine and risperidone. In addition, there is emerging evidence for the newer atypical neuroleptic aripiprazole as a treatment for tics, with its unique action as a partial dopamine agonist [13]. The dopamine depletors tetrabenazine [14] and reserpine are effective anti-tic agents, but the patient needs to be carefully watched for signs of depression and parkinsonsim. In the United States, tetrabenazine is only approved for the treatment of chorea associated with Huntington's disease and is available through specialty pharmacies. In the case of tic exacerbations associated with prominent restlessness or ADHD, the alpha-adrenergic receptor agonists clonidine and guanfacine are useful, although less potent. Selected patients with prominent, disabling focal tics may benefit from botulinum toxin injections. This form of treatment is best suited for patients whose tics can be readily targeted for treatment with the toxin. Several case series and one double-blind, placebo-controlled trial demonstrate reduction of motor tics and the premonitory urge [15, 16]. The double-blind trial studied relatively mild patients with multifocal tics, and failed to show a change in the indices of overall patient well-being. Other case reports have described the improvement of disruptive vocal tics with intralaryngeal botulinum toxin injections [17, 18]. Education is an important arm of intervention, and the Tourette Syndrome Association (www.tsa-usa.org) has special programs that can be organized to inform teachers and students about tic disorders. These programs aim to defuse misunderstanding and stigmatization related to tic exacerbations.

In the case of Patient Vignette 1, the exacerbating influences included recent stress and resulting poor sleep. The patient was counseled about stress management techniques, but given the dramatic character of her new tics including falls and near falling episodes, the decision was made to start medication. The neurologist opted to start 2 mg of pimozide each evening after checking an electrocardiogram and verifying that the QT interval was normal. The pimozide was helpful in promoting sleep the first night and tics improved slightly. Over a 2-week period, the tics improved substantially and although they are still present, the emergency situation was considered to have passed.

Neurological Complications from Tics

Occasionally, violent motor tics can result in secondary neurologic injury, particularly radiculopathy or compressive neuropathy. In a previous report of two cases of secondary compressive neuropathies in patients with GTS [19], both patients developed peripheral nerve or radicular injury within the area involved by violent tics. In Patient Vignette 2, a hip-thrusting tic led to a compressive neuropathy at the sciatic notch. Severe motor tics have also been reported to cause cervical myelopathy [20]. Rapid recognition and treatment of the tic disorder are essential to prevent permanent neurological deficits. The tics should be treated according to the treatment principles outlined in the previous section. Botulinum toxin injections can be particularly useful for the treatment of severe cervical tics. In addition, physical therapy can often facilitate recovery from the neurologic injury. Patient 2 was taking haloperidol (1 mg/day) at the time of his presentation. The dose was gradually increased to 4 mg/day, with improvement of the leg tics. He was also referred to the physical therapy department for rehabilitation of his leg weakness.

Pain Related to Tics

Tic disorders can cause acute pain syndromes that require urgent management. Riley and Lang reviewed pain in tic disorders [21] and classified these conditions into four categories: (1) pain resulting from the actual performance of the tic (such as neck pain caused by sudden neck movements); (2) pain resulting from a traumatic injury from being struck by a body part involved in a tic, or pain to a body part striking against nearby objects; (3) pain caused by effort of tic suppression (excessive isometric muscle contraction), or self-inflicted pain in order to reduce tic expression; and (4) pain caused by behavioral abnormalities accompanying the tic disorder such as self-mutilating compulsions. Pain caused by tic disorders may be a source of significant disability for patients, and the same treatment principles discussed in management of tic exacerbations apply.

Abrupt Tics Secondary to Central Nervous System Disorders

The abrupt onset of new tics in a patient with other neurological signs, particularly at an atypical age for first presentation of tics, warrants the careful search for an underlying cause. Numerous acquired and genetic conditions as well as exposure to various drugs and toxins may cause secondary tics [22]. Central nervous system infections, autoimmune disorders, metabolic and toxic encephalopathies, stroke, head trauma, and psychogenic disorders all have been implicated in triggering tics. During the pandemic of encephalitis lethargica (1926–1927), tics were frequently observed as one of a variety of different movement disorders secondary to the infection

[23]. This disorder is now rarely seen, but tics have been described in encephalitis secondary to other infectious agents such as herpes simplex virus [24, 25] and human immunodeficiency virus [26]. The other infection-related phenomenon is that of tic disorders caused by an autoimmune response triggered by the underlying infection. Sydenham's chorea is the prototype example, following beta-hemolytic streptococcal infection. Tics have been reported to occur at the onset, or following Sydenham's chorea, [27, 28] as in the case of Patient Vignette 3 in the beginning of the chapter, a clinical presentation showing encephalopathy and chorea along with motor tics. There is also an ongoing debate whether streptococcal infection and rheumatic fever cannot only lead to Sydenham's chorea, but also trigger pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection (PANDAS) [29]. Treatment of these cases includes antibiotics and appropriate tic treatment as necessary. Patient 3 was started on amoxicillin by the infectious disease specialists, and clonidine by the treating neurologist with good response of her movements and behavioral disturbances.

Cases of tics occurring after carbon monoxide poisoning have also been described [30]. The documentation of tics attributable to metabolic disturbances such as hypoglycemia is questionable. Strokes can cause the abrupt onset of a tic disorder. Most documented cases describe multifocal or facial tics following cerebral infarction, but unilateral tics in the distribution of the accompanying neurological deficit have also been reported [31]. In one instance, magnetic resonance imaging findings linked an anatomic region to a case of post-stroke tics [32]: An 8-year-old boy suffered a left hemiparesis, followed by the development of hemidystonia and facial tics. The MRI scan demonstrated a lesion in the right middle cerebral artery territory including the head of the caudate nucleus. A few cases of tics following or exacerbated by head trauma have also been reported [33]. Even though it is conceivable that traumatic brain injury induces tics, pathophysiologic mechanisms remain unknown, and neuroimaging studies of affected patients have been unrevealing.

Psychogenic tics can be seen in somatoform disorders, factitious disorders, and malingering [22]. They can be hard to diagnose because they share common characteristics with organic tics, namely, suppressibility, distractibility, and variability. Certain atypical features evoke a diagnosis of psychogenic tics: abrupt onset in the context of a life-stressor, entrainment of tics with synkinetic hand movements, lack of response to antidopaminergic therapy, resolution with suggestion, placebo, psychotherapy or financial settlement, association with other false neurological signs (such as give-way weakness), and psychiatric comorbidity. In these cases, the underlying psychiatric disorder needs to be treated in order to ameliorate the tics.

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

New Involuntary Movements from Tic Drugs

The chronic tic patient may present for an urgent consultation because of the onset of new abnormal movements. In this context, it is important to differentiate tic exacerbations from new movement disorders secondary to anti-tic medications. Kompoliti and Goetz [34] reported on 12 tic patients with treatment-induced movement disorders. Both acute (akathisia, acute dystonia) and tardive (tardive dystonia, tardive chorea, withdrawal-emergent chorea) phenomena were observed during treatment with typical neuroleptics (pimozide, haloperidol, fluphenazine). All patients had been misdiagnosed as having tic exacerbations by the referring physicians. Akathisia was the most common phenomenon in this series. Akathisia affects trunk and leg muscles, is associated with an inner feeling of restlessness, and typically starts after neuroleptic initiation or dose increase as seen in Patient Vignette 4 at the beginning of the chapter and the corresponding video. Usually, a significant decrease in the neuroleptic medication is required to achieve relief of akathisia. If the neuroleptic dose cannot be reduced, the addition of anticholinergics, amantadine, beta-blockers, or mirtazapine may be helpful. In the case of Patient 4, the neuroleptic dose could not be decreased because of severe complex vocal tics, and the patient was treated successfully with benztropine.

Acute dystonia, especially oculogyric crisis, can also occur in association with the start of a neuroleptic or an increase in dosage. This frightening and often painful disorder requires addition of an anticholinergic agent to the neuroleptic, usually in the form of an intramuscular or intravenous dose followed by oral anticholinergic, often for the duration of neuroleptic therapy. Reports of tardive syndromes in tic patients are few [35, 36], but the phenomenon needs to be recognized and appropriately managed. As opposed to tics that are generally perceived as "voluntary" and suppressible, patients usually perceive tardive dystonic or choreic movements as "involuntary" and not suppressible [37]. Unlike tics, dystonic or choreic movements usually remain unchanged or even increase during distraction or the performance of skilled tasks. The first step in the management of these tardive syndromes consists of withdrawal of the neuroleptic if possible. Should the tardive symptoms persist and are primarily dystonic, oral anticholinergic drugs can be used, but these drugs often increase choreic movements. Tardive dystonia may be amenable to treatment with botulinum toxin if specifically problematic muscle groups are targeted. The off-label use of tetrabenazine can also be considered in this context as it has shown to ameliorate tardive symptoms and also treats tics [38].

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Chapter 17
Malignant Phonic Tics

Joseph Jankovic

This chapter contains video segments that can be found on the accompanying DVD.

Abstract Phonic tics are typically associated with motor tics and the combination usually suggests the diagnosis of Tourette syndrome. Although phonic tics are often mild, in some cases they may be severe and disabling. In addition to causing vocal cord and throat irritation, coprolalia can be socially isolating and lead to adversarial and even legal difficulties for the affected individual. When such "malignant phonic tics" fail to improve with anti-dopaminergic drugs, botulinum toxin treatment or even deep brain stimulation may be required.

Introduction

Motor tics are among the most common, childhood-onset, genetic movement disorders, affecting about 20 % of all school children, 3–6 % of whom have persistent tics and satisfy the diagnostic criteria for Gilles de la Tourette syndrome (TS) [1, 2]. Tics, the clinical hallmark of TS, are relatively brief, intermittent movements (motor tics) or sounds (vocal or phonic tics) [3–5]. Motor tics typically consist of sudden, abrupt, transient, often repetitive and coordinated (stereotypic) movements that may resemble gestures and mimic fragments of normal behavior. They typically vary in intensity and are repeated at irregular intervals. Although the diagnostic criteria for definite TS require the presence of "vocal tics" [6], we believe that because the sounds that patients with TS make do not always involve the vocal cords, the term

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"phonic tic" is preferable and will be used in this review. Phonic tics are actually motor tics involving respiratory, laryngeal, pharyngeal, oral, or nasal musculature. Contractions of these muscles may produce sounds, such as barking, excessive throat clearing, grunting, inhaling, sniffing, yelping, clicking of the teeth, and other noises. Phonic tics are often the most distressing and debilitating symptoms of TS. Complex vocal phenomena include echolalia (repetition of others' words), palilalia (repetition of one's own words), and coprolalia (socially inappropriate words or phrases, obscene utterances, shouting of profanities) [7]. The latter phenomenon usually leads to the most troublesome social, and sometimes legal, problems [8].

Clinical Symptoms

Patients with TS rarely present with an emergency complication of their disease. Nevertheless, we have seen patients who sustained life-threatening injuries such as evulsing their own cornea or the entire eye, or evisceration by cutting an abdominal wall with a razor in response to an inner obsession and the need to satisfy a sexual urge. Some of our patients have become quadriparetic as a result of compressive myelopathy caused by repetitive, violent "whiplash" tics of the neck [9]. Others may present because of severe scratches or other self-injurious behaviors [10]. Some TS patients may present to the emergency room or clinic with loud, uncontrollable barking, yelping, shouting of obscenities, or other vocal utterances. Of 332 TS patients evaluated at Baylor College of Medicine Movement Disorders Clinic during a 3-year period, 17 (5.1 %) met the criteria for "malignant TS," defined as ≥2 emergency room (ER) visits or ≥1 hospitalizations for TS symptoms or its associated behavioral co-morbidities [11]. The patients exhibited tic-related injuries, self-injurious behavior (SIB), uncontrollable violence and temper, and suicidal ideation/attempts. Compared to patients with nonmalignant TS, those with malignant TS were significantly more likely to have a personal history of obsessive–compulsive behavior/disorder (OCB/OCD), complex phonic tics, coprolalia, copropraxia, SIB, mood disorder, suicidal ideation, and poor response to medications.

Understanding the phenomenology and recognizing associated symptoms of tic disorders allow correct diagnosis and treatment [1, 2]. Often misconstrued as a disorder of psychological origin as a result of its peculiar behavioral and vocal spectrum, TS has frequently been misdiagnosed as a "mental illness," and patients were historically confined to psychiatric institutions. The discovery in the 1960s that dopamine receptor-blocking drugs (neuroleptics) markedly improve tics helped change the image of TS from a bizarre psychiatric disorder to a neurobiological and neurobehavioral condition.

In previous studies, 8–60 % of TS patients exhibited coprolalia, inappropriate obscene utterances, or profanities [7] (Videos 17.1–17.5). The severity of phonic tics may be measured by the volume of voice projection, effect on respiration, frequency of tics, and their social impact. In a study of 597 individuals with TS from seven countries, coprolalia occurred at some point in the course of the disease in 19.3 % of males and

14.6 % of females, and copropraxia in 5.9 % of males and 4.9 % of females [7]. A few cases of refractory coprolalia, severe and frequent vocal outbursts unresponsive to conventional anti-tic medications, have been reported [12–14]. Scott et al. [12] described a TS patient who exhibited severe coprolalia with racial slurs, sniffing, and grunting refractory to treatment with fluoxetine, fluphenazine, guanfacine, pimozide, and tetrabenazine (Video 17.5). He blurted out obscenities and profanities while riding the school bus, resulting in school absences owing to embarrassment. A stranger in a public bathroom also attacked him after he blurted out a racial slur. He expressed a need to repeat his vocal utterances until they seemed "just right." Salloway also reported a refractory case of phonic tics responsive to BoNT type A (OnabotulinumtoxinA) injections [13]. Trimble [14] described a TS patient with coprolalia refractory to behavioral therapy, clonidine, and neuroleptics. The patient's coprolalia was so severe that he was threatened with eviction from his residence. The patient also reported strong premonitory "feelings in the brain," rather than in the throat.

Disinhibition resulting from a dysfunction of the cortico-striato-thalamo-cortical circuits has been implicated in the pathophysiology of phonic tics, coprolalia, and other complex vocalizations [15–17]. Motor and phonic tics have been classified as "unvoluntary" movements, with a semi-volitional component and underlying sensory phenomenon [3, 18]. Motor and phonic tics are preceded by premonitory sensations, and patients commonly report that they perform the movements voluntarily in response to an involuntary sensory urge [19, 20]. TS subjects receiving BoNT injections for motor and phonic tics report not only a reduction in the movements, but also improvement in the premonitory sensory perception and local urge that frequently precede the tic [21–23]. The limbic system and ventral basal ganglia may be involved in generating aberrant impulses to the motor cortex [17].

Treatment

Several behavioral and pharmacological treatments have been used to treat severe phonic tics (Fig. 17.1) [1, 2, 24–26]. Dopamine receptor-blocking drugs are often tried first for moderate to severe motor tics, but these are often associated with a variety of adverse effects, including sedation, weight gain, and tardive dyskinesia. Haloperidol and pimozide are the two medications currently approved for the treatment of tics by the US Food and Drug Administration (FDA). We prefer fluphenazine and risperidone, although the atypical neuroleptics aripiprazole, olanzapine, quetiapine, and ziprasidone and other third-generation neuroleptics may also be helpful, but they all can cause tardive dyskinesia [27]. Tetrabenazine, a synthetic benzoquinolone that presynaptically depletes monoamines and possesses D2 blocking activity, has also shown to reduce tic severity without incurring the risk of tardive dyskinesia [28, 29]. Antiadrenergic drugs such as clonidine and guanfacine possess moderate benefit for tics [30, 31].

Behavioral techniques utilizing habit-reversal training and distraction tasks may provide some benefit, but few studies have systematically examined these approaches.

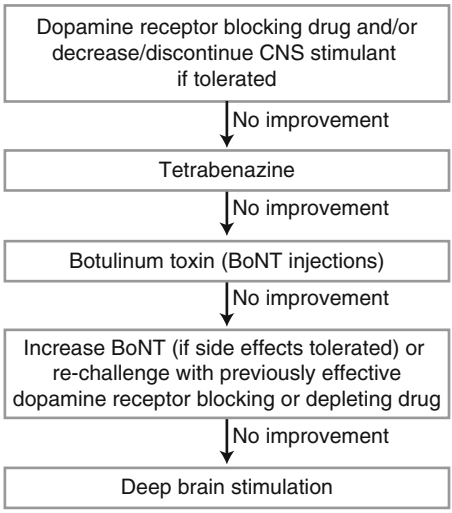

Fig. 17.1 Treatment algorithm for severe phonic tics

Many reports are hampered by small sample size and limited follow-up [32]. Overall, case studies using behavior reinforcement-based interventions are disappointing in reducing tic severity.

BoNT injections have shown to be particularly useful in treating focal motor and phonic tics [12, 21–23] (Table 17.1). BoNT injections are routinely used in the treatment of focal dystonia, hemifacial spasm, and tremor [33]. Scott et al. [12] were the first to report a patient with TS whose severe coprolalia markedly improved with unilateral vocal cord injection of BoNT. After injection of 30 mouse U of BTXA into the left vocal cord under electromyographic guidance, the patient reported reduction of coprolalia by "at least 75 %," with only moderate hoarseness and hypophonia (Video 17.5). The premonitory urge to shout was also markedly decreased. A repeat injection of 25 U produced similar benefit, and the patient was able to return to school. Trimble et al. [14] later reported a patient with refractory vocal tics and coprolalia who also responded to BoNT. Selective serotonin reuptake inhibitors, neuroleptics, and behavior therapy failed to improve his severe coprolalia, echolalia, and vocalizations of birdlike noises. Both thyroarytenoid muscles were injected under local anesthesia and electromyogram with 3.75 mouse U of BoNTA (AbobotulinumtoxinA). He reported an excellent response, with reduction in intensity of obscene outbursts. Mild side effects included a breathy, weak voice (hypophonia) and slight aspiration of liquids. The severity of the premonitory sensation remained unchanged after the injection. Kwak et al. [21] reported four patients with phonic tics in a large series of various motor tics treated with BoNT. The mean dose given to the vocal cords was 17.8 ± 6.5 mouse U (range 10–23.8). Transient side effects included mild dysphagia and hypophonia. The study reported a global response score of 2.7 ± 1.5 in 35 patients injected with BoNT in various muscle sites. BoNT injections have thus become an effective treatment option for patients with severe, loud, and disabling involuntary vocalizations.

Table 17.1 Case reports of botulinum toxin injections for phonic tics

Study	Number of patients	Site of injection	Response	Premonitory response	Side effect
Kwak et al. 2000 [21]	4	Thyroarytenoid muscle	Marked reduction in frequency and intensity	Reduced	Hypophonia, mild dysphagia
Trimble et al. 1998 [14]	1	Thyroarytenoid muscle	Excellent response	Unchanged	Hypophonia, mild aspiration
Salloway et al. 1996 [13]	1	Thyroarytenoid muscle	Improvement	Not specified	Hypophonia
Scott et al. 1996 [12]	1	Thyroarytenoid muscle	Decreased markedly	Reduced	Hypophonia, moderate hoarseness

If all pharmacologic therapy and BoNT therapies fail and the patient continues to be disabled by the tics, then deep brain stimulation (DBS) may be considered as an option, although this procedure has not been specifically evaluated in the treatment of phonic tics [34, 35].

Conclusion

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

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Chapter 18
Serotonin Syndrome

Mark Forrest Gordon and Adena N. Leder

This chapter contains video segments that can be found on the accompanying DVD.

Abstract Serotonin syndrome presents with neuromuscular, autonomic, and mental status changes. Severe cases of serotonin syndrome, also called serotonin toxicity, are characterized by neuromuscular excitation (clonus, hyperreflexia, myoclonus, rigidity, tremor), autonomic stimulation (hyperthermia, tachycardia, tachypnea, diaphoresis, flushing), and altered mental state (anxiety, agitation, confusion). These more severe cases may come to the clinician's attention on an emergency basis. The diagnosis of serotonin syndrome should be considered in a patient presenting with any combination of clonus, myoclonus, rigidity, and/or tremor. Serotonin syndrome is associated with the use of one or more serotonergic agents. Severe cases generally occur with combinations of serotonergic drugs, most commonly including a serotonin reuptake inhibitor and a monoamine oxidase inhibitor. Excessive serotonin (5-hydroxytryptamine) in the central nervous system has been implicated. Certain patient populations may be predisposed to developing serotonin toxicity, based on their use of various medications or other substances with serotonergic properties. When evaluating a patient with clinical features of neuromuscular excitation, autonomic stimulation, and/or altered mental state, prompt identification and management are critical, and treatment considerations are often complex.

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Patient Vignettes

A 34 year-old aerobics instructor with a history of migraine with aura and recent postpartum depression began taking fluoxetine for depression and migraine prophylaxis 6 months ago. At her most recent clinic appointment, she also started sumatriptan to abort her migraines. Two weeks later, 1 hours after her second subcutaneous 6 mg dose of sumatriptan, she presented to the emergency room with diaphoresis, agitation, confusion, dysarthria, staggering gait, and occasional myoclonic jerks in the lower extremities.

Introduction

In 1960, Oates and Sjoerdsma [1] first identified the serotonin syndrome in depressed patients. These patients exhibited diaphoresis, mental status changes, restlessness, ataxia, and lower-extremity hyperreflexia. The authors attributed this syndrome to increased levels of serotonin from concurrent use of L-tryptophan and monoamine oxidase inhibitors (MAOIs).

The serotonin syndrome has three manifestations: cognitive, autonomic, and neuromuscular, as outlined in Table 18.1 [2]. Each of these groups includes various

Table 18.1 Clinical manifestations of the serotonin syndrome

Cognitive and behavioral features
Confusion/disorientation
Agitation/irritability
Coma/unresponsiveness
Anxiety
Hallucinations (visual and auditory)
Autonomic features
Hyperthermia
Diaphoresis
Sinus tachycardia
Hypertension
Dilated pupils
Nausea
Flushing
Neuromuscular features
Myoclonus (especially in the legs)
Hyperreflexia (in the legs more than the arms)
Muscle rigidity
Restlessness/hyperactivity
Tremor
Ataxia
Extensor plantar responses

features that may or may not be present. When diagnosing the serotonin syndrome, at least one feature from each group should be present. Rarely, the serotonin syndrome causes high fever, seizures, nystagmus, oculogyric crisis, opisthotonus, dysarthria, and paresthesias.

Criteria for Diagnosis of Serotonin Syndrome

In 1991, based on an analysis of 12 literature reports (10 case reports and 2 case series) of 38 cases of serotonin syndrome, Sternbach [3] proposed provisional criteria for the diagnosis of serotonin syndrome.

1. Coincident with the addition of or increase in a known serotonergic agent to an established medication regimen, at least three of the following clinical features are present.
   (a) Mental status changes
   (b) Agitation
   (c) Myoclonus
   (d) Hyperreflexia
   (e) Diaphoresis
   (f) Shivering
   (g) Tremor
   (h) Diarrhea
   (i) Incoordination
   (j) Fever
2. Other etiologies (e.g., infectious, metabolic, substance abuse, or withdrawal) have been ruled out.
3. A neuroleptic had not been started or increased in dosage prior to the onset of the signs and symptoms listed above.

The Hunter Serotonin Toxicity Criteria (HSTC), proposed by Dunkley [4] in 2003, are validated criteria to establish the diagnosis of serotonin syndrome. These criteria were validated in a retrospective study of over 2,000 overdoses of one or more serotonergic agents and are highly sensitive (84%) and specific (97%). The HSTC has a much higher sensitivity for serotonin syndrome than Sternbach's criteria [5, 6].

The HSTC demonstrated that clonus is the single most important sign required to diagnose serotonin syndrome. Based on this analysis, serotonin syndrome was described as a spectrum of signs and symptoms including clonus (either spontaneous or inducible), hyperreflexia, tremors, agitation, diaphoresis, hypertonicity, and hyperthermia with a history of use of one or more serotonergic agents. Ocular clonus may also occur.

Excessive serotonin (5-hydroxytryptamine [5-HT]) in the central nervous system produces a condition commonly known as "serotonin syndrome," however recently some authors prefer the term "serotonin toxicity" to better reflect that the condition

is due to the toxic effects of serotonin excess [5–7]. This excess CNS serotonin can be due to several pharmacological mechanisms, including inhibition of the metabolism of serotonin (MAOIs), prevention of the reuptake of serotonin in nerve terminals (serotonin reuptake inhibitors), and increased serotonin precursors (tryptophan) or serotonin release (serotonin-releasing agents) (Table 18.2) [5]. The resulting

Table 18.2 Mechanisms of action and names of serotonergic agents

Increase serotonin synthesis
L-Tryptophan
Decrease serotonin metabolism
Monoamine oxidase inhibitors:
Isocarboxazid (Marplan)
Iproniazid
Phenelzine (Nardil)
Selegiline (Eldepryl)
Tranylcypromine (Parnate)
Clorgyline
Pargyline
Moclobemide
Linezolid (Zyvox)
Furazolidone
Procarbazine (Matulane)
Increase serotonin release
Amphetamines
Cocaine
Methylenedioxymethamphetamine (MDMA; Ecstasy)
Fenfluramine (Pondimin)
Reserpine (Serpasil)
Inhibit serotonin uptake
Tricyclic antidepressants:
Clomipramine (Anafranil)
Imipramine (Tofranil)
Selective serotonin reuptake inhibitors:
Paroxetine (Paxil)
Sertraline (Zoloft)
Fluoxetine (Prozac)
Fluvoxamine (Luvox)
Citalopram (Celexa)
Serotonin and noradrenaline reuptake inhibitors:
Venlafaxine (Effexor)
Milnacipran (Savella)
Duloxetine (Cymbalta)
Sibutramine (Meridia)
Other uptake inhibitors
Amphetamines
Cocaine
Dextromethorphan

(continued)

Table 18.2 (continued)

Tramadol (Ultram)
Meperidine (Demerol)
Fentanyl (Duragesic)
Methadone
Propoxyphene (Darvon)
Pentazocine (Talwin)
Direct serotonin receptor agonists
Buspirone (Buspar)
Lysergic acid diethylamide (LSD)
Sumatriptan (Imitrex)
Nonspecific increase in serotonin activity
Electroconvulsive therapy
Lithium (Eskalith, Lithobid)
Dopamine agonists
Amantadine (Symmetrel)
Bromocriptine (Parlodel)
Bupropion (Wellbutrin)
Levodopa (Sinemet, Stalevo)
Selective Serotonin Receptor Agonists
Triptans:
Sumatriptan (Imitrex)
Zolmitriptan (Zomig)
Rizatriptan (Maxalt)
Naratriptan (Amerge)
Almotriptan (Axert)
Frovatriptan (Frova)
Eletriptan (Relpax)

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excess CNS serotonin acts on serotonin receptors and produces the clinical effects. The exact role of the various serotonin receptors is not completely clear, but there is good evidence that the severe life-threatening clinical effects, such as rigidity and hyperthermia, are mediated by 5-HT2A receptors.

Serotonin toxicity is characterized by neuromuscular excitation (clonus, hyperreflexia, myoclonus, rigidity, tremor), autonomic stimulation (hyperthermia, tachycardia, tachypnea, diaphoresis, flushing), and alteration in mental state (anxiety, agitation, confusion). Depending on the degree to which intrasynaptic serotonin is elevated in the central nervous system, serotonin toxicity can be mild (serotonergic features that may or may not concern the patient), moderate (toxicity which causes significant distress and deserves treatment but is not life-threatening), or severe and life-threatening (a medical emergency characterized by rapid onset of severe hyperthermia, muscle rigidity, and multiple organ failure) [5, 6].

A greater increase in 5-HT levels and a higher incidence of fatalities from serotonin toxicity occur when combining an MAOI + paroxetine, a potent and highly

selective serotonin reuptake inhibitor (SSRI), as compared to an MAOI + fluoxetine (a weaker SRI). Although the serotonergic toxicity of SSRIs increases with dose, generally SSRIs alone do not precipitate life-threatening serotonin toxicity in healthy adults, even when taken in overdose. Severe toxicity resulting in death most commonly occurs with combinations of MAOIs and SSRIs or MAOIs and serotonin-releasers, such as amphetamine [5, 6]. Serotonin syndrome generally presents abruptly and can progress quickly, especially in patients taking a combination of serotonergic medications. The length of an episode of serotonin syndrome depends on the duration of action or the elimination half-life of the implicated drugs [6].

Neurochemistry

Serotonin (5-HT), as illustrated in Fig. 18.1, is a monoamine neurotransmitter that is synthesized from the amino acid tryptophan. Tryptophan is transported into the brain from the plasma. Since tryptophan is one of the eight essential amino acids, the body cannot synthesize tryptophan from other amino acids and it must be ingested with foods. Foods that are high in tryptophan include dairy products, beef, poultry, barley, brown rice, fish, soybeans, legumes, and peanuts [4].

Once inside the serotonergic neuron in the central nervous system and the enterochromaffin cells of the gastrointestinal tract, dietary tryptophan undergoes enzymatic conversion to form 5-HT:

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

The rate-limiting step of the pathway is the production of 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase. Serotonin is a monoamine present throughout the body. Ninety-nine percent of total body serotonin is located intracellularly [8]. Most of the body's serotonin is located in the periphery and mostly stored in platelets and enterochromaffin cells. Only 1–2% of its entire body content is in the central nervous system. Serotonin is unable to cross the blood brain barrier. The primary metabolic pathway for serotonin is degradation by monoamine oxidase (MAO),

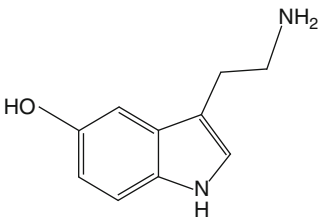

Fig. 18.1 The chemical structure of serotonin

especially by the MAO-A form. The major metabolite of MAO metabolism of serotonin is 5-hydroxyindoleacetic acid (5HIAA), which is excreted primarily in the urine.

At least 13 different serotonin receptors have been identified [9, 10]. The 5-HT1A, 5-HT1B, 5-HT1C, 5-HT1D, and 5-HT2 receptors are single-subunit proteins that are members of the G protein receptor superfamily. This receptor family is characterized by the presence of seven transmembrane domains, an intracellular carboxy terminus, and an extracellular amino terminus. It is the interaction of the receptor with the G protein that allows the receptor to modulate the activity of different effector systems, such as ion channels, phospholipase C, and adenyl cyclase [5].

The 5-HT1 receptor family contains receptors that are negatively coupled to adenyl cyclase (activation of these receptors down-regulates cyclic AMP) and includes the 5-HT1A receptor. The 5-HT1A receptor is coupled via G proteins to two distinct effector systems: (1) the inhibition of adenyl cyclase activity and (2) the opening of potassium channels, which results in neuronal hyperpolarization.

The serotonin autoreceptors and the serotonin transporter limit the availability of serotonin in the synapse. The 5-HT1A and 5-HT1D serotonin receptors are presynaptic receptors that act as autoreceptors to prevent further 5-HT release when they sense the presence of 5-HT. Additionally, the highly selective serotonin transporter (SERT), located on the presynaptic membrane, removes serotonin from the synaptic cleft. Once transported into the presynaptic neuron, serotonin is recycled back into presynaptic vesicles where it is protected from metabolism. The abundance of serotonin in the synaptic cleft is the major determinant of the strength and duration of signaling on the postsynaptic serotonin receptor. Binding of serotonin to its autoreceptor and the activity of the SERT, both of which are located on the presynaptic membrane, control the availability of serotonin in the synaptic cleft. As noted by Mohammad-Zadeh [8], the negative feedback created by stimulation of the 5-HT autoreceptor decreases further release of serotonin, while the SERT actually removes serotonin from the synaptic cleft.

Several serotonin receptors are postsynaptic, including 5-HT1A, 5-HT1D, and 5-HT2A (the latter one also known as the 5-HT2 receptor). These receptors are responsible for postsynaptic nerve stimulation or inhibition. Previously, both 5-HT1A and 5-HT2 were implicated in the serotonin syndrome, however Gillman [7] states that activation of the 5-HT2A receptor (not the 5-HT1A receptor) is needed to cause a serious serotonin syndrome. Hyperthermia, the primary risk of serious morbidity and death in serotonin syndrome, is mediated in a dose-related manner by the action of 5-HT or 5-HT agonists on 5-HT2A receptors, and is ameliorated or prevented by 5-HT2A antagonists, such as cyproheptadine, but not by 1A antagonists [7].

Serotonin syndrome is directly related to the synaptic concentration of serotonin (5-HT) and the concentration-dependent action of serotonin at postsynaptic serotonin 5-HT2A receptors [6, 7]. Gillman [7] states that serotonin syndrome is not "an idiosyncratic response, but a predictable and inevitable result of toxicity (mediated via the final common pathway of elevated intrasynaptic serotonin)."

The evidence implicating serotonin in causing the serotonin syndrome is largely based on animal (rat) models, including radioligand binding studies [9]. Human studies have been anecdotal, and the mechanism of serotonin syndrome in humans remains unproven.

Neuroanatomy

Within the central nervous system, serotonin is synthesized and stored in the presynaptic neurons (i.e., serotonergic neurons, pineal gland, and catecholaminergic neurons). Serotonin is located in nine groups of cell bodies isolated to the pons and midbrain [8]. Serotonergic neurons are restricted to midline structures of the brainstem. Most serotonergic cells overlap with the distribution of the raphe nuclei in the brainstem.

A rostral group (B6–8 neurons) project to the thalamus, hypothalamus, amygdala, striatum, and cortex. The largest group of serotonergic cells is B7, which is continuous with a smaller group of serotonergic cells, B6. Groups B6 and B7 together comprise the dorsal raphe nucleus.

A more caudal group (B1–4 neurons) of serotonergic cells is found in the mid-pons to caudal medulla and projects to other brainstem neurons, the cerebellum, and the spinal cord. In the medulla, serotonergic neurons lie in the nuclei raphe magnus, raphe obscurus, and raphe pallidus, which give rise to descending spinal projections.

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

The Role of Serotonin

Serotonin has been implicated in appetite, emotion, and motor, cognitive and autonomic (sympathetic) function. Studies of the firing rate of serotonergic soma in the raphe nuclei suggest that serotonin (5-HT) modulates the nervous system. Serotonergic activity correlates with behavioral arousal, motor output, circadian

rhythm, neuroendocrine function, eating, and sleeping. Precursors of 5-HT, releasing agents, reuptake inhibitors and receptor agonists and antagonists have been used to assess serotonergic function [5].

Epidemiology

Serotonin syndrome is an iatrogenic disorder related to drugs that augment serotonin transmission. It occurs in patients treated for depression (the most common group), bipolar affective disorder, obsessive-compulsive disorder, eating disorders with depression, Parkinson's disease, migraines, HIV/AIDS, and sepsis, as well as in patients who abuse drugs. Serotonin syndrome occurs in pediatric and adult patients. The patient's age and sex are not known to predispose to the development of serotonin syndrome.

Drugs Associated with Serotonin Syndrome

There are many other serotonergic drugs reported to produce serotonin syndrome. Table 18.2, derived from Mills [2] and subsequent authors [6, 11], lists mechanisms of action and names of serotonergic drugs.

There are several drug mechanisms that cause excess serotonin, but severe serotonin toxicity (serotonin syndrome) generally occurs with combinations of serotonergic drugs (often acting at different sites), most commonly including a serotonin reuptake inhibitor and an MAOI [5]. Less severe toxicity occurs with other combinations, overdoses, and even single-drug therapy in susceptible individuals.

An overdose with a serotonin reuptake inhibitor rarely, if ever, causes fatal serotonin toxicity. Life-threatening ST generally occurs only when MAOIs are combined with either serotonin reuptake inhibitors (selective or nonselective) or serotonin releasers, such as amphetamine or the recreational drug, Ecstasy. Death can also occur from a large overdose of an older irreversible MAOI (i.e., tranylcypromine) alone. The newer reversible MAOIs (i.e., moclobemide) do not cause ST alone in overdose [6].

Selected Patient Profiles

The following patient populations may have particular risk of developing serotonin toxicity, based on their use of certain medications or other substances with serotonergic properties. The clinician should be especially mindful of the coadministration of serotonergic medications or other substances. When evaluating a patient with clinical features of neuromuscular excitation, autonomic stimulation, and/or altered

mental state, the identification that the patient falls into one of these profiles and is using one or more serotonergic medications or other substances should prompt the clinician to consider the diagnosis of serotonin syndrome.

The Patient with Psychiatric Disease

Antidepressants are the most common class of drugs to produce serotonin syndrome. Specifically, MAOI, selective and nonselective serotonin reuptake inhibitors, and tricyclic antidepressants cause the serotonin syndrome.

Fluoxetine has unique pharmacokinetics, which makes it prone to cause serotonin syndrome. The half-life of fluoxetine is 1–4 days, but its active metabolite, norfluoxetine, has a half-life of 7–14 days. To decrease the risk of serotonin syndrome, when discontinuing fluoxetine, due to the long elimination half-life of norfluoxetine, a patient should wait 5 weeks before starting another serotonergic agent [12] or an MAO-I [13]. Durson [14] reported a patient who developed serotonin syndrome while taking carbamazepine and fluoxetine.

Lithium may enhance the serotonergic effect of serotonin reuptake inhibitors (SRI), potentially increasing the risk of serotonin syndrome when lithium and SRIs are used concomitantly, compared to when SRIs are used alone. In two case reports, patients taking lithium and venlafaxine (an antidepressant with dual selective reuptake inhibition) developed serotonin syndrome, possibly due to lithium's increasing the serotonergic effect of venlafaxine or diminishing its renal excretion [6, 15, 16].

The serotonin syndrome is most commonly the result of the interaction between serotonergic agents and MAOIs. MAO-A has greater affinity for serotonin, whereas MAO-B has a higher affinity for dopamine. Classical MAOIs produce irreversible inhibition of MAO enzyme activity. MAO enzyme activity is regenerated in approximately 2 weeks due to the gradual production of uninhibited MAO enzyme. Therefore, when a patient changes from an MAOI to a different class of serotonergic agents, a 2-week period must elapse between the two drugs. Serotonin syndrome may also occur with moclobemide, a reversible inhibitor of monoamine oxidase-A (known as "RIMA") [17].

Combining MAOIs with serotonin selective or nonselective reuptake inhibitors or serotonin releasers may precipitate a rapid deterioration to life-threatening and sometimes fatal serotonin toxicity [6]. Depending on their serotonin reuptake inhibitor potency, tricyclic antidepressants (TCAs) combined with MAOIs can also precipitate life-threatening serotonin toxicity. Clomipramine, one of the most potent TCAs, has serotonergic effects at both therapeutic levels and in overdose. When combined with MAOIs, clomipramine is known to cause serotonin toxicity and death from ST. Imipramine also has clinically significant serotonergic potency. Amitriptyline, a less potent SRI, is not known to cause symptoms of serotonin toxicity if taken in overdose. Amitriptyline can be combined with an MAOI without the risk of serotonergic side effects or serotonin toxicity [6].

A 73-year-old man with a 7-year history of Parkinson's disease, progressive motor impairment, and depression currently takes levodopa/carbidopa and selegiline. Sertraline was recently added, and three nights ago, he abruptly stopped his levodopa/carbidopa and selegiline. Upon arrival in the Emergency Room, he is confused, shivering, and stiff and has involuntary movements.

The Patient with Parkinson's Disease

Increased concentrations of dopamine in the CNS can induce the serotonin syndrome by indirect serotonin release. Patients with Parkinson's disease (PD) may have an increased risk of serotonin syndrome due to the high rate of depression among PD patients, with many PD patients concurrently using an antidepressant and a dopaminergic agent. Levodopa, bromocriptine (an ergot dopaminergic and 5-HT1A agonist), and selegiline (an MAO-B inhibitor) have been associated with SS. Sun-Edelstein [6] noted that attempts to use bromocriptine to treat patients with misdiagnosed neuroleptic malignant syndrome who actually had serotonin syndrome triggered a worsening of serotonergic signs and symptoms. Since ergots, such as bromocriptine, also have 5-HT2 antagonist activity, the relationship of bromocriptine to the development of SS is uncertain.

Fernandes [18] reported a diagnosis of possible serotonin syndrome in a 76-year-old woman with a 10-year history of PD, treated with carbidopa, levodopa, and entacapone. After a 4-day accidental overdose of rasagiline 4 mg per day, she developed agitation, loss of consciousness, labile blood pressure, tachycardia, fever, and a tremor "not typical of Parkinson's disease."

Toyama and Iacono [19] suggested that parkinsonian patients might be protected from the serotonin syndrome by decreased serotonergic functioning, shown by loss of serotonergic neurons and decreased serotonin metabolites. A chart review by Waters [20] on 23 patients receiving combined fluoxetine and selegiline and another chart review by Toyama [19] on 25 patients receiving combined SSRI and selegiline both revealed no serious side effects. Nevertheless, it remains unclear how safe it is to use an MAOI-B with an antidepressant.

A Common Mistake: Misdiagnosis of Serotonin Syndrome as Neuroleptic Malignant Syndrome

Neuroleptic malignant syndrome (NMS) is another lethal disorder that is most often seen in psychiatric patients. This condition is also seen in parkinsonian patients when withdrawing dopaminergic agents. The mechanism is thought to be blockade of central dopamine receptors in the basal ganglia and hypothalamus and blockade of peripheral postganglionic sympathetic neurons in smooth muscle. The clinical picture may mimic that of serotonin syndrome. The American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR)

Table 18.3 Comparison of the serotonin syndrome and the neuroleptic malignant syndrome

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

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[21] defines NMS as the development of severe muscle rigidity and elevated temperature in association with two or more of the following: diaphoresis, dysphagia, tremor, incontinence, changes in level of consciousness, mutism, tachycardia, elevated or labile blood pressure, leukocytosis, and laboratory evidence of muscle injury (elevated creatinine phosphokinase).

Table 18.3, presented below, derived from Mills [2], compares the serotonin syndrome and the neuroleptic malignant syndrome. The clinician must be able to distinguish serotonin syndrome and neuroleptic malignant syndrome, because the management is different.

The Patient with a Severe Infection

Linezolid, an antibiotic of the oxazolidone family, is a reversible, nonselective MAOI used in the treatment of vancomycin-resistant *Enterococcus faecium* infections, nosocomial pneumonia caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumoniae* (including multi-drug resistant strains), and skin infections caused by *Staphylococcus aureus* (methicillin susceptible and -resistant strains), *Streptococcus pyogenes,* or *Streptococcus agalactiae* [22]. Linezolid should not be used in patients taking any medication which

inhibits MAO-A or MAO-B or within 2 weeks of taking such medication [22]. Serotonin syndrome has been described from the interaction of linezolid and SSRIs, such as citalopram, sertraline, paroxetine, and fluoxetine [22, 23].

The Patient with Pain

Some narcotic analgesics, such as the phenylpiperidine series opioids (including meperidine, tramadol, methadone, fentanyl, dextromethorphan, and propoxyphene), are weak serotonin reuptake inhibitors (increase CNS serotonin) and can precipitate life-threatening serotonin toxicity reactions when combined with MAOIs [6]. Zornberg [24] described a patient taking meperidine and selegiline who developed possible serotonin syndrome. Meperidine, dextromethorphan, and tramadol are contraindicated in patients using MAOI, including selegiline, and should be used with caution in patients using other serotonergic drugs. In contrast to the above narcotics, morphine, and its analogues, such as codeine, oxycodone, and buprenorphine, do not have any known action as serotonin reuptake inhibitors, and therefore are not associated with serotonin syndrome, either alone or in combination with MAOIs [6].

Duloxetine and milnacipran are serotonin and noradrenaline reuptake inhibitors. Duloxetine is indicated for the management of fibromyalgia, diabetic peripheral neuropathic pain, and chronic musculoskeletal pain [25]. Milnacipran is indicated for the management of fibromyalgia [26]. The concomitant use of these drugs with MAOIs in contraindicated. If concomitant treatment with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of these drugs with serotonin precursors (such as tryptophan) is not recommended. Due to the risk of serotonin syndrome, caution is advised when using these drugs with certain narcotic analgesics that are serotonin reuptake inhibitors, such as tramadol. Yacoub [27] described a patient with depression treated with paroxetine (a selective serotonin reuptake inhibitor) who 8 days after adding on milnacipran for fibromyalgia, developed altered mental status, autonomic dysfunction, and skeletal muscle rigidity, diagnosed as serotonin syndrome. The authors hypothesized that the concomitant use of these two serotonergic agents produced serotonin syndrome.

The Recreational Drug Abuser

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

a hallucinogen. Initially in the 1980s, MDMA was used as a psychotherapeutic adjunct. Today MDMA is used in dance clubs. Its popularity is likely due to its positive effect on mood and sense of well being. There are several administration routes: oral, injection, smoking, and nasal. According to Parrot [28], about 85–90% of recreational Ecstasy users (ravers) reported an increase in body temperature, an increase in sweating, and dehydration. Other physical reactions from MDMA include bruxism and trismus, which is why many ravers chew gum. Deaths at UK "rave" parties were attributed to serotonin syndrome following ingestion of MDMA [29]. The factors that may contribute to death from MDMA ingestion are unknown, however they may include dosage, individual sensitivity, tolerance, variability in drug metabolism, and concomitant use of antidepressants or other recreational drugs, including cocaine, amphetamines, cannabis, or alcohol.

Dextromethorphan (DXM) is a cough suppressant found in over-the-counter (OTC) cold medications. DXM may be abused in high doses by adolescents to generate euphoria, visual and auditory hallucinations, and dissociative "out of body" experiences similar to those caused by the hallucinogens phencyclidine (PCP), and ketamine. Illicit use of DXM is referred to on the street as "Robo-tripping" or "skittling." These terms are derived from the most commonly abused products, Robitussin and Coricidin [30].

Annually, about one million US youth and young adults (age 12–25 years) misuse OTC cough and cold medicines that contain DXM [31]. The Drug Abuse Warning Network (DAWN ED) reports that nearly 8,000 emergency department visits in the USA each year were associated with the nonmedical use of DXM during 2006–2008 [32].

Dextromethorphan potentiates serotonin levels. Recreational usage of products containing DXM can lead to serotonin syndrome. Schwartz [33] described two cases of serotonin syndrome associated with supra-therapeutic doses of DXM and therapeutic levels of an SSRI.

Genetic polymorphisms of CYP2D6 of the CYP-450 system produce differences in an individual's ability to metabolize DXM (dextromethorphan). CYP2D6 metabolizes dextromethorphan to dextrorphan, its active metabolite. Poor metabolizers via CYP2D6 produce less dextrorphan, experience a higher risk of developing adverse effects (e.g., nausea, vomiting, and dysphoria) from DEX, and are less likely to abuse DXM. Conversely, extensive metabolizers via CYP2D6 produce more dextrorphan, experience more of the euphoric and mind-altering effects, and are more likely to abuse DXM [34].

Patients who coadminister DXM with drugs that may inhibit CYP2D6 (e.g., dextromethorphan itself, venlafaxine, amitriptyline) have a higher risk of adverse effects and are less likely to abuse the drug. Forget [35] recommends avoiding DXM in patients taking a tricyclic antidepressant or other inhibitors of CYP2D6.

An additional concern from abuse of DXM-containing products is the development of potential toxicity from the other ingredient, such as delayed hepatic toxicity from acetaminophen, increased blood pressure from pseudoephedrine, and central nervous system, cardiovascular and anticholinergic toxicity from antihistamines. The abuse of DXM in high doses with alcohol or other drugs is particularly dangerous and potentially lethal [30].

The Patient with Cough

Dextromethorphan is an antitussive agent in many over-the-counter cough medications. Doctors need to be aware that since dextromethorphan is an opioid with serotonin reuptake inhibitor activity, it has the potential to cause ST in patients taking MAOIs.

The Patient with Migraine Headaches

Classically, the serotonin syndrome was described in patients with psychiatric disease or Parkinson's disease, but more recently it has been identified in migraineurs.

The pathophysiology of migraine is thought to involve the neurotransmitter serotonin. It has been hypothesized that patients with recurrent migraines have chronically low systemic 5-HT. Agents that increase serotonin in the CNS are effective in treating migraine. Sumatriptan selectively activates the 5-HT1D receptors. Dihydroergotamine (DHE), another 5-HT agonist, is more potent at the 5-HT1A than the 5-HTD receptor. Additionally the SSRIs, which are used for migraine prophylaxis, inhibit serotonin reuptake.

Several cases of serotonin syndrome were identified in migraine patients treated with prophylactic and/or abortive agents [36, 37]. The responsible agents include sumatriptan with lithium, methysergide, and sertraline and DHE with lithium, imipramine, and paroxetine. Serotonin syndrome is largely under-recognized in the migraine population.

In 2006, the United States Food and Drug Administration (FDA) [38] alert warned about the potential life-threatening risk of SS when triptans are used with SSRIs or SNRIs. This alert was based on a total of 29 cases (reported to the FDA or derived from the published literature) of presumptive SS occurring in association with the combination of triptans and SSRIs.

In an American Headache Society Position Paper [39], Evans reviewed the potential risk of serotonin syndrome (based on the Sternbach Criteria or the Hunter Serotonin Toxicity Criteria) when combining triptans with other serotonergic agents. Of the 29 cases used as the basis for the FDA alert, 10 cases actually met the Sternbach Criteria for diagnosing serotonin syndrome. No cases fulfilled the Hunter Criteria for serotonin toxicity. The study concluded that the currently available evidence does not support limiting the use of triptans with SSRIs or SNRIs or the use of triptan monotherapy, due to concerns for serotonin syndrome.

Evans [39] commented that "Based upon their pharmacology, the involvement of triptans in contributing to a serotonin syndrome, either alone or in combination with other medications, seems implausible." Triptans are high-affinity agonists at 5-HT1B/5-HT1D/5-HT1F subtype receptors with lower affinity for 5-HT1A receptors. Available evidence supports a model of serotonin syndrome due to activation of 5-HT2A receptors, with some questionable involvement of 5-HT1A receptors. Similarly, Gillman [7] concluded that there was neither significant clinical evidence nor theoretical reason to speculate about serious SS from triptans and SSRIs.

Methylene Blue and the Parathyroid Surgery Patient

Methylene blue (MB; methylthioninium chloride), a potent inhibitor of MAO-A, is a phenothiazine derivative used in medicine for staining and therapeutic purposes. Its most common intravenous use is for parathyroid surgery where it accumulates in the target tissue to assist surgical identification. Ng and Cameron [40] presented a literature review that identified nine case reports and two retrospective reviews; 26 patients developed an acute confusional state after MB infusion; 24 of these patients were taking an SRI, and one was taking clomipramine. Serotonin syndrome was a possible diagnosis in all 25 of these patients. They concluded that serotonin reuptake inhibitors could interact with methylene blue to cause a serious adverse reaction consistent with serotonin syndrome. The level of risk for MB to induce SS is uncertain [7].

Patients with HIV Infection

Human immunodeficiency virus (HIV)-positive patients are at risk for developing the serotonin syndrome. Since depression is prevalent among HIV-positive patients, they often take serotonin reuptake inhibitors. Drugs that inhibit the metabolism of serotonin reuptake inhibitors can produce serotonin syndrome. Antiretroviral therapy inhibits serotonin metabolism via the cytochrome P450 enzymes. Although ritonavir specifically inhibits the 2D6 isoenzyme, the exact mechanism of inhibition remains unknown as many of the antiretrovirals inhibit the 3A4, rather than 2D6 isoenzyme. DeSilva [41] described five cases of serotonin syndrome, which occurred in HIV-positive patients who were taking fluoxetine with protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Fluoxetine is metabolized by P450 2D6 to an active metabolite, norfluoxetine, which is then further metabolized by 2D6. Fluoxetine has been associated with serotonin syndrome likely due to its very long half-life.

The Pediatric Patient

Serotonin syndrome must be considered in the pediatric population, now that behavioral disorders are more frequently treated with serotonergic formulations. Additionally, unintentional exposures of children to serotonergic drugs may occur due to the rising number of serotonergic antidepressants being prescribed to adults.

Several case reports describe children who developed the serotonin syndrome after overdosing on serotonergic antidepressants and even while on therapeutic doses of these drugs, sometimes in combination with other serotonergic drugs [42, 43].

Dextromethorphan, an opioid with serotonin reuptake inhibitor activity, is widely used in cough syrups. It should be given cautiously to children who take behavior-modifying medications since it may trigger a serotonin syndrome.

The Patient Who Uses Herbal Remedies

In addition to traditional prescription antidepressants, herbal antidepressants may also cause serotonin syndrome. The mechanism of St. John's Wort (*Hypericum perforatum*) is not entirely clear. It is hypothesized that it may reduce the expression of serotonin receptors, increase the numbers of 5-HT1A and 5-HT2A receptors, and inhibit synaptosomal serotonin uptake. Parker [44] reported a patient who developed cognitive and autonomic symptoms following 10 days of monotherapy with St. John's Wort. Other herbal remedies that may also increase the activity of serotonin include ginseng, Brewer's yeast, and yohimbine.

Laboratory Studies

There are no specific labs that will help to positively identify the serotonin syndrome. Laboratory data are useful to eliminate other causes of disease and to identify any complications of serotonin syndrome. Additionally, it is not necessary to demonstrate increased drug levels of the serotonergic agents. In fact, the majority of patients do not have elevated drug levels. The serotonin metabolite, 5-HIAA, can be measured, but does not aid in diagnosing serotonin syndrome.

In neuroleptic malignant syndrome, serum creatinine kinase and polymorphonuclear leukocytes are generally increased, whereas in serotonin syndrome these levels are either normal or mildly increased. Carcinoid syndrome, which can mimic the serotonin syndrome, can be ruled out by checking 5-HIAA, the marker for carcinoid. An EEG may be necessary to rule out seizures.

Complications of serotonin syndrome include: rhabdomyolysis (with increased CK), hypoxia (due to respiratory muscle rigidity or coma), disseminated intravascular coagulation (from multiple organ failure), metabolic acidosis (due to seizures or ventricular tachycardia), and aspiration pneumonia (from decreased level of consciousness). Hyperthermia increases the morbidity and mortality from serotonin syndrome [45]. The hyperthermia has been attributed to activation of the 5-HT2A receptor [45].

Management of the Patient

Serotonin syndrome must be promptly recognized. Treatment considerations are often complex. Table 18.4 reviews the management of serotonin syndrome.

Table 18.4 Management of serotonin syndrome

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

An Overview

Supportive care is initiated to control agitation, hyperthermia, and autonomic dysfunction, which are commonly manifested as fluctuations in blood pressure and heart rate [46]. All serotonergic agents must be discontinued. The severity and rapidity of symptoms help determine the management. The clinician may consider pharmacotherapy with a benzodiazepine and/or nonspecific serotonin receptor blockers, such as cyproheptadine, chlorpromazine, and methysergide. Supportive therapy, discontinuation of serotonergic drugs, and administration of benzodiazepines often alleviate mild cases of serotonin syndrome [46].

In more severe cases, intensive care unit monitoring and treatment may be necessary. Interventions such as external cooling, muscular paralysis with neuromuscular blocking agents, endotracheal intubation and mechanical ventilation, control of autonomic instability, and sedation with an intravenous benzodiazepine may be indicated.

The Role of Benzodiazepines

Benzodiazepines are integral to the treatment of mild-to-moderate SS [46]. Benzodiazepines may have a protective role due to nonspecific inhibitory effects on serotonergic transmission. The benzodiazepines also treat the muscle hypertonia. Aside from benzodiazepines, other agents that may modify serotonergic excess include nonspecific serotonin receptor blockers, such as cyproheptadine, chlorpromazine, and methysergide.

The Role of Serotonin Receptor Blockers

Oral Cyproheptadine

Due to the currently accepted mechanism for the development of serotonin syndrome, treatment with a 5-HT2A antagonist is advised. Cyproheptadine is a first generation

histamine-1 receptor-blocking agent with nonspecific antagonist properties at 5-HT1A and 5-HT2 receptors. The dose of cyproheptadine that binds 85–95% of serotonin receptors is 12 mg orally (or crushed and administered through nasogastric tube) initially, followed by 4–8 mg every 6 h [6]. Patients with the serotonin syndrome often respond within hours of receiving 4–8 mg of cyproheptadine by mouth [47]. Cyproheptadine is available only in tablet and liquid forms; there is no parental formulation. Cyproheptadine may cause sedation, which can be useful for the agitation in SS [46].

Intravenous Chlorpromazine

If charcoal has already been given, intravenous chlorpromazine must be administered, rather than cyproheptadine. Currently, chlorpromazine, which shows nanomolar affinity for cloned human 5-HT2A receptors, is the only intravenous 5-HT2A antagonist that is effective in the treatment of serotonin toxicity [6, 46]. The initial dose of chlorpromazine is 12.5–25 mg intravenously, followed by 25 mg orally or intravenously every 6 h, although higher doses have been used with apparent safety and effectiveness. Chlorpromazine treatment should be preceded by fluid loading as it can precipitate hypotension through α (alpha)-2 adrenoceptor antagonism. Patients who require acute parenteral therapy for the serotonin syndrome are often hypertensive and are not ambulatory, so the risk of orthostatic hypotension is minimized. Chlorpromazine should be avoided if the drugs that precipitated serotonin toxicity have pronounced cardiotoxic or epileptogenic properties (i.e., venlafaxine), as it may aggravate those symptoms. Chlorpromazine, as a neuroleptic, may cause hyperthermia as an idiosyncratic response and thus potentially aggravate the hyperthermia of SS. Chlorpromazine should not be given to a patient with neuroleptic malignant syndrome as it may worsen the condition [6, 46].

Induction of Paralysis

As Boyer and Shannon [46] noted, paralysis should be performed with nondepolarizing agents, such as vecuronium. Succinylcholine should be avoided due to possible arrhythmia due to hyperkalemia from rhabdomyolysis.

Treatment of Hyperthermia

In serotonin syndrome, the appropriate therapy for hyperthermia is neuromuscular paralysis, as the hyperthermia results from excess muscle activity, rather than an alteration in the hypothalamic temperature set point. Consequently, antipyretic drugs are not typically needed to treat the fever during serotonin toxicity. Physical

restraints should be avoided since they may increase the isometric muscle contractions associated with lactic acidosis and hyperthermia.

Treatment of the Pediatric Patient

The treatment of serotonin syndrome in children is similar to that in adults. Recognition of the syndrome and discontinuation of the offending agent(s) are critical. Supportive care, maintenance of high urine output, and prevention of rhabdomyolysis are crucial. Cyproheptadine is recommended in severe cases of serotonin syndrome in children. Dosages of cyproheptadine need to be adjusted according to the child's age and/or size.

Electroconvulsive Therapy as an Alternative Treatment

A few case reports suggest that serotonin syndrome may also benefit from electroconvulsive therapy (ECT). For example, Nisijima [45] reported a depressed patient with diaphoresis, tremor and myoclonus, who was diagnosed with serotonin syndrome (by Sternbach's criteria). The patient was refractory to medical therapies. The serotonin syndrome resolved and the depression lessened with ECT.

The Prognosis

The prognosis of serotonin syndrome is generally good, with improvement often within 24 hours of symptom onset. The syndrome may be present for longer periods in cases involving serotonergic drugs with long duration of action, active metabolites, or long half-lives [6, 46].

Prevention

To decrease the risk of serotonin syndrome, it is important to avoid prescribing more than one serotonergic agent. If it becomes necessary to do so, the patient should be monitored closely for serotonin syndrome. MAOIs should not be used with other serotonergic agents. When switching agents, a 5-week washout period is necessary after discontinuing fluoxetine, and a 2-week washout period is necessary after discontinuing an MAO-I.

When prescribing a serotonergic agent, it is important to obtain a clear history of other drugs or herbs that the patient is currently taking or has recently discontinued (and record the date of cessation).

Conclusion

Serotonin syndrome is an uncommon, but potentially life-threatening condition related to excess serotonergic activity. The clinical features seen in serotonin syndrome represent a concentration-dependent range of toxicity due to an increase in the intrasynaptic concentration of serotonin in the central nervous system [4]. The critical serotonin receptor required for activation of serotonin toxicity is the 5-HT2A receptor.

Fortunately, knowledge of drug mechanisms, pharmacodynamics, and interactions can help prevent this syndrome. Since the implicated medications are employed in various clinical situations, health care providers must be familiar with the agents associated with serotonin syndrome. Prompt identification and management of suspected cases are necessary.

Any opinion(s) expressed by Dr. Gordon are his personal opinion(s) and do not necessarily reflect the position of Boehringer Ingelheim Pharmaceuticals, Inc.

Any opinion(s) expressed by Dr. Leder are her personal opinion(s) and do not necessarily reflect the position of Neurological Specialties of Long Island, PLLC.

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Chapter 19
Risks and Dangers from Hyperekplexia and Other Startle Disorders

Frederick Andermann and Eva Andermann

This chapter contains video segments that can be found on the accompanying DVD.

Abstract While quite rare, startle syndromes represent a movement disorder emergency, due to the risk of apnea and sudden death in infants if the disorder is missed. Prompt recognition and treatment leads to improved quality of life in this unusual disorder.

Patient Vignette

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

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Introduction

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

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

Hyperekplexia

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

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

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

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

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

Affected individuals possess normal intelligence, but occasional patients have some degree of mental retardation and epileptogenic electroencephalogram (EEG) abnormalities may be present [6]. This suggests more widespread cerebral involvement. Patients with hereditary hyperekplexia respond dramatically to clonazepam, which abolishes most clinical features except for head retraction on nose and forehead tapping [7, 12].

Because of intermittent excessive startle in family members of clearly affected individuals, we wondered about the possibility of a minor form of the disorder in addition to the full-blown or major form of startle disease [6, 7]. The mother of two affected girls, while going through a difficult divorce, startled excessively and literally rose off the chair when the phone rang, but these features disappeared as her life settled down. Later studies by Tijssen and colleagues suggested that this minor form merely represents excessive physiological startle, because these individuals did not have the identified molecular mutation [13].

Startle disease is inherited as an autosomal dominant, with a high penetrance of more than 90% and with variable expressivity. Sporadic and autosomal recessive forms have been described, and the familial and sporadic cases appear to have the same clinical phenotype. Sporadic cases may represent either a new mutation in the proband, autosomal recessive inheritance, germline mosaicism, or lack of penetrance in affected relatives [7, 14, 15].

In the last decade, the molecular basis of startle disease has been linked to an abnormality of the inhibitory glycine receptor (GLYR) [16]. Two different missense mutations have been identified in the same base pair of exon 6 of the $\alpha 1$ subunit of the inhibitory glycine receptor GLRA1:G1192A and G1192T. These result in amino acid substitutions at codon 271 of arginine>leucine and arginine>glutamine,

respectively. Mutations were found in four of seven families tested. The first mutation was confirmed in a Swiss family reported by Schorderet [17] and in the original German Dutch family described by Suhren.

The finding of two point mutations at the same position suggested that the arginine at position 271 is critical for the function of the inhibitory GLYR. The mutation was not present in individuals in the German Dutch family affected with the minor form—that is, in individuals with only an excessive startle reaction to unexpected stimuli [18]. Functional studies of the inhibitory GLYR showed that picrotoxin is a competitive antagonist of the α1 subunit of the human GLYR. The two mutations described transform picrotoxin from an allosterically active competitive antagonist to an allosteric potentiator at low concentrations and to an uncompetitive antagonist at higher concentrations. Thus the allosteric transduction pathways of both agonists and antagonists converge at a common residue, suggesting that this residue may act as an integration point for information from various extracelluar ligand-binding sites [19].

Functional studies have shown that agonist binding in the GLYR initiates opening of a chloride-selective channel that modulates the neuronal membrane potential. Missense mutations substituting arginine 271 with either leucine or glutamine change GLYR single-channel conductances to lower conductance levels. The binding of the glycinergic agonists β-alanine and taurine to mutated GLYRs does not initiate chloride current, but competitively antagonizes currents activated by glycine. Thus, arginine 271 mutations result in uncoupling of the agonist-binding process from the channel activation mechanism of the receptor.

In summary, there has been an enormous amount learned regarding the molecular basis of hyperekplexia during the last decade. Nine mutations of the GLYRA1 gene have been identified: five dominant and four recessive. One of the recessive mutations is a null mutation, and two others occurred in a compound heterozygote. In a number of familial cases, no mutation of GLYR has been identified. This suggests nonallelic genetic heterogeneity and the possibility of mutations in other GLYR subunits exists. Recent studies have also indicated that the genetics of hyperekplexia is complex, like many genetic disorders. Five genes are now known to be associated with hyperekplexia: GLRA1, encoding the glycine receptor subunit α1; SLC6A5, encoding the presynaptic sodium-and chloride-dependent glycine transporter; GLRB, encoding glycine receptor subunit beta; GPHN, encoding the glycinergic clustering molecule, gephyrin; and ARHGEF9, encoding collybistin [20]. Three mouse models of hyperekplexia have been identified, one with a missense mutation of GLYRA1, one with an insertion mutation at GLYRB, and one null allele at GLYRA1 [21].

These molecular advances should lead to improved genetic counseling, prevention of neonatal deaths and complications, increased knowledge of the mechanisms involved in abnormal startle, and eventually rational therapy. For the time being, treatment with clonazepam or with valproic acid in low doses brings about adequate, although incomplete, improvement [7, 11, 19]. There are also patients with symptomatic hyperekplexia as a result of central nervous system pathology. Patients with static perinatal [22], postanoxic [1], posttraumatic encephalopathy [2], sarcoidosis [1], and paraneoplastic etiology [2] have been described. Brainstem lesions [23, 24] may also produce this clinical picture. These various

symptomatic startle abnormalities must be distinguished from startle epilepsy, which is sometimes difficult given the paucity of EEG abnormalities in some patients with frontal epilepsy. The prognosis of symptomatic hyperekplexia depends on the underlying cause.

Startle Epilepsy

In startle epilepsy, auditory, tactile, or more rarely, visual stimuli trigger seizures. The coexistence of neurological abnormalities facilitates the diagnosis. Startle epilepsy may occur in patients with infantile hemiparesis, quadriparesis, diffuse encephalopathy, and secondary generalized epilepsy, Down syndrome and, very rarely, in patients with normal intelligence and normal neurological exams. The disorder is thus best considered as a syndrome with diverse etiologies and often-serious prognosis [25]**.** The pathophysiology of startle epilepsy has been studied by Chauvel [26]. Seizures start in the muscles first involved in the startle reflex and propagate to the contralateral limb and then to the ipsilateral side. The abnormality is usually frontal or frontoparietal, involving the supplementary motor area in the vicinity of the paracentral lobule [27, 28]. Using functional neuroimaging, Fernandez and colleagues demonstrated initial activation over the precuneus, supplementary motor area, cingulate gyrus, and the precentral/perirolandic area [29]. Even in patients with normal MRIs, ictal MEG demonstrated activation in central frontal regions [30]. Aguglia and Gastaut found mesial frontal atrophy in 40% of patients with startle epilepsy, frontocentral spikes in 50%, evoked frontocentral spikes in 33%, and frontal spike foci in all [31]. A more recent study by TIbussek confirmed the heterogeneity of patients with startle epilepsy [32].

Startle epilepsy is quite variable in its response to antiepileptic medication. Some patients are easily controlled and remain with only minor, although still abnormal responses to startle. In others, the abnormal response progresses to falling with attendant risks of injury despite optimal antiepileptic medication. In the presence of identifiable structural lesions, surgical treatment after appropriate localization studies is quite effective. In others, particularly in the absence of a visible lesion, the potential for surgical treatment is low and occasional patients are confined to life in a wheelchair. Jimenez and Roldan have suggested a specific response of startle epilepsy to clonazepam, but this has not been confirmed by himself or others [33]. More recently, Gurses and colleauges reported efficacy with levetiracetam in previously treatment-refractory patients [34].

Jumping and Other Culture-Bound Syndromes

Excessive startle is also a feature of the culture-bound syndromes first described in the late 1800s. The Jumping Frenchmen of Maine, loggers from the Beauce region of Quebec working in the Moosehead Lakes area of Maine, were described by Beard [35]. Their clinical features were excessive startle, echolalia, echopraxia, and forced

obedience. Later studies by Kunkle have stressed the occasional late appearance of symptoms after a nonspecific illness [36]. The familial nature is obviously not compatible with a learned process, though good family studies are not available. Drs. Maire Helene and Jean Marc St. Hilaire described several jumpers who, in response to startle, adopted a fighting stance and swore [37]. They, like Rabinovitch [38], assumed that this was a learned behavior designed to amuse bystanders by startling susceptible individuals, but this is unlikely to explain the genetic features.

In patients with culture-bound syndromes, forced obedience to such orders as "throw it," "punch," or "hit" may bring about not only embarrassment but also occasionally danger. An analogous disorder, Myriachit, Amurath, or Icotta, has been described in Siberia, the former by Hammond, then surgeon general of the USA [39]. Latah in Malaysia, Goosey in the USA, Jaun in Myanmar, Bah Tsche in Thailand, Mali Mali and Silok in Philippines, and Panic I Lapland probably represent analogous, if not identical, disorders [40]. The studies of Simons [41] and Tanner [42] were carried out in Latah subjects in Malaysia. They stressed the behavioral features and the social utilization of such behaviors. Imu, a behavioral disorder in the Ainu of Hokkaido in Northern Japan, likely represents the same process. The early descriptions come from Uchimura, who also filmed affected persons [43]. The current perspective among Japanese neurologists on Hokkaido suggests that the process occurred mainly in women, and that it is currently dying out.

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

Conclusion

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

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Chapter 20
Perioperative Emergencies Associated with Deep Brain Stimulation

Takashi Morishita, Adam P. Burdick, and Michael S. Okun

Abstract Deep brain stimulation (DBS) has become an established procedure for movement and neuropsychiatric disorders. With the increased use of DBS, DBS-related problems have emerged as more common, and awareness of these issues has become more important for clinicians. Adverse events vary widely depending on the situation. We deal only with emergent situations here and separate the possible scenarios into: (1) perioperative (intra- and early postoperative) and (2) postoperative (following 2–4 weeks) settings. With ten clinical vignettes, we address how clinicians should appropriately detect and manage the emergent/urgent issues in a DBS cohort.

Patient Vignettes

We present nine illustrative cases of perioperative emergencies associated with deep brain stimulation (DBS) from our experience and one case from the literature [1]. Much of the data and discussion for this chapter is drawn from our clinical experience and also from several recent publications [2–11].

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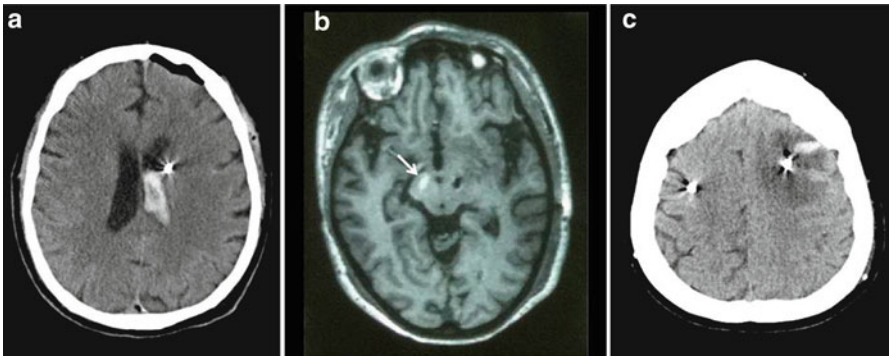

Fig. 20.1 Images of hemorrhagic complications. (**a**) A computed tomography (CT) scan shows left ventricular hemorrhage following the surgery. (**b**) A T1-weighted image performed on the postoperative day 1 shows the microbleeding in the subthalamic nucleus. (**c**) A CT scan image shows edematous lesion surrounding the left deep brain stimulation (DBS) lead with intracerebral hemorrhage

Patient 1: Intraventricular Hemorrhage

A 73-year-old man with a 16-year history of Parkinson's disease (PD) underwent unilateral subthalamic nucleus (STN) DBS. Following the procedure, he became somnolent, and a postoperative computed tomography (CT) scan revealed a hematoma in the left lateral ventricle (Fig. 20.1a). The hematoma involved the third ventricle and the Sylvian aqueduct, and the patient developed acute obstructive hydrocephalus. The patient thus underwent an emergent ventriculostomy on the same day. The management issues mandated 1 week of bed rest postoperatively, and he then developed a deep venous thrombosis, aspiration pneumonia, atrial fibrillation, a urinary tract infection, and sepsis. The total hospitalization was 40 postoperative days. Following 8 months of rehabilitation and anticoagulant therapy, implantation of an Implantable Pulse Generator (IPG) was scheduled.

Patient 2: Intracerebral Hemorrhage

A 63-year-old woman with PD underwent simultaneous bilateral STN DBS. Following the microelectrode recordings (MERs) on the right side the patient developed mild left hemiparesis intraoperatively. DBS was implanted only in the left hemisphere and IPG was also implanted on the same day. Postoperative magnetic resonance imaging (MRI) scan revealed microbleeding in the right STN (Fig. 20.1b).

Patient 3: Venous Infarct

A 67-year-old woman with PD underwent right STN DBS with good results; she requested contralateral stimulation. Six months after the right DBS implantation, a left STN DBS lead was implanted. She was discharged on postoperative day 1 after an uncomplicated hospital course, but that evening experienced word finding difficulties and an altered level of consciousness. When these symptoms persisted through the following morning, her husband brought her to the emergency room. On examination, except for a significant but incomplete expressive aphasia and disorientation, she was neurologically intact, including writing, repetition, and comprehension. A CT scan of the head demonstrated edema and hemorrhage surrounding the superficial aspect of the DBS lead (Fig. 20.1c). Her aphasia improved over the next several days, but some confusion persisted for several weeks. Her speech and cognition ultimately recovered completely, but she did report occasional slurring of her speech with fatigue.

Patient 4: Intraoperative Seizure

A 65-year-old man with PD underwent unilateral globus pallidus interna (GPi) DBS. Following MER macrostimulation to test the threshold levels of stimulation-induced side effects, it was noted that when the voltage was increased, a focal seizure was precipitated in the right upper extremity, and the seizure developed into a complex generalized subtype. Propofol was intravenously administered immediately, and the seizure was terminated. The DBS procedure was completed and the postoperative CT scan revealed no lesions and no intracranial hemorrhage. The patient recovered without any neurological deficit.

Patient 5: Neuroleptic Malignant Syndrome [1]

A 54-year-old man with a 14-year history of PD underwent STN DBS. He was preoperatively on levodopa, carbidopa, entacapone, and pramipexole, and these medications were discontinued 18 h prior to the procedure. DBS surgery was performed uneventfully, however, the patient developed tremor, muscle rigidity, and high fever 3 hours postoperatively. Laboratory investigation revealed extremely high creatinine kinase levels. The patient was intubated and admitted to the intensive care unit (ICU). Although treatment including administration of dantrolene, levodopa, and apomorphine was immediately initiated, the hospital stay was extended to 4 months.

Patient 6: Myocardial Infarction

A 58-year-old male with PD underwent unilateral STN DBS placement. In addition to PD his past medical history was significant for coronary artery disease (CAD) (previously treated with angioplasty), hypertension, diabetes mellitus (DM), and hyperlipidemia. An implantable pulse generator (IPG) was placed 4 weeks following the DBS lead and this was done under general anesthesia. Following IPG implantation the patient died of a myocardial infarction in his sleep on postoperative day 1.

Patient 7: Infection

A 43-year-old man with a 9-year history of PD underwent unilateral STN DBS. He arrived for a routine clinic appointment and staple removal on postoperative day 17. Following the staple removal there was purulent drainage from the cranial incision site, and the pectoral incision revealed tender erythema. He was admitted to the hospital urgently, and both the IPG and the extension wire were removed. A course of intravenous antibiotics was administered and completed prior to reimplantation.

Patient 8: Intracerebral Infection

A 71-year-old man with a history of medically refractory essential tremor (ET) underwent a unilateral thalamic DBS implantation. Four weeks following surgery, the patient presented to clinic complaining of headache and progressive dysphagia. An emergent head CT scan revealed a brain abscess along the DBS lead tract. An edematous lesion surrounding the DBS lead that was enhanced with contrast media was seen on CT scan (Fig. 20.2). An emergent craniotomy and DBS lead removal was performed.

Patient 9: Lead Migration

A 26-year-old man with tardive dystonia due to exposure to a neuroleptic drug used for his severe depression underwent bilateral GPi DBS. Preoperatively he suffered severe and painful retrocollic jerky movements of the head. Postoperatively his subjective pain and head jerking improved, although these symptoms were incompletely controlled. Six months following the operation the benefits waned, and a CT scan revealed that the left and the right leads had migrated 15.6 and 4.6 mm ventrally from their initial position (Fig. 20.3). The patient underwent successful lead replacements.

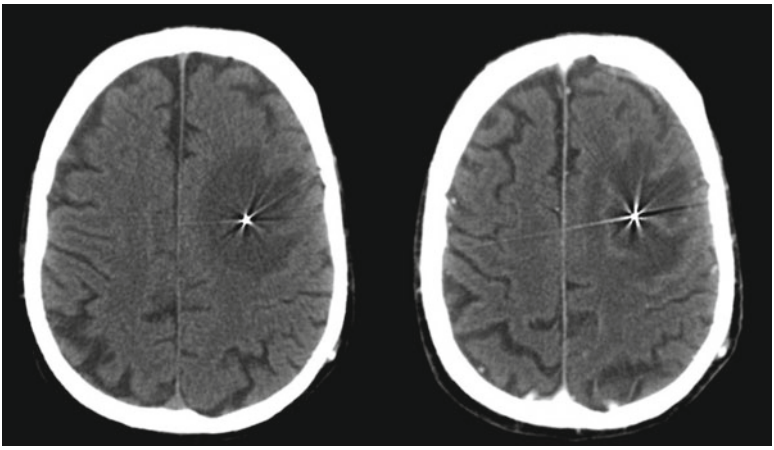

Fig. 20.2 Computed tomography (CT) scan images of a brain abscess following DBS lead implantation. A CT scan image without contrast (*left*) revealed a low density area which indicated an edematous lesion surrounding the DBS lead. The lesion was enhanced with contrast media (*right*) (adapted from [2], used with permission of Elsevier)

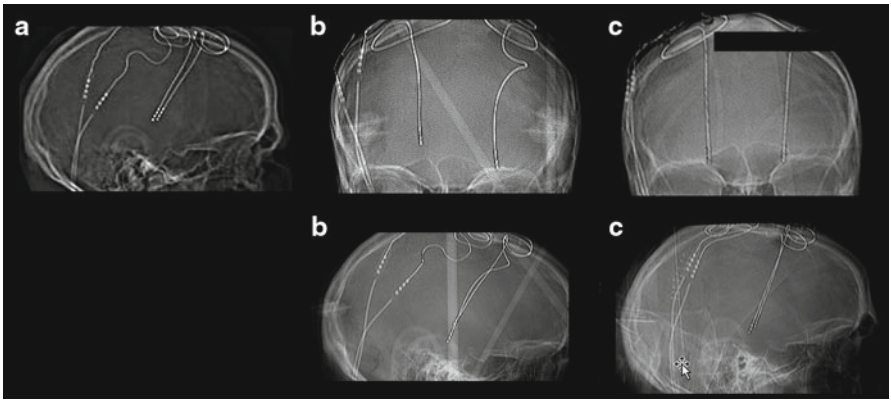

Fig. 20.3 Ventral lead migration shown by serial X-rays. (**a**) A skull X-ray at 1 month postimplantation. (**b**) A skull X-ray at 14 months following first operation. The left and right leads had moved approximately 16 and 5 mm downwards from the initial position, respectively. (**c**) A skull X-ray at 1 month following lead replacement (adapted from [2], used with permission of Elsevier)

Patient 10: Hardware Malfunction

A 52-year-old man with a history of PD underwent bilateral STN DBS. Two months following the procedure he presented to the emergency room with head trauma due to fall. There was a wound noted over the right DBS lead that was

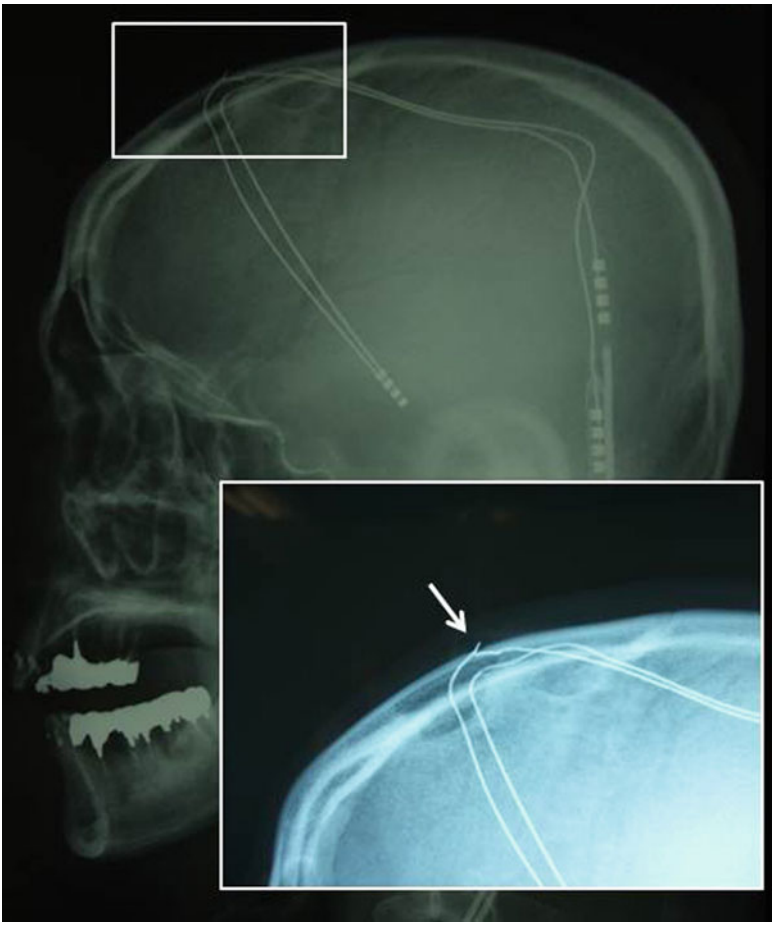

Fig. 20.4 A plane skull X-ray film showing the lead fracture following head trauma. *An arrow* indicates the fractured lead

observed to be exposed. Vigorous wash with normal saline and debridement were performed to clean the wound. Following the head trauma, he complained of loss of efficacy of DBS. The impedance was greater than 2,000 Ω, and a head X-ray revealed a lead fracture (Fig. 20.4).

Introduction

DBS has become an established procedure for movement and neuropsychiatric disorders, as recent reports have revealed the efficacy of DBS for many indications [12–16]. With the increased use of DBS, DBS-related problems have emerged as

more common and more important for clinicians. When an adverse event occurs, clinicians should consider the most probable diagnoses and develop an appropriate treatment plan. DBS-related issues may manifest in unusual ways, and the differential diagnoses usually vary widely with the situation [2, 4, 17]. We therefore separate the possible scenarios into: (1) perioperative (intra- and early postoperative) and (2) postoperative (following 2–4 weeks) settings. With the ten clinical vignettes described above, we address how clinicians should appropriately detect and manage the "don't miss" emergent/urgent issues in a DBS cohort.

Perioperative Management

Intracranial Hemorrhage

Clinicians should be cautious about intracranial hemorrhage, as this complication has a high propensity to result in neurological deficits. Damage to blood vessels by MER and/or macrostimulation passes can potentially result in intracranial hemorrhage. Several authors argue that MER, especially multi-track MER, increases the risk of intracranial hemorrhage, but this topic remains controversial [18, 19]. The incidence of hemorrhage ranges from 0.4 to 5.3% [1, 7, 20–26]. As delay of identification and management may prove critical, clinicians should remain alert for hemorrhagic complications.

In the operative setting, intracerebral (ICH) and intraventricular hemorrhage (IVH) are the most frequent forms of serious bleeding encountered in DBS therapy. Hemorrhage may manifest as an epileptic seizure, altered mental status (Patient 1) or hemiparesis (Patient 2) [1]. When these symptoms emerge suddenly, clinicians should consider the possibility of ICH or IVH, and an immediate CT scan should be undertaken. Delay of identification and management of ICH may result in significant morbidity, and emergent care should be employed to prevent both primary and secondary complications. When an intracranial hemorrhage is diagnosed postoperatively, neurosurgical evaluation should be rapidly performed, preferably by the neurosurgeon who implanted the DBS system. Although most patients can be managed conservatively by optimizing blood pressure and with rest and neurorehabilitation, when the ICH is large, causes mass effect, and/or obstructive hydrocephalus, neurosurgical management such as craniotomy or intraventricular drainage may be necessary (Table 20.1).

Intracranial hemorrhage may result from venous infarction as shown in Patient 3, and in this case the symptoms emerged in a delayed fashion [3, 19]. Patients with venous infarction may present to the emergency room complaining of altered mental status or with motor problems such as hemiparesis. It is typical of venous infarcts that they occur a few hours to days following DBS surgery. Venous infarction is associated with damage to the cortical veins and to venous lakes, and the damage may result in venous stasis and/or venous hypertension. In severe cases, the impaired venous circulation may result in ICH. Therefore, careful preoperative targeting

Table 20.1 Management of DBS-related emergencies

Issues	Management
Intraoperative emergencies	
Intracerebral hemorrhage	If the hemorrhage is very large or has symptomatic mass effect, an emergent craniotomy may need to be performed
Intraventricular hemorrhage	Ventriculostomy if necessary for obstructive hydrocephalus
Subdural hematoma	Bur hole irrigation should be performed when the hematoma is symptomatic
Air embolus	Wax edges of the bur hole, occlude the bur hole with gel foam and saline, lower patient's head, jugular venous compression, administer oxygen
Dyskinetic storm	Sedative agents may be administered in select cases. Reducing the dopaminergic medication may help. In some cases ICU care is necessary
Epileptic seizure	Sedative agents such as propofol or a benzodiazepine such as diazepam should be administered immediately
Early postoperative emergencies (<2–4 weeks)	
Venous infarction	Conservative supportive therapy is usually all that is necessary. An emergent craniotomy may be performed if hemorrhage is life threatening
Myocardial infarction	Do not ignore chest pain in a patient who has just had a subclavicular IPG placed. Immediate diagnosis by 12-lead electrocardiogram and laboratory investigation, and cardiology consult should be performed
Neuroleptic malignant syndrome	IV fluid and L-dopa should be administered immediately. If necessary nasogastric tube should be placed for patients with difficulty in oral intake. ICU care is necessary. Administering dantrolene is an option
Behavioral/cognitive issues	Identify and treat the underlying issues (e.g., UTI and pneumonia). Selective dopamine blockers (e.g., clozapine, quetiapine) may be used, but nonselective blockers should be avoided if possible. Use a one-to-one sitter to avoid secondary injury, e.g., from falling
Infection-UTI/pneumonia	Hydration and appropriate antibiotics. Care should be taken to adjust PD medications as levels may be altered by antibiotics. Surgical debridement or removal of hardware as necessary
Postoperative emergencies (≥2–4 weeks)	
Suicide ideation/attempt	Admit the patient to the hospital for multi/interdisciplinary care, and treat underlying cause. May need both medication adjustment and programming. Check lead location
Severe depression	Behavioral therapy, counseling, medication adjustment, and/or stimulation adjustment. Check lead location. Consider admission for multi/interdisciplinary management
Infection-lead	The lead should be removed and appropriate antibiotics should be administered
Infection-IPG	The IPG and usually the extension cable should be removed and appropriate antibiotics should be administered
Lead migration	Lead replacement, or surgical alteration of lead position
Lead fracture	Lead replacement, if an appropriate candidate
Lead electrical short	Lead replacement, or potentially reprogramming at a different contact
IPG malfunction	IPG replacement, manage potential rebound symptoms
Accidental on/off	Turn on the IPG. Educate the patient and the family so they can use on/off devices
Symptom rebound (motor and/or non-motor)	DBS hardware workup including impedance check, battery check, X-ray study, and assess for tolerance

DBS deep brain stimulation, *ICU* intensive care unit, *UTI* urinary tract infection, *PD* Parkinson's disease, *IPG* implantable pulse generator

utilizing a high-quality MRI (with contrast) to avoid these superficial venous structures is helpful to prevent the occurrence of venous infarctions. Management of venous infarction is usually nonsurgical and includes optimizing the venous return, appropriately managing blood pressure, and avoiding dehydration (Table 20.1). A longer hospital stay following intracranial hemorrhage may result in secondary complications such as pneumonia and pulmonary embolism. Early initiation of rehabilitation may be useful to avoid secondary complications.

Subdural Hematoma

The bur hole opening for DBS, though small, can lead to the development of a subdural hematoma (SDH). A SDH forms with the accumulation of blood products in the space between the surface of the brain and the dura. The incidence of SDH after DBS has been estimated at 0.08–4.2% of leads [11, 27]. During DBS lead placement a burr hole and dural opening are created and left open for up to several hours. The exit of cerebrospinal fluid and entry of air can enlarge the subdural space, and combined with sagging or shift of the brain can lead to stretching of bridging veins. This brain sag and stretching of bridging veins can be exacerbated by atrophy, a finding not uncommon in the older population that is typically seen with DBS. Damage to bridging veins can lead to the development of a postoperative SDH. Furthermore, in this older DBS age group many patients take antiplatelet agents for cardiovascular health. They are also at an increased risk of falls due to their movement disorder diagnoses, although in one recent series of four SDH's after DBS there was no associated fall or trauma [11].

Subdural hematomas can enlarge to the point of herniation and neurologic deficits, brain damage, and death. A SDH in the setting of a patient with an implanted DBS lead presents a unique situation in that the operation to alleviate the pressure of the SDH, which is typically a straightforward bur hole or craniotomy, can lead to damage or removal of the DBS system, which negates a large investment of resources and commits the patient to another procedure for reimplantation of the DBS lead if so desired.

Patients with chronic SDH's can have a simpler burr hole procedure to evacuate the blood products without sacrificing the lead. Care must be taken to avoid the DBS burr hole and locking mechanism, as well as the distal lead as it traverses the subgaleal plane towards the extension cable. Therefore, when a DBS patient presents with an SDH that needs surgical intervention, the first question is whether it can be treated with burr holes. If it is an acute SDH that does not look amenable to burr holes, can the patient wait a few weeks until the clot liquefies? Finally, if a large craniotomy is necessary to remove the acute solid-phase blood products, or if the SDH has organized membranes, fashioning a craniotomy that has a "plank" of bone that attaches the burr hole and locking mechanism to the rest of the patient's skull may save the lead. Care must be taken during the opening of larger scalp flaps that the lead, which can be scarred into the scalp flap, isn't accidentally pulled or dislodged as the scalp flap is elevated.

Some surgeons are concerned that with the removal of the SDH, the DBS lead will cause damage to the brain as it shifts back to its original position. In our experience, once the SDH has resolved, the DBS lead can regain efficacy and causes no new injury. There often is a significant delay (4–18 months) between the time of SDH evacuation and achievement of clinical efficacy of the DBS system, so providers must be patient to allow this to happen before prematurely repositioning the lead in the belief that it is ineffective [11].

In summary, for an SDH, the well being of the patient must always come first even if it means sacrificing the lead. However, there are many strategies that can be used to salvage the DBS lead and still achieve clinical DBS efficacy while taking care of the SDH. The informed neurosurgeon can thus do the patient a favor by not damaging or removing the system whose implantation risks the patient has already endured.

Air Embolus

Air embolus is a relatively common complication of neurosurgical procedures, and neurosurgeons are cautious when a craniotomy is performed especially when done in a sitting position. Clinicians should be aware that DBS surgeries may result in a venous air embolus, and recent studies have shown that the incidence of air embolus during DBS surgeries can be as high as 1.3–3.2% [6, 28]. Entrainment of air into the venous system through diploic veins when fashioning a burr hole is the usual mechanism. Even though the clinical course is commonly benign, this complication can result in termination of the procedure [28]. It is therefore important to preoperatively adjust the head position of the patient making it as close to supine as possible. Waxing the edges of the burr hole, avoiding cortical veins and dural venous structures, keeping the burr hole filled with saline or occluded with a gel foam (or other material) plug are other ways of preventing the entry of air into the venous system.

DBS-related air embolus may manifest differently than in other neurosurgical procedures, since in DBS the patient is commonly awake rather than under general anesthesia [6, 28, 29]. When tachycardia, oxygen desaturation, and/or cough are seen, clinicians should consider the possibility of a venous air embolus. In a recent series, the use of an external Doppler device was shown to be potentially helpful to detect air embolus during DBS, although the cough was the best predictive sign [6]. When air embolus occurs, care should be taken to lower the head position, wax bone edges of the burr hole, vigorously irrigate the surgical field, and support the patient's cardiopulmonary status (Table 20.1).

Dyskinetic Storm

Following MER and/or macrostimulation passes, immediate improvement of the symptoms may be observed, and the improvement has been referred to as the

"microlesion effect" or implantation effect. Microlesion effects have been considered to be a positive response and may in some cases predict good prognosis [30–32]. Dyskinesia may be seen intraoperatively as a part of a microlesion effect in PD. Clinicians should be aware that intraoperative dyskinesia may develop into a severe situation referred to as "dyskinetic storm" [5, 31]. Dyskinetic storm may be an emergency as the head is usually fixed to the stereotactic frame during the operation. To secure the integrity of the head ring and to ensure the patient's respiratory condition, this situation should be quickly corrected. Emergent administration of sedative agents (such as intravenous (IV) propofol) may be required to stabilize the situation (Table 20.1). If a dyskinetic storm persists or begins after the operation, judicious withdrawal of dopaminergic medications and/or the monitored administration of propofol can be used to dampen the dyskinesias.

Intraoperative Seizure

An intraoperative seizure can be induced by an intracranial hemorrhage, pneumocephalus, and intraoperative electrical stimulation (micro- and macrostimulation) as shown in Patient 4 [1]. As the patient's head is fixed to the stereotactic frame, a generalized seizure may put the patient in a hazardous situation. When an intraoperative seizure is encountered, antiepileptics or sedative agents (e.g., IV propofol) should be immediately administered (Table 20.1). Some authors recommend the use of IV lorazepam or thiopental in severe cases [1]. Intubation may be required in severe cases, although most cases are self-limited and can be managed conservatively [1]. If the patient recovers to be alert following the seizure, the procedure may in select cases be continued if the neurological examination is normal.

Neuroleptic Malignant Syndrome

Discontinuation of PD medications for DBS surgery may result in neuroleptic malignant syndrome (NMS) as shown in Patient 5. NMS can occur as a postoperative emergency and is usually characterized by parkinsonism (rigidity, bradykinesia, and possibly tremor), fever, and in some cases rhabdomyolysis. NMS usually results either from exposure to dopamine blockers or from sudden withdrawal of dopamine (e.g., carbidopa/levodopa). It should be kept in mind that patients with PD usually undergo DBS in the off medication condition, so physiology can be recorded in the abnormal state. Therefore they are at theoretical risk for NMS, although usually NMS occurs after more than 24 hours of medication withdrawal [33]. Abrupt cessation of dopamine or dopamine agonists should be avoided postoperatively, and therapy restarted even if a nasogastric feeding tube is required. If NMS occurs, patients should be admitted to the ICU so that they can receive supportive care, fluids, and appropriate treatments. Administering dantrolene is an option [34]. NMS

may innocently occur as postoperative hallucinations and/or behavioral anomalies that may prompt the clinical team to follow a course of dopamine cessation. In other cases, physicians may have stopped oral medications following surgery and forgotten to restart them. If NMS is encountered, we advocate restarting dopaminergic therapy as an urgent course of action.

Behavioral and Cognitive Problems

Behavioral and cognitive problems are often seen following DBS surgery, and the incidence of perioperative confusion and hallucinations were reported in a large single center study to be as high as 5.0 and 2.8% [17]. Early postoperative behavioral/cognitive problems were reported as usually temporary, however in some cases they required emergent/urgent management. If left unaddressed these problems may result in secondary complications such as falls and subsequent traumatic injury. Risk factors for mental status changes following DBS include advanced age and/or preexisting neurological compromise [35]. These issues are relatively common in the PD cohort [9]. The use of anticholinergics (including not only anti-parkinsonian medications but also medications for neurogenic bladder) can also be a risk factor, and discontinuation of these medications may be required in high risk cases [36]. In addition, previous reports have shown that STN DBS has a higher incidence of postoperative mental status change than GPi DBS (although this is not an absolute distinction) [15, 37–39]. Therefore, all patients should have neuropsychological testing preoperatively, and the risks should be fully discussed. Tailoring approaches may be helpful to address these potential issues on the preoperative setting [2, 40]. When the estimated risk of behavioral and cognitive problems is high, GPi DBS and/or staged unilateral DBS implantation may be preferable procedures in some centers. If patients become restless and violent postoperatively due to hallucinations/delusions, administering selective dopaminergic blockers such as quetiapine or clozapine may be useful (Table 20.1) [41]. Use of nonselective dopaminergic blockers that lead to drug-induced parkinsonism as well as other movement disorders (e.g., olanzapine, risperidone, and haloperidol) should be avoided [33, 34].

Myocardial Infarction

Several studies reported cases with myocardial infarction (MI) following DBS surgery [1, 9]. Although DBS has been considered to be a safe procedure even for patients with cardiac problems [42], medical comorbidities such as CAD may be considered to increase the risk of postoperative MI as seen in Patient 6 [2, 35]. Medication lists should be also checked because specific medications such as meperidine, MAO-B inhibitors, bromocriptine, and tricyclic antidepressants (TCAs) may increase the risk of general anesthesia [43]. Although MI can be encountered

following any surgical procedure under general anesthesia, clinicians should have a higher level of suspicion when the patient complains of chest pain following DBS so as not to mistake cardiac chest pain for postoperative chest pain. Chest pain is a common symptom for patients who have undergone DBS surgery as the battery packs (IPGs) are implanted in the chest wall in the majority of cases [9]. As MI is a life-threatening condition, the patient should be admitted to ICU and cardiology consultation should be performed (Table 20.1).

Postoperative Management

Suicide Attempt and Ideation

Suicidal ideation should be treated as an emergency as the mortality rate can be high if suicide is attempted. A meta-analysis revealed as high as approximately 52% of cases with suicide ideation and/or attempts were reported to complete suicide following DBS (data from 1996 to 2005) [44]. The same study revealed that most of the patients with suicidal ideation and/or attempts had undergone DBS for PD, and a recent multicenter study of an STN DBS PD cohort revealed several important factors that were risks for suicide attempts: preoperative history of impulse control disorders or compulsive medication use, postoperative depression, postoperative apathy, and being single [45]. Previous suicide attempts, younger age of the patient, and younger onset of PD were also shown to be risk factors for suicide attempts. In addition, there have been several reports of suicide in patients with dystonia who underwent DBS, therefore clinicians should be aware that this issue is not limited to PD [46–48]. Preoperative neuropsychological and psychiatric evaluation is therefore highly recommended as a preventative measure for all patients who will undergo DBS surgery [35, 49].

Appleby reported the mean time difference between implantation and the development of suicidality was 2.4 years, and other authors have reported even shorter durations [44]. Screening for suicidal ideation following DBS therefore should be routine, and if discovered, the issue should be treated as an emergency. Also of note is that stimulation of the limbic components of deep brain basal ganglia structures may result in acute depression [49–53]. Patients with suicide attempts and/or ideation should be admitted to the hospital for multi/interdisciplinary care including cognitive behavioral therapy, counseling, and/or medication/stimulation adjustment(s) (Table 20.1).

Hardware Infection

Hardware-related infections are not uncommon complications of DBS. The incidence of infection and/or erosion following DBS surgery has been reported to range

between 0 and 15.2% [1, 7, 22, 54–60]. Even the most vigilant surgical technique cannot guarantee that there will be no postoperative infectious complications. Although risk factors have not been clearly elucidated, medical comorbidities such as uncontrolled diabetes mellitus may increase the infection rate. Several authors have advocated the use of pre- and postoperative prophylactic antibiotics, however the efficacy has not been clear [58]. One recent study did however report a reduction in the infection rate by locally injecting anti-staphylococcal antibiotics (e.g., neomycin, polymixin) directly into the operative wound, although this remains controversial [60].

The devices in an infectious scenario may require emergent removal as shown in Patients 7 and 8. Cultures should be sent anytime hardware is removed or a potentially infectious IPG pocket is aspirated. Several factors should be considered when managing a DBS infection (1) whether the infection is deep or superficial, (2) whether the brain lead is involved or not, and (3) whether there are single or multiple sites of involvement [54]. Management of a hardware infection should be performed in an attempt to minimize hardware removal. Emergent hardware removal may be required in cases with a deep infection, however select cases with a superficial infection may be managed with administration of antibiotics. When the brain lead and/or multiple sites are involved, most clinicians remove all hardware including lead, extension, and IPG. However, in cases where only the IPG or extension cable appears infected, removing only the infected hardware in an attempt to preserve the brain lead is an option. In any cases with hardware removal following an infection, a course of 6–8 weeks of IV antibiotic therapy is required before device(s) reimplantation (Table 20.1).

Lead Migration

Lead migration can be seen in patients complaining of loss of efficacy of their DBS device(s), and this issue can be the result of a malfunction of the anchoring devices, skull growth, vigorous head movements, and rarely from compulsive manipulation of the IPG referred to as "Twiddler's syndrome" [2, 4, 61, 62]. Yianni reported lead migration in 3 of 133 patients (2.3%), and all 3 patients underwent DBS for dystonia [61]. The authors hypothesized that axial movements contributed to lead migration, as seen in Patient 9. When lead migration is noted, clinicians should be cautious as it may result in severe mood changes due to the spread of the stimulation to other regions such as the amygdala [63]. Skull growth in children is another cause of lead migration [2]. Twiddler's syndrome may also result in dorsal lead migration [62]. This adverse event highlights the importance of obtaining and reviewing postoperative imaging. When lead migration is noted, changing the active contact (deeper or shallower depending on the direction of migration) should be attempted prior to surgical revision [10].

Hardware Malfunction

When a DBS patient reports sudden loss of efficacy, the clinician should consider hardware malfunction [2, 4, 37]. Mechanical stress to the device may result in lead fracture, a break in the extension cable, or an IPG failure. A recent single center prospective study revealed that the incidence of hardware malfunction was 2.0% [7]. On the other hand, another study reported that 8 (6%) of 133 cases had lead fracture, and 7 of 8 broken electrodes in their cases were encountered in patients with ET [58]. They speculated that head tremor may have contributed to the adverse events [58]. Twiddler's syndrome has also been reported to result in lead and/or extension cable fractures [8, 62, 64, 65]. Head and neck trauma may also result in lead and/or cable fracture (Patient 10), and it is theorized this may occur more commonly in dystonia. Clinicians should be aware that DBS patients complaining of a fall are relatively commonly encountered in the emergency room [9]. When clinicians encounter situations predisposing the patient to a hardware malfunction, skull X-rays and/or CT scan should be performed (Fig. 20.4).

To confirm the diagnosis, the impedance and current drain for each of the four lead contacts should be measured with the DBS programming/interrogation device. High impedance along with a low current drain is consistent with a lead fracture or with an extension cable break. On the other hand, low impedance with possible high current drain may indicate a short circuit. In short circuits, palpating the IPG or the extension cable tract may cause a shock-like sensation. When any contacts with normal impedances/current drain values exist, reprogramming should be attempted (Table 20.1). A plain film X-ray also yields useful information to identify a fracture along the course of the lead or extension wire. When the location of the problem cannot be precisely identified, replacement of the extension wire and retesting impedances in the operative setting is recommended. This procedure may save the intracranial lead replacement in select cases [4].

Accidental On/Off and Symptom Rebound

Clinicians should be aware that symptom rebound may include not only motor symptoms but also non-motor manifestations such as suicidal ideation (author observations) as well as severe depression. Several cases of severe symptom rebound following battery failure have been reported [66, 67]. The more beneficial DBS proves for clinical symptoms, the more dramatic the rebound symptoms may be. Sudden worsening of symptoms should always prompt a battery status check by an experienced DBS programmer. If the device is on, hardware malfunction should be considered. The management includes checking impedances and current drain at each of the four DBS contacts and imaging studies as described above in the "Hardware Malfunction" section. If the device is off, resuming stimulation may be

all that is necessary. When symptom rebound is seen following trauma, an X-ray film may be helpful to identify the cause such as DBS lead and/or extension cable fracture.

When the DBS device unpredictably turns off, the clinician must investigate potential environmental triggers (the device has a duty log to assist in documenting these occurrences). Exposure to magnetic forces (e.g., a magnetized ice freezer or store security devices) is the most commonly reported etiology [57]. Educating the patient to recheck the DBS device on a regular or semi-regular schedule may be useful. Additionally, documentation of daily activities and relevant environments that they frequent may help in identifying the source of the problem. Education is important so that the patients avoid strong magnetic fields, have their remote device with them at all times in order to recheck battery (on/off) status, and learn prevention strategies for accidental on/off's (Table 20.1).

Conclusions

Patient screening and standardized procedures may prevent avoidable complications. Preoperative evaluation by a multidisciplinary team assesses the detailed risks in each patient, and the DBS procedure and the perioperative management should be tailored for individual needs. Tailoring the approach in selecting the optimal target (e.g., GPi or STN), procedure (e.g., staged or simultaneous implantation of DBS leads), and perioperative medication adjustment may help avoiding unnecessary complications. Development of DBS technologies will likely lead to new treatment options, but clinicians should remain vigilant and aware that the perioperative management is vital for managing patient-specific risks.

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Chapter 21
Psychogenic Movement Disorders

Daniel Schneider and Daniel T. Williams

Abstract Psychogenic conditions are a diagnostic and treatment challenge for physicians of all specialties. Psychogenic literally means "generated from the psyche" and is frequently used in neurological literature as a blanket term to encompass a variety of psychiatric conditions that mimic neurological symptoms including conversion disorder, malingering, factitious disorder, and others. While commonly used, the term "psychogenic" has a number of limitations and these are discussed in the text.

In this chapter we review the literature on psychogenic movement disorders, focusing on both those with a loss of motor function (i.e., weakness) and those with a "gain" of abnormal motor function (i.e., psychogenic tremor, dystonia, myoclonus, parkinsonism, tics, etc.). Some have characterized psychogenic disorders as a diagnosis of exclusion but we discuss why this is not the current paradigm and give particular emphasis on the positive and negative findings that help to make the diagnosis. We also review the limited evidence regarding the pathophysiology and treatment of these disorders and conclude with practical tips regarding the care of these patients.

Case Report

Jon had a long-standing history of motor and vocal tics dating from age 5. A Diagnosis of Tourette's disorder was first established at age 10. A variety of medications were tried in an effort to control his tics, including benzodiazepines, neuroleptics, anticonvulsants, and tetrabenazine, but none of these were of sustained

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benefit. Jon developed severe anxiety, obsessive–compulsive symptoms, school avoidance, and depression. His tics and psychiatric symptoms worsened over time, despite the efforts of numerous neurologists, psychiatrists, and Tourette specialists. By age 15, Jon's head tics became so severe that there was concern regarding cervical spinal injury and he was admitted via the emergency room to our neurology ICU, where intravenous barbiturate anesthesia was only partially successful in attenuating his symptoms. His family subsequently sought independent opinions at three other medical centers, resulting in a variety of additional pharmacological trials with concomitant psychotherapy geared to coexisting psychopathology as well as an attempt to attenuate postulated psychogenic factors contributing to the tics, which were thought to be at least in part psychogenic. Despite these intensive treatments, Jon's tics persisted at a level of damaging severity, including a bone fracture, and severe depression prompting two psychiatric hospitalizations. Lithium was added because of a concern regarding possible bipolar mood disorder. Finally, the family sought elective deep brain stimulation (DBS) for the treatment-resistant disabling tics, but this prompted an institutional review because of the disagreement by some clinicians who feared that a prominent psychogenic tic component had been inadequately treated. After another admission to our pediatric neurology inpatient service, collaborative pediatric neurology, movement disorder, and psychiatry consultants reached a consensus that the primacy of a neurologically based movement disorder warranted DBS, allowing the surgery to proceed. Immediately after the DBS surgery, the tics were first totally abolished, then maintained at a drastically reduced, subclinical level with appropriate monthly modulation of the DBS over a now 4-month follow-up. Jon has returned to school, with a marked improvement of his psychiatric status, allowing a gradual tapering of his neuroleptic, benzodiazepine and lithium doses in monthly psychiatric follow-up.

While this case is unusual in the complexity of differential diagnostic and treatment considerations involved, it illustrates the need for both open-minded humility and thoughtful collaboration in this fascinating neuropsychiatric domain.

Introduction

The appearance of a chapter on psychogenic movement disorders in a text concerning movement emergencies may surprise some readers. Yet, upon reflection, it should not. Most physicians can relate to the experience of being urgently requested to consult in one's office or local emergency department on a patient who is eventually given the diagnosis of a psychogenic neurological disorder. These disorders seem to account for anywhere between 3 and 10 % of new patient visits in specialty neurology clinics [1–4]. The distress experienced by these patients and their families can be equivalent to or exceed that of other emergent neurological conditions, and the

consequences of misdiagnosis and delay of treatment no less severe [5, 6]. Over the next few pages we will explore what is known about these conditions while focusing on information to assist in their diagnosis and treatment in emergent situations.

A Note on Terminology

Before beginning, we need to take a moment to clarify our definitions. Throughout this chapter we will be using the term "psychogenic" to describe movements that are both without a clear structural etiology and believed to be of psychiatric origin. There are a number of psychiatric diagnoses that would fit these criteria, but the most well-known example is Conversion disorder or Conversion Hysteria. As defined by the DSM-IV-TR [7], Conversion disorder is diagnosed when symptoms resemble neurological complaints but cannot be fully explained by the known physiology of the condition they most resemble. The defining characteristic of Conversion disorder is that the symptoms are not deliberately or consciously feigned, but occur outside of the patient's awareness. This is in contrast to similar syndromes like Malingering and Factitious disorder, where the movements are voluntarily produced.

By utilizing the label "psychogenic," we are placing ourselves in accord with much of the recent neurology literature concerning this type of presentation, though other terms like "functional" [8], "nonorganic" [9], "hysterical" [10], and "conversion" [11] can also be found. While using this term, we recognize its significant limitations. In 1972, Aubrey Lewis [12] wrote a useful review of the history of "psychogenic" as a descriptor. He highlighted its varied use and frequently imprecise definitions over the years. This same problem persists, and in casual conversation, the word "psychogenic" might mean anything from Conversion disorder specifically, to any Somatoform disorder, to a mixture of all Somatoform disorders as well as Malingering and Factitious disorder and even other psychiatric-induced motor symptom such as stress-induced exaggerated physiologic tremor (defined in the DSM as "psychological factors affecting a medical condition"). Some neurologists have championed this vagueness as one of its virtues [13], stating that it is not the role of the neurologist to make these distinctions. Yet, we need to be cautious in this approach. Vagueness in diagnosis impairs communication. It makes conceptualizing and evaluating research difficult and makes discussion of prognosis and treatment nearly impossible.

There is another limitation. "Psychogenic" implies a theory of etiology (i.e., symptoms arising from the psyche—the mind or soul). This immediately begs the question of how do we operationalize the word "psyche"? Do we imagine this to be separate from the brain? How do we test this? This may seem to be a trivial issue, but it is at the heart of our understanding of this disorder. By placing the etiology in a nonanatomical construct like "psyche," we shape the way patients and physicians conceive of the diagnosis. This can affect numerous areas including funding for

research, the design of studies, how disability claims are judged, and how family members and friends respond to patients. The medical field has tried this before, and the story of the rise and fall of "hysteria" should be a fair warning to encourage humility in this regard. We base this theory of etiology on the correlation between conversion symptoms, stress, and other psychiatric syndromes, but we know the importance of caution when making conclusions about causation from observations of correlation. The fact is that we have limited understanding of these symptoms, including how they arise or how they are perpetuated. Further, by characterizing symptoms as originating from the psyche we are left with describing non-psychogenic symptoms as "organic," a distinction that is difficult to justify based on our modern understanding of neurophysiology and highlights some of the theoretical difficulties of this conceptualization.

While we have chosen to use "psychogenic" in this chapter despite these limitations (as well as its opposite: "organic"), we encourage the reader to keep these caveats in mind. We made this decision for the simple reasons that the other common terms are even more problematic and "psychogenic" is a phrase with which most neurologists are familiar. Other terms could certainly be introduced, but doing so would be well beyond the scope of this chapter.

Pathophysiology

The pathophysiology of psychogenic movement disorders is not well understood. The key pathological and physiological features are an absence of structural abnormalities by traditional means of investigation (i.e., imaging, pathology, evoked potentials, EMG, EEG, etc.). Conversion disorder has garnered the most interest due to the mysterious nature of its chief clinical symptom: the lack of conscious awareness of motor phenomena that by all other measures (i.e., distractible, suggestible, irregular, cause fatigue, etc.) should be under conscious control. Psychodynamic explanations focusing on the transformation, or "conversion," of unconscious psychic phenomena into somatic complaints dominated the literature for decades [14]. Unfortunately these theories have been difficult to subject to scientific scrutiny. Recent literature has tried to investigate the neurobiological substrates of motor conversion. Here we must make a distinction between negative motor symptoms (e.g., weakness) and positive motor symptoms (e.g., tremor, dystonia, parkinsonism, tics, and myoclonus). Psychogenic seizures could also be considered within the context of positive motor conversion symptoms, but a full investigation of these phenomena must be considered outside the scope of this chapter.

Theories to explain weakness have focused largely on functional imaging findings that support either mechanisms limiting the generation of motor intention [15, 16] or mechanisms impairing the execution of these motor intentions [17, 18]. Studies have also been done that establish abnormal processing of sensory [19, 20]

and cognitive information [21–24] in patients with these conditions. Limited work has been done on positive motor symptoms, but mechanisms for abnormal limbic processing [25] as well as mechanisms to explain the interruption of conscious awareness [26] have been investigated. There is a single study looking at blood flow abnormalities in patients with psychogenic gait [27], and a case report of two patients with abnormal F-DOPA PET uptake despite clinical psychogenic parkinsonism and improvement of the scans over time or with improvement of their symptoms [28].

A final note should be made about the few studies that have included subjects with voluntary production of symptoms as a comparator group to those with presumed conversion symptoms [15, 18, 23, 26]. Although these studies are small, the fact that differences were found on functional imaging provides support for our clinical differentiation of patients with consciously and unconsciously produced symptoms, and provides hope that a physiological test might be devised to help differentiate these two conditions in the future.

Diagnosis

Accurate diagnosis of psychogenic movement disorders is of fundamental importance for those treating emergent conditions. Virtually all movement disorders seen by neurologists have a psychogenic equivalent. Even movements difficult to voluntarily reproduce like palatal tremor have been documented as psychogenic [29, 30]. Physicians frequently fear making a diagnosis of psychogenic because of the concern that a misdiagnosis could irreparably damage the physician–patient relationship or even lead to legal repercussions. However, the opposite should be equally concerning. The misdiagnosis of a psychogenic condition as organic can lead to significant iatrogenic harm by physicians through unnecessary treatments and surgeries [31, 32]. Further, in the field of movement disorders, many conditions have limited or no medical treatment, but this is not true for psychogenic diseases. Failure to consider a psychogenic etiology could lead to a significant delay in providing disease-altering treatment.

It has been noted that the diagnosis of psychogenic disease is a two-stage process: neurological and psychiatric [33]. First a neurological diagnosis must be made to differentiate organic from nonorganic disease. A psychiatrist is not well qualified to perform this task and they should not be asked to take on this role. Recent studies reveal that when physicians make the diagnosis of psychogenic, they tend to be correct. Stone performed a meta-analysis of reports in the literature since 1965 and found that only about 4 % of subjects reported after 1970 were misdiagnosed as psychogenic [34]. Unfortunately, there is no similar study to evaluate the frequency of physicians diagnosing someone initially with an organic condition but then changing their diagnosis to psychogenic. Typically, diagnostic certainty is graded on a scale of 1–4 (see Table 21.1), with levels one and two (“documented” and

Table 21.1 Diagnostic certainty for psychogenic movement disorders (created from [42])

CLASS I: Clinically documented—persistently relieved by psychotherapy and/or other adjunctive therapies like suggestion or administration of placebo
CLASS II: Clinically established—physical exam and history consistent with psychogenic movement disorder
CLASS III: Probable—inconsistent and incongruent movements but no other supporting features, Consistent and congruent movements but other physical exam features supportive of psychogenic etiology, consistent and congruent movements in a patient with multiple other known somatizations
CLASS IV: Possible—presence of psychiatric disturbance in the patient but no obvious signs or symptoms that clearly support a psychogenic etiology

Table 21.2 General clinical clues to psychogenic disease

Abrupt onset
Spontaneous remissions or paroxysmal disorders
Inconsistent symptoms
Incongruous movements and postures that are often bizarre
Delayed, often excessive, startle response
Stuttering speech broken into syllables or meaningless speech
Nonanatomic sensory abnormalities
Response to suggestion or placebo
Excessive fatigue or exhaustion
History of somatization or recent psychic trauma

"clinically established," respectively) being known collectively as "Clinically Definite" disease [31, 35, 36].

Once a neurological diagnosis has been established, it is the role of a psychiatrist to help differentiate unconsciously generated symptoms (conversion disorder) from consciously generated symptoms (factitious disorder and malingering). It is also the psychiatrist's role to put the symptoms into a larger perspective of other somatoform disorders such as somatization disorder (of which, conversion symptoms is just one of the eight required symptoms necessary for diagnosis), and evaluate other comorbid psychiatric syndromes like mood, anxiety, psychotic, and personality disorders [37]. It is well beyond the scope of this chapter to discuss the psychiatric differential diagnosis in detail, but one point is important for the neurologist making the initial diagnosis. Emergent psychiatric symptoms such as suicidality and psychosis should be assessed during the evaluation. The presence of these symptoms, or any indication that the patient might be a danger to self or others, would require more urgent psychiatric evaluation then would otherwise be expected.

The neurologic diagnosis is not a "diagnosis of exclusion" as is the conventional wisdom, but is instead based on a mixture of positive and negative findings like any other medical condition. Table 21.2 lists a number of general features in the history and physical exam that might make one consider a psychogenic diagnosis, and Table 21.3 lists features of interest in specific syndromes. None of these signs or

Table 21.3 Clinical clues to specific psychogenic syndromes

Tremor	*Gait*
Entrainment of tremor	Coarse vertical tremor
Reduction or disappearance with distraction	Knee buckling
Absence of finger tremors (when they would otherwise be expected)	Bizarre postures without falling
Increase in tremor with inertial loading	Falls always away from examiner or away from harm
Reduction when handling treasured objects	Zigzag gait
Maintains consistent amplitude whether in rest, posture or action	Large amplitude body sway on standing
	Improvement on distraction
	Improved gait walking in squatting position
	Multiple falls without harm
Dystonia	*Weakness*
Beginning as a fixed posture	Give-way weakness
Beginning in lower extremity as an adult	Hoover sign
Twisting facial movements that move mouth to one side	Collapsing weakness
Dystonic movements that move in multiple axes	"Dragging" monoplegic gait
	Dropping plegic arm to always avoid striking self
	Ipsilateral Sternocleidomastoid weakness
Myoclonus	Unable to move affect limb once placed into a posture
Variable in appearance	Abductor sign
Jerking that starts too slowly or lasts too long	Improvement with distraction

symptoms are sufficient in themselves for a diagnosis, and unfortunately there is no definitive laboratory test or pathognomonic sign that indicates psychogenic disease. This is why it is important to gather multiple points of information, both supporting psychogenic disease and ruling out other potential causes, before making a diagnosis. Simply noting that one has never seen a patient with a certain symptom is not enough for a diagnosis, nor is noting a single sign and basing one's entire diagnosis on that sign. An illustration of this latter concept is from a study by Gould in 1986 [38]. They looked at 30 patients following an acute structural lesion to the CNS (25/30 with an acute stroke) and evaluated seven historical and physical signs typically associated with psychogenic disease (i.e., history of hypochondriasis, secondary gain, *la belle indifference*, nonanatomical sensory loss, pain or vibration splitting the midline, changing boundaries of hypalgesia, give-way weakness). They found that all patients had at least one of these findings, one patient had all seven, and the average was more than three signs and symptoms. Despite this fact, none of these patients were misdiagnosed as psychogenic because an entire history and examination was undertaken and appropriate testing was done. It is on the collection of multiple points of data that diagnoses are made and one should always be cautious when this is not the case.

One of the features of psychogenic movement disorders is suggestibility, with the most well-known form of this being response to placebo. While its absence does not rule-out the disorder, the presence of placebo response is diagnostic for the disease. The difficulty is the ethical ambiguity of providing a patient with a substance (such as IV NaCl injections) without giving them full disclosure since that very disclosure might decrease the effectiveness of the intervention. Some have argued that given the enormous benefit with only minimal risk, the procedure is appropriate. For others, the lack of informed consent has been a difficult problem to ignore. This is not a debate that can be solved here, but given that the use of placebo is not uncommon, physicians should be aware of the controversy [32, 39–41].

Psychogenic Tremors

The clinical presentation of psychogenic tremor is variable. Symptoms can be intermittent or continuous and affect a single body part, multiple limbs, or even the entire body. Unlike a Parkinson's or essential tremor, the symptoms are often irregular and inconsistent in presentation. The psychogenic tremor may decrease with distraction or suggestion (such as by using a placebo or telling the patient that the vibration of a tuning fork "can disrupt a tremor") and may entrain with movements of voluntary movement of other limbs. This means that the frequency of the tremor can be manipulated to follow the frequency of movements of other limbs, a specific example of irregularity not seen in organic tremors. Other clues such as absence of finger tremors, constant amplitude with changes from rest to posture to action, and failure of the tremor to attenuate when the limb is weighted have also been described [42–46].

Physiological testing can provide valuable assistance in making the diagnosis [44, 47]. Measures of the regularity, frequency, and amplitude of the tremor as well as objective measurement of entrainment, distraction, and changes with weight placed on the affected limb are all helpful. Further, tremor analysis allows one to assess the presence of coactivation of antagonist muscles at the onset of the tremor that is atypical of organic tremors. One difficulty is that with the possibility of so many pieces of data, it not entirely clear how much weight to put on each individual variable or how many are necessary before stating the likelihood of psychogenic disease to be high. One attempt to navigate this problem is Piboolnurak's use of a tree-based statistical algorithm [44]. Here they used the clinical diagnosis as the gold standard and evaluated the results of physiological testing on 71 tremor patients (23 with psychogenic tremor, 22 with Parkinson's disease, 11 with dystonic tremor, and 15 with essential tremor) and 21 age-matched controls. They fed the results into a statistical program and came up with "decision trees" which looked at patients with various mixtures of positive and negative tests and the likelihood that they had psychogenic disease or another type of tremor.

Psychogenic Dystonia

Compared to tremor, making the diagnosis of psychogenic dystonia is much more difficult and frequently requires a movement disorder specialist. The reason for this lies in the nature of dystonia itself. Dystonia, at least primary dystonia, is a "functional" disorder in traditional sense of a disease without evidence of a structural lesion on pathology or imaging. For many years, all dystonia was believed to be psychogenic for this very reason. Factors such as the *geste antagoniste* (a phenomenon where sensory stimulation on a specific area of the body can reduce or alleviate the dystonic symptoms) and the presence of a "null point" (where the symptoms seem to resolve when the affected body part is placed in a specific posture) appeared to some to support its characterization as psychogenic. However, for a number of reasons, the pendulum swung in the opposite direction and many believed that all dystonia was organic. It was not until the 1980s when it became clear that although most cases of dystonia are organic, there were a subset that could only be understood as psychogenic [35, 48, 49].

Given this history, we should not be surprised that the diagnosis of psychogenic dystonia can be difficult if one is not familiar with the usual phenomenology of dystonia. Incongruent findings include twisting movements occurring along multiple axes or in an inconsistent pattern, symptoms beginning with a fixed posture (something that usually only occurs later for someone with organic dystonia), and symptoms beginning in the lower limbs in an adult. Suggestibility, particularly with a placebo, can be helpful in making a diagnosis as well as the presence of other non-dystonic movement or sensory abnormalities with a psychogenic appearance [35, 48].

Fixed postures add an additional layer of diagnostic complication. When the diagnosis of psychogenic dystonia is suspected, it may be useful to have the patients evaluated under anesthesia. Although the condition might be psychogenic, patients are still at risk for developing contractures. This should be evaluated prior to the initiation of treatment since contractures will not improve with standard treatment of psychogenic symptoms. Further, for some patients, the knowledge that the fixed posture can be eliminated under anesthesia can have an important therapeutic benefit [50].

The value of physiological testing with psychogenic dystonia has been limited as it has been difficult to find a test with reliable variability between psychogenic and organic dystonia. For instance, Espay [51] assessed cortical and spinal inhibitory circuits in 10 patients with psychogenic dystonia, 8 with organic dystonia, and 12 healthy controls. They found no differences in either psychogenic or organic patients, despite clear differences compared to controls. However, three small studies have recently appeared that hold some promise for physiological testing. One showed an abnormality in brain plasticity in organic patients but not psychogenic patients [52]. Another found more synchronous EMG changes between arm muscles and higher signal to noise ratios in organic dystonia compared to a single psychogenic patient [53]. A third revealed an abnormal blink reflex on EMG testing in

patients with organic blepharospasm (i.e., eyelid dystonia) vs. those with presumed psychogenic disease [54]. Although all three of these studies were small, if replicated on a larger scale they might indicate a way for physiologic testing to assist in making this diagnosis in the future.

Psychogenic Gait

Psychogenic gait may have multiple clinical presentations. One study reviewed videos of 37 patients with this syndrome and listed nine possible characteristic findings including: fluctuation of impairment (19/37 patients), excessive slowness resembling "slow-motion movement" (13/37 patients), hesitation (a phenomenon like freezing that does not improve after the first step) (6/37 patients), "psychogenic Rhomberg" tests (defined by improvement with distraction, falling toward or away from the examiner no matter where that examiner was standing or large amplitude swaying building up after a latency) (12/25 patients), "walking on ice" gait pattern (11/37 patients), "uneconomic postures" with waste of muscle energy (odd posturing while walking that frequently displaces the center of gravity in awkward positions) (11/37 patients), sudden buckling of the knees (10/37 patients), astasia (4/37 patients), and a vertical, coarse, shaking tremor while standing (slower than typical for orthostatic tremor) (3/37 patients) [56].

Other studies have described other characteristic clinical exam findings [56, 57], but most boil down to a mixture of a lack of evidence for organic disease plus abnormal movements that do not seem to have a functional benefit to maintain balance. Additional abnormal movements like tremor or weakness that do not appear to have an organic origin are also common. There are no established physiological tests for psychogenic gait [47].

Psychogenic Parkinsonism

The evaluation for psychogenic parkinsonism is similar to that for psychogenic gait and tremor as described above. Additionally they may have slowness that disappears with distraction or is atypical for parkinsonism in that there is no motor decrement with repeated movements. Aside from tremor analysis, the only physiological tests that have been used in this disorder are F-DOPA PET [58] and SPECT Dopamine transporter (DaT) scans [59–62] to look for evidence of decreased activity of the dopamine system. The assumption is that psychogenic disease should not have decreased dopamine activity while organic parkinsonism should. Unfortunately, this theory has never been formally validated. Criticisms have arisen both from reports of some patients with presumed parkinsonism who do not have abnormal scans (i.e., SWEDDs) [63] and from a recent report of two patients with abnormal scans but with clinically documented psychogenic parkinsonism and scans that revert to normal with an improvement in symptoms or with time [28]. At this point, PET and SPECT cannot be considered reliable investigations for this disorder.

Psychogenic Myoclonus

In many ways, deciding whether a movement is or is not myoclonus is quite straightforward. Clinically, a myoclonic movement is a simple, brief movement with a very quick onset. To some degree this can be identified with the naked eye, but it can be determined with good accuracy by EMG recording of motor unit potentials [47]. The difficulty is making sure that other hyperkinetic abnormal movements like tics and chorea are also ruled out before assigning a diagnosis of psychogenic myoclonus.

Psychogenic Tics

This is one of the most difficult psychogenic disorders to identify. Like dystonia, tics are a functional disorder in the traditional sense of the word, but they also have voluntary characteristics unlike many other movement disorders and can be suppressed. Additionally, compulsive behaviors need to be considered given the high comorbidity of OCD and tics.

The diagnosis is generally made by reviewing the entire history and physical exam for supporting signs or symptoms that might indicate psychogenic tics [64]. Abnormal movements that are not typical of tics, such as wild thrashing, or inconsistent, non-stereotyped patterns are helpful in making the diagnosis [65]. Other factors such as purely vocal tics or tics starting in adulthood can be suggestive, but both have described in the literature as occurring with organic tics [66].

Psychogenic Weakness

The diagnostic literature for psychogenic weakness is broad with multiple signs and symptoms being championed over the years as helpful in making the diagnosis [67–70]. Stone [70] looked at nine "positive physical signs" in a study of 109 patients with a diagnosis of psychogenic weakness. These included four motor signs (i.e., collapsing weakness, dragging monoplegic gait, Hoover's sign, and Hand strike), four sensory symptoms (i.e., increased vibration sense, decreased vibration sense, midline split, and decreased temperature sense), and one cognitive symptom (i.e., *la belle indifference*). The motor signs were quite common (collapsing weakness and Hoover's sign occurred in 70 % and 56 % of patients), while the sensory symptoms were less common and the *la belle indifference* was found in only three patients [70].

While there are many clinical maneuvers to assess psychogenic weakness, few have been validated in formal studies and the sensitivity and specificity of each are not well defined. This is important because occasionally physicians will treat a favorite sign or symptom as pathognomonic of psychogenic disease, when in fact there is little evidence to support this type of thinking. For instance, in Gould's 1986

paper [38], one of the signs they looked for in their patients with known CNS lesions was "give-way weakness." This is the tendency to provide submaximal effort during confrontational strength testing and is often considered a sign of psychogenic weakness. They found that 10 of the 30 patients displayed this sign, despite the known structural etiology of their injuries. Another example is from the study by Stone mentioned above. They found that 60 patients (56 %) displayed a "Hoover's sign," but they also found that 1 of 7 controls also had the sign. It is always possible that a patient can have both psychogenic and organic illness, so one must use caution when interpreting these results. They illustrate that humility and caution are needed when interpreting the significance of any single sign.

Physiological testing has been more helpful in ruling out psychogenic weakness then ruling it in. Imaging studies and neurophysiology tests designed to evaluate the integrity of the nervous system (such as EMG and evoked potentials) should all be negative or have findings that do not account for the patient's complaints. There has also been at least one attempt to use physiological testing to quantify the results of the clinical exam. Ziv [71] looked at ways to quantify testing for the Hoover's sign as well as equivalent tests in the upper extremities.

Treatment

The evidence basis for treatment of psychogenic disease is limited. In a retrospective report of 22 patients followed after intensive inpatient treatment consisting of an individualized combination of psychotherapy, pharmacotherapy, ECT, physical therapy, hypnosis, and placebo trial, the results were encouraging. A total of 18 of 22 patients showed improvement after the intensive treatment. With an average follow-up of nearly 2 years, 13 remained improved (6 with complete remission) while 5 had initially improved but then had some return of symptoms [42]. These data are promising, particularly if we could decrease the likelihood for relapse. However, the conclusions that can be drawn are limited because it was a retrospective analysis, there was no placebo group, and it was only a single study at a single center. Furthermore, it is not clear if all patients need this kind of intensive inpatient treatment with multiple treatment modalities or if some could be handled in a more limited fashion as outpatients.

If we ask what the prognosis is for patients without the benefit of this intensive treatment approach, the answer is not entirely clear. There have been a number of retrospective analyses [1, 72–75] and a few prospective analyses [76, 77], but rarely are the types of psychogenic disease differentiated (i.e., conversion vs. factitious or malingering). Also, most are limited by high numbers of patients being lost to follow-up, and many are not careful to specify how many received treatment and the nature and intensity of that treatment. To illustrate the importance of this last point, one study [1] was able to follow 20 of 28 patients originally identified over a 2-year period. During that time, ten (50 %) improved to some degree, but only five had formal treatment. Given these limitations, we can say that most of the studies find

Table 21.4 Best evidence for treatment options

Medications
Voon [78]—treated 15 patients with Paxil or Celexa. Switched to Effexor if these failed. Symptoms remitted in 7/15 patients after 8 weeks and MADRS had significant improvement
Rampello [79]—treated 18 patients: 6 with Haldol and 12 with Sulpiride. Improvement in both groups, Sulpiride more than Haldol
Psychotherapy
Case reports showing benefit of CBT and psychoanalysis but no formal studies [80, 81, 84–86]
Transcranial magnetic stimulation
Schonfeldt-Lecuona [96]. Case series of 4 (3 after 1 rediagnosed as malingering). One resolved and 2 were significantly improved
Three other single case reports [95, 97, 98]
Hypnosis
Moene [92] looked at 44 patients in either hypnosis or treatment as usual groups and found improvement in treatment group
Moene [93] No benefit when hypnosis added to psychotherapy
Drug interviews
Poole [94] reviewed 55 papers using abreaction during treatment. Poor quality studies but seemed to be beneficial, particular when suggestion was utilized or catharsis occurred
Physical therapy
Multiple case reports [80–91]

that after a variable number of years (range 2–12), around 50 % of patients have improved to some degree (range 17–90 %), with a much lower percentage having a full remission (range 9–63 %).

The efficacy of individual treatment modalities has been evaluated, particularly for conversion symptoms, but rarely as more then retrospective analyses or collected case reports (see Table 21.4). The best evidence for medication treatment points to the use of two classes of medications: antidepressants and neuroleptics. Voon performed a small trial giving 15 patients an antidepressant and found some improvement [78]. Rampello performed a small trial with 6 patients given Haldol and 12 given Sulpiride and found improvement across both groups but more with Sulpiride [79]. The evidence for psychotherapeutic techniques like CBT and psychoanalysis [80, 81] and physical therapy techniques (often mixed with forms of behavioral therapy) [82–91] is limited to mainly case reports. There have been two non-blinded, randomized controlled trials looking at the effects of hypnosis. One found benefit of using hypnosis over remaining on a wait-list for treatment [92], the other looked at patients in an inpatient "comprehensive treatment program" with both CBT-oriented group therapy and individualized physical therapy, and found that patients with added treatment with hypnosis did no better than those without it [93]. The effectiveness of drug interviews has also been evaluated. A meta-analysis of all case reports in English of patients given barbiturates or benzodiazepines and subsequently interviewed with the purpose of encouraging an emotional catharsis or suggesting improvement, found that overall the treatment seemed to be beneficial,

though the ability to draw conclusions was limited by the different protocols employed and the lack of control groups [94]. Finally, a small number of case reports have recently been published describing benefit from TMS stimulation of the motor cortex contralateral to the symptomatic area [95–98].

In summary, there is evidence that an intensive, multidimensional treatment approach is helpful, but it is not clear how much better this is from using more limited treatment approaches, and how long or what type of follow-up is necessary to decrease the likelihood of relapse. From an anecdotal perspective, a treatment approach centered on psychotherapy and some physical therapy is common. Medication treatment, often with an SSRI or a tricyclic, is reasonable particularly if there are comorbid psychiatric conditions. Hypnosis can be a valuable tool, particularly in patients that are susceptible to it, but is not essential for good outcomes. Other modalities such as TMS and drug interviews are used more rarely, but may be helpful in resistant cases.

Concluding Thoughts: Informing the Patient of the Diagnosis

Throughout this chapter we have tried to acquaint the reader with multiple aspects of psychogenic movement disorders, particularly the evidence currently available for making appropriate diagnostic and treatment decisions. We are aware of the limited nature of this evidence and we would like to conclude with a topic for which there is little evidence to guide us, presenting the diagnosis.

Ideally the patient should be told as soon as the diagnosis becomes the main diagnostic consideration for the treating physician. Some physicians will wait until the second visit in an effort to build rapport, perhaps ordering a diagnostic test between visits to show the patient that their complaints are being taken seriously. Others will tell the patient at the end of the first visit, particularly if they believe that no further diagnostic testing is needed. In either case, the patient needs to be informed of the diagnosis since their active participation in treatment is critical for success.

In many ways, the informing of the diagnosis is the first step in treatment. As such it needs to be handled in a compassionate way. We see no harm in assuming all symptoms are unconscious from the start and allowing further psychiatric evaluation to change this diagnosis if necessary. Many patients already fear that their movements are of psychic origin and are worried that the physician will think they are intentionally faking or not take their suffering seriously. A common introduction is to discuss various ways in which stress affects our bodies (i.e., stomach upset, diarrhea, constipation, headache, shortness of breath, racing heart, etc.) and then introduce the movement symptoms as another example of "stress-induced" bodily symptoms. This is effective for many patients, as it makes clear that you believe that they are suffering and not "faking" the symptoms. However, some patients have difficulty with this explanation, particularly when they are not aware of their stress. Should this occur, one option is to explain that stress is an inevitable component in

everyone's life, whether they are aware of it or not. Exploring its possible role in contributing to the distressing symptoms with the aid of a mental health professional trained in this area may help to strengthen an integrated treatment strategy. Another tactic is to avoid attributing a specific etiology from the start and instead focusing on just the clinical syndrome. In other words, explaining that for an unknown reason some people lose conscious control of specific bodily movements or sensations of which they should otherwise have voluntary control. This frequently occurs in the context of an obvious stressor but not always. One of the authors (DS) gives this phenomenon the name "anepignosia" from the Greek for "lack of awareness" and then explains to the patient that while we do not understand why it happens in some people, we know that undergoing physical therapy and psychotherapy to relearn control improves symptoms.

The exact method by which a physician presents the diagnosis is probably less important than the fact that it is done early, with compassion, and that the reasons for the diagnosis are made clear to the patient. The fact that both positive and negative factors in the history and physical exam are being utilized is often important since patients fear that a "diagnosis of exclusion" might mean something dire has been missed. Requests for second opinions should be welcomed but the number of these opinions limited. One of the most devastating consequences of this condition is unnecessary medical and surgical procedures, and this risk can increase with the more doctors they see. Finally, the fact that a psychogenic disorder may carry a better prognosis than an organic disorder is helpful to clarify to patients, as well that many people appear to improve with appropriate treatment.

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Chapter 22
Anti-NMDA Receptor Encephalitis and Other Autoimmune and Paraneoplastic Movement Disorders

Jessica Panzer and Josep Dalmau

This chapter contains video segments that can be found on the accompanying DVD.

Abstract A substantial number of movement disorders are mediated by immunological mechanisms. In some instances the immune response is triggered by the presence of a tumor that ectopically expresses a neuronal protein, leading to a brain autoimmune response or paraneoplastic syndrome. Other immune-mediated movement disorders may be post-infectious, likely triggered by molecular mimicry or other, as yet unknown, mechanisms. There is a new and expanding group of syndromes that are associated with antibodies against cell surface or synaptic proteins and may cause early and prominent movement disorders. Anti-NMDA receptor encephalitis is the most frequent of these disorders that may occur with or without tumor association, affect children and adults, and can be severe but responsive to treatment. Recognition of this and other immune responses to synaptic proteins is important because, different from classical paraneoplastic syndromes, they often respond to immunotherapy. Because the presentation and clinical course of immune-mediated syndromes often develop very quickly, and because failure to recognize and treat these disorders may lead to morbidity or even mortality, we believe that this qualifies these syndromes as movement disorder emergencies. This chapter focuses on anti-NMDAR encephalitis and other autoimmune or paraneoplastic movement disorders, with emphasis on their clinical presentations, differential diagnoses, immunological associations and antigens, and treatment strategies.

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Patient Vignette

A 22-year-old woman, previously in excellent health, developed a subacute deterioration over several weeks characterized by progressive obtundation, decreased responsiveness, autonomic instability and eventual respiratory insufficiency leading to ventilator support. Diffuse myoclonus and orobuccal-lingual dyskinesias were noted. Due to the recent recognition of the NMDA-receptor antibody association with ovarian teratoma, a search for a teratoma was initiated and confirmed, with high titers of paraneoplastic antibodies. Her hospital course was marked by months of intensive care treatment, with a persistent state of wakeful inattention, multiple medical complications, and slow improvement despite treatment with IVIG, plasmapheresis and steroids. She was eventually treated with cyclophosphamide, with good long-term recovery.

Introduction

Paraneoplastic and autoimmune mechanisms may result in movement disorders [1]. Paraneoplastic disorders (PND) occur in patients with cancer and can affect any part of the nervous system, including the basal ganglia and brainstem, causing abnormal movements. Many PND are immune-mediated; the patient's immune response against the cancer is misdirected against neurons, causing the syndrome. Other immune-mediated movement disorders may be post-infectious, likely triggered by molecular mimicry or other, as yet unknown, mechanisms. The etiology of many immune-mediated movement disorders however remains idiopathic, with no clear oncologic or infectious trigger [2]. There is a new and expanding group of syndromes that are associated with antibodies against cell surface or synaptic proteins and may cause early and prominent movement disorders [3]. Anti-NMDA receptor encephalitis is the most frequent of these disorders that may occur with or without tumor association, and although severe may respond to treatment. Because the presentation and clinical course of immune-mediated syndromes often develops quickly, and failure to diagnose can be lethal, we classify these disorders as movement disorder emergencies. This chapter focuses on anti-NMDAR encephalitis and other autoimmune or paraneoplastic movement disorders, with emphasis on their clinical presentations, differential diagnoses, immunological associations and antigens, and treatment strategies.

General Concepts

With a few exceptions, such as opsoclonus–myoclonus–ataxia syndrome in children with neuroblastoma, the majority of classic paraneoplastic syndromes resulting in movement disorders were until recently considered to affect adults or elder individuals.

This concept has changed in the last 4 years with the discovery of several syndromes associated with antibodies against cell surface or synaptic proteins, such as NMDAR, which often affects children and young individuals. Moreover, while symptoms related to classical paraneoplastic antibodies to intracellular antigens (e.g., anti-Hu or CRMP5) rarely improve if the tumor is not treated, and even so the improvement is usually mild or limited, those related to antibodies to cell surface or synaptic proteins may show dramatic responses to immunotherapy even before the tumor is identified or treated [3]. This, however, should not discourage physicians from searching for an underlying neoplasm, because if identified, removal of the tumor along with instituting immunotherapy usually expedites recovery and reduces relapses.

For most of these autoimmune encephalitic disorders (paraneoplastic or not), there is usually early evidence of cerebrospinal fluid (CSF) inflammatory changes, including lymphocytic pleocytosis and a variable increase in CSF protein concentration, IgG index, and oligoclonal bands [4]. This CSF inflammation fades over time and these parameters normalize. Therefore, CSF abnormalities and identification of antineuronal antibodies in serum or CSF are important clues for diagnosis and treatment. Some antibodies, usually targeting intracellular antigens (Hu, CRMP5, Ma2, amphiphysin) almost always associates with cancer, and the associated disorders are likely mediated by cytotoxic T-cell responses [5]. Other antibodies directed against cell surface antigens (NMDAR, LGI1) are excellent diagnostic markers of characteristic syndromes that can occur with or without tumor association, and probably result from a direct pathogenic effect of the antibodies. Of these, the most common and best studied is anti-NMDAR encephalitis [6].

Anti-NMDAR Encephalitis and other Disorders Resulting in an Excess of Movements

Anti-NMDAR Encephalitis

This disorder usually affects young women and children of both sexes [7]. This is a multistage illness that progresses from psychosis, memory deficits, seizures, and language disintegration to a state of unresponsiveness with catatonic features and autonomic and breathing instability [8]. Abnormal movements are prominent at this stage [9]. Dyskinesias are the most frequent and are observed in 80 % of patients. While they may involve any part of the body, orobuccolingual dyskinesias are particularly prominent. They manifest as pouting, grimacing, tongue protrusion and rolling, palatal elevation, nares flaring, smiling-like motions, frowning, bruxism, oculogyric crisis, and forceful jaw opening and closing severe enough to cause tongue, teeth and lip injuries [7, 8, 10]. Less commonly, chorea, ballismus, or opisthotonic postures may occur [11–13]. These hyperkinetic movements may alternate with catatonia, catalepsy, dystonia, and rigidity [14]. Due to the initial neuropsychiatric disturbances patients may be given antipsychotic medications, and the orobuccolingual dyskinesias may be misinterpreted as tardive dyskinesias, while hyperthermia,

rigidity, and elevated creatinine kinase or rhabdomyolysis that can occur even in the absence of antipsychotic medication may falsely be ascribed to neuroleptic malignant syndrome [15]. Motor or complex seizures can occur at any time during the disease. The overlap of abnormal movements and epileptic seizures may confound recognition of the seizures, or lead to unnecessary escalation of antiepileptics for movements that are misinterpreted as seizures [7, 16].

The association of anti-NMDAR encephalitis with an underlying tumor is related to the gender and age of the patient. In adult women, over 50 % have an ovarian teratoma, while only one-third of teenage girls have a proven teratoma. Girls and boys under age 14 and adult men only rarely have a tumor [6, 17].

The diagnosis can be made by recognition of the characteristic and progressive clinical syndrome. Half of the patients will have MRI findings that may include mild or transient T2/FLAIR signal hyperintensity in the hippocampi, cerebellum, cerebral cortex, subcortical regions, basal ganglia, or brainstem [8, 10]. The finding of CSF pleocytosis and mild fever at presentation can lead to an initial diagnosis of viral encephalitis, however viral studies will be negative and the progression of the clinical syndrome usually points to synaptic autoimmunity as the cause [18]. Other diagnoses that may be considered include encephalitis lethargica, late-onset autism, and childhood disintegrative disorders [19]. Primary inherited dystonias, such as DYT1 dystonia or dopa-responsive dystonia, can be excluded by the typically acute onset of symptoms in anti-NMDA receptor encephalitis, the presence of MRI changes, CSF inflammatory changes, and other associated symptoms such as encephalopathy and seizures [20]. In children with possible anti-NMDA receptor encephalitis and chorea, Sydenham's chorea (SC) may be considered. However, while patients with SC may have neuropsychiatric symptoms such as obsessive–compulsive disorder (OCD), anxiety, and paranoia [21], frank psychosis or encephalopathy is rare. Further, the MRI in SC is most often normal or shows only subtle basal ganglia changes [22]. As anti-NMDAR encephalitis progresses, the onset of autonomic instability and seizures also helps distinguish it.

Treatment is successful in 75 % of cases and is centered on removal of any associated tumor and immunotherapy, usually corticosteroids, IVIG, or plasmapheresis. Refractory patients may respond to cyclophosphamide or rituximab [6, 23, 24]. A quarter of patients may experience relapses, particularly those without a tumor or those who receive suboptimal immunotherapy. Relapse may occur months or years after the initial recovery [8, 10, 17]. A clinical presentation with isolated symptoms or with partial aspects of the full-blown syndrome is common. Treatment with immunotherapy of the first episode reduces the risk of relapses [25].

Paraneoplastic Chorea and CRMP5 Antibodies

Choreic movements can occur in association with antibodies to collapsin response mediator protein5 (CRMP5, also termed CV2). When these antibodies are found, the disorder is almost always paraneoplastic and the chorea is part of a diffuse

encephalomyelitis that may include limbic encephalitis, cerebellar ataxia, peripheral neuropathy, uveitis, optic neuritis, or retinitis [26–28]. The most commonly associated tumors are small cell lung cancer and thymoma [29]. In these patients brain MRI often shows abnormal FLAIR hyperintensities involving limbic regions, striatum, basal ganglia, brainstem, or white matter, which may resemble a leukoencephalopathy [30].

The associated neurological symptoms and MRI findings help to exclude many of the genetic causes of chorea such as Huntington's disease, neuroacanthocytosis, and Wilson's disease. Inflammatory causes of chorea such as systemic lupus erythematosus (SLE) or antiphospholipid antibody syndrome (APS) should be considered and might prove more difficult to exclude, since these disorders may present with chorea and other neuropsychiatric symptoms prior to any other systemic manifestations [2]. Discovery of the underlying tumor or appropriate serologic testing to screen for SLE/APS should clarify the diagnosis.

CRMP5 is an intracellular antigen that regulates neurite outgrowth, neuronal polarity, and dendritic branching in the developing brain [31, 32]; its role in the adult brain is not yet defined. CRMP5 expression is seen within almost all high-grade neuroendocrine lung tumors, including SCLC, but not in other lung tumors [33]. Exposure to this tumor antigen likely results in an immune response against CRMP5 expressed in brain.

The management of paraneoplastic chorea focuses on treatment of the tumor and, since the auto-antigen is intracellular, immunotherapy targeting T-cell-mediated mechanisms. Antibodies against CRMP5 may modify progression of the underlying oncologic disease; median survival is longer in patients with SCLC and anti-CRMP5 related encephalitis as compared to those patients with SCLC and anti-Hu related encephalitis, independent of the severity of the neurologic disease [34].

Pseudoathetoid Movements in Paraneoplastic Sensory Neuronopathy

Paraneoplastic sensory neuronopathy (PSN) may develop in isolation but is most often a fragment of paraneoplastic encephalomyelitis. Patients typically develop asymmetric pain and paresthesias that progresses to involve other extremities, and sometimes the trunk or cranial nerves. Eventually the severe involvement of all modalities of sensation results in dystonic or pseudoathetotic postures as well as a debilitating sensory ataxia [35].

Patients who develop PSN alone or as a component of paraneoplastic encephalomyelitis often have anti-Hu antibodies, and the associated cancer is almost always a SCLC, although other cancers (e.g., non-SCLC or breast carcinomas) may be found especially in those patients with PSN without anti-Hu antibodies [36]. The pathological substrate is an immune-mediated degeneration of the neurons of the dorsal root ganglia, likely caused by cytotoxic T-cells. The sensory neuronopathy may mimic disorders such as Guillain–Barré syndrome, particularly if there is also involvement of lower motor neurons and peripheral nerves [37].

PSN is poorly responsive to treatment and at best, patients will stabilize or have mild improvement after oncologic and immunologic therapies [38]. In some patients rituximab has been effective [39].

Opsoclonus–Myoclonus–Ataxia Syndrome

Opsoclonus is characterized by involuntary, arrhythmic, chaotic, multidirectional saccades without intersaccadic intervals. When paraneoplastic, opsoclonus is variably associated with encephalitis, myoclonus, and ataxia of the trunk and limbs (opsoclonus–myoclonus–ataxia syndrome, OMAS) and most commonly occurs in children between 6 months and 6 years of age [40, 41]. Half of these children will be found to have an associated neuroblastoma. In adults, the tumors more frequently associated include SCLC and breast or ovarian cancer. Other than a small subset of patients with breast or ovarian cancer who develop Ri antibodies [42], OMAS has not been consistently associated with any specific antineuronal antibody.

The differential diagnosis includes post-infectious cerebellitis, toxic ingestions, and posterior fossa tumors [43]. OMAS can be distinguished from cerebellitis by the presence of opsoclonus and the lack of symptomatic improvement within the expected timeframe. Early recognition of OMAS in children is important, because delay in the initiation of immunomodulatory treatment has been shown to increase long-term neurological deficits [44]. In adults, other degenerative or inflammatory causes of ataxia should be considered, but the presence of opsoclonus is relatively specific for this disease.

Treatment of OMAS in children involves resection of the neuroblastoma, if present, and immunotherapy, including corticosteroids, ACTH, IVIG, plasmapheresis, rituximab, or cyclophosphamide [44, 45]. Several case series suggest that high dose pulsed dexamethasone therapy may be beneficial [46, 47]. Although the opsoclonus and ataxia often improve or resolve, children are frequently left with motor, speech, behavioral, and sleep disorders. Relapses are frequent, usually during intercurrent illnesses or attempts to reduce immunotherapy; few children have a monophasic disease course [48]. In adults with idiopathic OMAS, corticosteroids or IVIG can accelerate improvement, but those with paraneoplastic disease only benefit from immunotherapy if the tumor is controlled [41, 49].

Myoclonic-Like Movements in Patients with LGI1 Antibodies

There is recent evidence that the target autoantigen related to limbic encephalitis and antibodies attributed to VGKC is in fact LGI1. Patients with these antibodies develop limbic encephalitis that at least in 40 % of cases is preceded or accompanied by myoclonic-like movements [50]. These movements are brief, short-lasting, repetitive and can involve face, arm, or leg [51]. In some patients they appear to

predominate in face and arm [52]. They can occur many times per day (in some patients 80–100 times) and have been described as "twitches," "myoclonus," or "stereotyped brief monomorphic movements" [53, 54]. Studies using continuous video EEG recordings have demonstrated that these movements are preceded by approximately 500 ms of electrodecremental events, typical of epileptic tonic seizures [51]. Using functional brain imaging, basal ganglia dysfunction was demonstrated in five of eight patients [52]. Recognition of the epileptic origin of these "myoclonic-like" movements is important because they usually precede the development of a full blown limbic encephalitis associated with LGI1 antibodies, and respond to immunotherapy [51, 52].

Tremor and Ataxia in Paraneoplastic Cerebellar Degeneration

Paraneoplastic cerebellar degeneration (PCD) is characterized by the acute to subacute development of severe pancerebellar dysfunction. In adults the rapidity of onset distinguishes PCD from inherited or neurodegenerative causes of cerebellar ataxia [55]. The disorder usually develops over days or weeks, but in some instances it has developed overnight, clinically suggesting a stroke. PCD has mostly been reported in association with gynecologic tumors, breast cancer, lung cancer (particularly SCLC), and Hodgkin's lymphoma. While almost all known paraneoplastic antibodies have been found in association with PCD, the most commonly associated are anti-Yo (also called PCA-1) in patients with breast or ovarian cancer [56]; anti-Tr in patients with Hodgkin's lymphoma [57], and antibodies to voltage-gated calcium channels (VGCC) in patients with SCLC [58]. Patients with Hodgkin's lymphoma can also develop cerebellar degeneration in association with antibodies against mGluR1 [59].

As with all paraneoplastic neurologic disorders, the best approach to treatment of PCD is identification and treatment of the underlying cancer and possibly immunotherapy. Except for some patients with Hodgkin's lymphoma and Tr or mGluR1 antibodies who may respond to treatment, most patients with PCD are refractory to treatment, suggesting that there is early and irreversible neuronal cell death [59, 60]. This is supported by autopsy studies demonstrating extensive loss of Purkinje neurons with relative preservation of other cerebellar neurons.

Disorders Resulting in a Paucity of Movement or Stiffness

Anti-Ma2 Encephalitis and Hypokinesis

Anti-Ma2 encephalitis is paraneoplastic and commonly occurs in young men with testicular tumors [61]. A few cases have been described in older men and women with lung or breast cancer [62]. In addition to short-term memory loss from limbic

encephalitis these patients also have involvement of the hypothalamus and brainstem leading to disorders of sleep and wakefulness such as hypersomnia or narcolepsy-cataplexy, hyperthermia, hyperphagia, and hypothalamic–pituitary dysfunction [63].

Parkinsonian features are prominent, including bradykinesia, masked facies, hypophonia, and rigidity; less frequently tremor is present. Dyskinesias may also occur, including forceful jaw opening and closure, and oculogyric crisis [64]. Rostrocaudal brainstem involvement often leads to progressive ophthalmoparesis, cranial neuropathies, and ataxia. Early eye movement deficits include vertical gaze paresis predominantly involving saccades, with relative preservation of pursuit and oculocephalic movements [65]. The facial and eye movement abnormalities can be confused for progressive supranuclear palsy or Whipple's disease [66]. Neuroimaging can be helpful, as half of patients with anti-Ma2 encephalitis will have FLAIR/T2 hyperintensities in the medial temporal lobes, hypothalamus, thalamus, or upper brainstem, at times with contrast enhancement [63, 64].

The parkinsonian features may respond to carbidopa/levodopa, and the facial dystonia usually improves with muscle relaxants or botulinum toxin injections [67]. However, all efforts should be made to identify and treat the underlying tumor, as this is critical to improving outcome. Case series have shown that 35 % of patients will improve after tumor treatment and immunotherapy, while immunotherapy in the absence of tumor treatment is ineffective [63, 68].

Stiff-Person Syndrome

Progressive muscle stiffness, aching, muscle spasms, and rigidity characterize this syndrome. Symptoms develop over months and are most prominent in the paraspinal muscles and lower limbs. The majority of cases (about 85 %) are idiopathic and not cancer associated [69]. These patients usually have antibodies against glutamic acid decarboxylase 65 (GAD65). GAD65 antibodies can occur also in patients with cerebellar ataxia and refractory epilepsy, which may overlap with SPS and rarely, are found in patients with paraneoplastic SPS, most often in association with thymoma [70]. Additionally, patients with SPS and anti-GAD65 antibodies may also have antibodies against $GABA_A$-receptor-associated protein (GABARAP), suggesting that both antibodies may play a role in the disorder [71].

When SPS is paraneoplastic the tumors more frequently found are SCLC and breast cancer. These patients will often have antibodies to amphiphysin. Compared to the idiopathic form of SPS, patients with paraneoplastic SPS are older and more likely to have asymmetric and distal symptoms [72, 73]. There has been one case report of a patient with SPS and mediastinal cancer who was found to have antibodies against gephyrin, a cytosolic protein associated with $GABA_A$ and glycine receptors [74].

Progressive encephalomyelitis, rigidity, and myoclonus (PERM) is likely related to SPS and is characterized by diffuse rigidity, painful spasms, and myoclonus. Antibodies against the $\alpha 1$ subunit of the glycine receptor have been reported in

some of these patients, as well as in patients with hyperekplexia, and atypical stiff-person or stiff-limb syndrome without GAD65 antibodies [75, 76].

For the non-paraneoplastic disorder, IVIG has been shown to be beneficial [77], but this remains unproven for the paraneoplastic syndrome. Paraneoplastic SPS should be managed by treatment of the underlying cancer and corticosteroids. Additional immunotherapy, such as IVIG or cyclophosphamide, can be considered in refractory cases, given that similar immunotherapies are used for other autoimmune encephalomyelitis [78]. Symptomatic improvement is provided by drugs that enhance GABAergic transmission such as diazepam, baclofen, sodium valproate, tiagabine, and vigabatrin [79].

Peripheral Nerve Hyperexcitability

Peripheral nerve hyperexcitability (PNH, also called acquired neuromyotonia or Isaacs' syndrome) results from spontaneous and continuous muscle fiber activity due to peripheral nerve dysfunction [80]. Patients develop muscle cramps, stiffness, muscle twitching, and pseudomyotonia. Other related symptoms include hyperhidrosis, fatigue, and exercise intolerance. Symptoms are most prominent in the calves, legs and trunk, but can also affect other body parts including the face and neck. At least a third of those affected also experience paresthesias. Approximately 25 % of patients with PNH have CNS symptoms (Morvan's syndrome) including confusion, mood changes, sleep disruption, and hallucinations [81].

In most cases, PNH has a non-paraneoplastic etiology. In addition to idiopathic cases, there are inherited causes of neuromyotonia such as that associated with voltage-gated potassium-channel (KCNA1) gene mutations. Multiple toxins, including gold, oxaliplatin, penicillamine, herbicides, insecticides, and toluene, may also cause neuromyotonia [82]. Patients with non-paraneoplastic PNH may have other autoimmune disorders, including myasthenia gravis, diabetes mellitus, chronic inflammatory demyelinating neuropathy, rheumatoid disease, systemic lupus erythematosus, and vitiligo [82, 83].

When paraneoplastic, the most commonly associated cancers are thymoma and SCLC [84]. In one series, patients with paraneoplastic PNH tended to be older and have more weakness and myokymia but less cramping and dysautonomia than those with non-paraneoplastic PNH [85].

Past research had suggested that antibodies to voltage-gated potassium channels (VGKC) might be causal in a significant subset of patients with PNH. However, in several disorders incorrectly attributed to VGKC antibodies, including PNH and Morvan's syndrome, antibodies to contactin-associated protein-like 2 (CASPR2) have now been identified as a target autoantigen [50, 86, 87]. The remaining cases are considered antibody negative at this time although further studies may identify specific antibody associations. Patients with CASPR2 antibodies may have additional antibodies, such as AChR or MuSK, giving rise to a complex manifestation

of symptoms that may suggest a motor neuron syndrome. Recognition of this disorder is important because patients respond to immunotherapy [88].

Other than oncologic therapy when appropriate, treatment recommendations for PNH are based on small cases series that have reported responses to plasmapheresis, IVIG, and prednisolone with or without azathioprine or methotrexate [89, 90]. Some patients have had symptomatic improvement with carbamazepine or phenytoin [91].

General Management Considerations

When a paraneoplastic movement disorder is suspected, the first concern should be the diagnosis and treatment of the underlying tumor as this offers the best chance for stabilization or improvement of the neurologic disorder [92]. For some disorders associated with antibodies to intracellular antigens (Hu, CRMP5, Ma2, amphiphysin) the search for a tumor should be aggressive (Table 22.1), and tumor screenings should be repeated regularly, every 6 months for at least 2 years. Moreover, the immunotherapy strategy for these disorders should consider that they are mediated by T-cells (amphiphysin may be an exception). Therefore, IVIG and plasma exchange usually fail in the treatment of the associated syndromes, and more aggressive immunotherapies, including rituximab (to reduce antigen presentation by B-cells) or cyclophosphamide should be promptly considered. Except for Ma2-associated encephalitis, which associates with improvement in ~30 % of the patients [63], the other disorders have limited response to treatments. Although GAD65 is an intracellular antigen, the related symptoms of the stiff-person syndrome (but less frequently cerebellar ataxia) may respond to IVIG [77]. Antibodies to amphiphysin may have a direct effect on the target antigen [93], but in many patients the response to plasma exchange or IVIG is unsatisfactory. The titers of most antibodies against intracellular antigens (except GAD65 and amphiphysin, which are located close to the cell surface) do not correlate well with the outcome of the disease.

In contrast, the disorders associated with antibodies against cell surface or synaptic extracellular epitopes (such as anti-NMDAR encephalitis or LGI1 encephalitis) are more responsive to immunotherapy. Patients who do not improve with first-line immunotherapies, such as corticosteroids, IVIG or plasma exchange, often improve with rituximab or cyclophosphamide. For anti-NMDAR encephalitis, there is evidence of a rapid and robust intrathecal synthesis of antibodies and intracerebral infiltrates of plasma cells, which probably explain the failure of plasma exchange, IVIG, and corticosteroids in some of these patients, particularly those with delayed diagnosis and treatment. Nevertheless, these patients often improve with cyclophosphamide and rituximab. Overall, 75–80 % of patients with syndromes related to cell surface antigens (NMDAR, LGI1, Caspr2) substantially improve or fully recover with immunotherapy, and treatment of the tumor when appropriate [3, 6]. As expected for antibodies with a potential pathogenic effect, the change of titers of these antibodies correlates well with the course of the disease; in some disorders, such as anti-NMDAR encephalitis, the CSF titers have better clinical correlation than serum titers.

Table 22.1 Paraneoplastic and autoimmune movement disorders

Neurologic syndrome	Movement disorder	Antineuronal antibody	Predominant tumor
Anti-NMDAR encephalitis	Orofacial dyskinesias, chorea, dystonia, stereotyped movements, ballismus, catatonia	NMDAR	Teratoma of the ovary
Encephalomyelitis	Chorea	CRMP5	SCLC, thymoma
Sensory neuronopathy	Pseudoathetoid movements due to sensory ataxia	Hu	SCLC
Opsoclonus–myoclonus–ataxia	Myoclonus, ataxia	Most cases without antibody; anti-Ri	Neuroblastoma, breast, SCLC
Anti-LGI1 limbic encephalitis	Myoclonic-like movements (tonic seizures)	LGI1 antibodies	Infrequently thymoma, SCLC
Cerebellar degeneration	Tremor, ataxia	Yo, Tr, VKCC, mGluR1, Ri, Hu	Breast, ovary and other gynecological tumors, SCLC, lymphoma
Brainstem encephalitis	Hypokinesis, rigidity, ophthalmoparesis	Ma2	Germ-cell tumor of the testis, non-SCLC
Stiff-person syndrome, muscle rigidity	Axial rigidity and muscle spasms	GAD 65, amphiphysin, GABARAP, GlyR	If amphiphysin antibodies: breast cancer, SCLC
Neuromyotonia	Myokymias, difficulty in muscle relaxation	Caspr2; many cases without antibodies	SCLC, thymoma

NMDAR N-methyl-D-aspartate receptor, *CRMP5* collapsin response mediated protein 5, *SCLC* small cell lung cancer, *LGI1* leucine-rich glioma inactivated 1, *mGluR1* metabotropic glutamate receptor type 1, *GAD65* glutamic acid decarboxylase 65, *GABARAP* GABA receptor-associated protein, *GlyR* glycine receptor, *Caspr2* contactin-associated protein-related 2

Muscle stiffness and rigidity may respond to pharmacologic treatment with GABAergic drugs, while muscle cramps and pseudomyotonia may respond to anti-convulsants that block sodium channels [79]. Although there is limited experience, some patients with anti-Ma2 or NMDA receptor encephalitis who had involuntary, forceful movements with the jaw that precluded feeding and carried the risk of tongue and mouth injuries benefited from local application of botulinum toxin [94].

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Chapter 23
Wilson's Disease

George J. Brewer

This chapter contains video segments that can be found on the accompanying DVD.

Abstract Wilson's disease is a rare disorder with protean clinical manifestations. The diagnosis of Wilson's disease is an emergency, because of the serious sequelae of a missed or delayed diagnosis, and because of the risk of permanent neurologic harm if the patient is mismanaged. With adequate clinical suspicion and careful application of anticopper strategies, most patients with Wilson's disease can expect to lead a normal life.

Patient Vignettes

Patient 1

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

The neurologist sat across the desk from the patient to discuss the diagnosis. Unbeknownst to either of them, the patient at this moment faced an emergency. Not an emergency-room emergency, but a diagnostic emergency. The correct line of

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thinking, including an appropriate differential diagnosis list, would lead to a work-up, the correct diagnosis, effective treatment, and prevention of further brain damage. Instead, the neurologist reassured the patient that he had essential tremor and that it would likely be never more than a minor inconvenience. The family history supported the diagnosis, the neurologist said.

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

Patient 2

The diagnosis of Wilson's disease had been quickly established in a 23-year-old female graduate student. She had presented with mild dysarthria and mild upper extremity tremor. She had been amenorrheic for about 1 year. The neurologist to whom the patient had been referred considered Wilson's disease as part of the differential and moved quickly to measure urine copper and blood ceruloplasmin, and ordered a slit lamp examination for Kayser–Fleischer rings. All tests came back positive.

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

Unfortunately, she was one of the one in four. She deteriorated rapidly. Two weeks after therapy initiation the dose of penicillamine was increased from 1 to 2 g and later to 4 g in an attempt to curb the storm. This seemed to accelerate the deterioration. By 3 months she was essentially anarthric and so dystonic that her face was locked in a continuous drooling grimace. She had severe, generalized tremor. Her back was twisted into a comma shape and she could walk only a short distance. She was so uncoordinated that she could not feed herself without flinging food around the room. She never recovered any of her neurological function despite years of anticopper therapy. She was not able to return to school or find employment. Meaningful life had all but been destroyed by penicillamine therapy.

Introduction

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

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

Wilson's disease was established as an autosomal recessive disorder [19], and the gene eventually cloned [20–22]. The gene is a copper-binding, membrane-bound ATPase called ATP7B. It bears close homology to ATP7A, the causative gene for Menke's disease [23–25]. More than 200 causative mutations have already been described [26]. The frequency of the disease is believed to be about 1 in 40,000 in most populations.

Clinical Presentations

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

on its severity, may include jaundice, hypoalbuminemia, ascites, peripheral edema, low levels of clotting factors, bleeding, and encephalopathy.

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

The third mode of presentation is neurological and involves about 50 % of patients, including the 25 % who first present with significant behavioral abnormalities. The neurological presentations typically occur when the patient is in his or her early 20s, although again the age of presentation is quite broad, from 15 to 60 years. Copper toxicity causes damage to the areas of the brain that coordinate movement, such as the lenticular nuclei; hence its classification as a movement disorder. The list of the more frequent signs is given in Table 23.1. The three basic problems are dystonia, incoordination, and tremor, which, working separately or together, accounts for most of the signs in Table 23.1. Almost all patients presenting neurologically have some dysarthria, which results from dystonia and incoordination of speech-related muscles. Speech abnormalities can be a variety of types, and no type is specific for Wilson's disease. Some patients have drooling as a result of facial dystonia. The facies, and other aspects of the disease including difficulty initiating walking, can closely resemble Parkinson's disease. Dysphagia may be present. Tremor occurs in perhaps one-third of Wilson's disease patients, presenting neurologically, and can be of a variety of types, none specific for Wilson's disease. Incoordination may begin with difficulty in fine movements, such as handwriting and buttoning buttons. Micrographia may occur, but it is more common for handwriting to simply look sloppy. As the disease progresses, incoordination may involve larger muscle groups and make it difficult to feed oneself and carry out other tasks. The patient may become prone to stumbling and falling. Dystonia can involve any muscle group, including the face, as previously described, the upper and lower extremities, the neck, and the muscles of the trunk that control posture. The dystonia may cause the extremities or other parts of the body to be pulled into abnormal and grotesque positions that interfere with function (as with patient 2).

Table 23.1 Neurological signs in patients with Wilson's disease presenting with neurological disease

Signs	Comment
Dysarthria	Present in almost all patients. The various abnormalities are not specific for Wilson's
Dystonia	Present somewhere in the body in about 2/3 of patients
Incoordination	Present in over ½ of patients
Dysdiadochokinesia	
Rigidity	Present in about ½ of patients
Facial expression abnormality	
Tremor	Present in about 1/3 of patients. Several different tremor types can occur, none specific for Wilson's disease
Abnormal eye movements	Present in about 1/3 of patients
Drooling	
Dysphagia	
Bradykinesia	
Motor impersistence	Present in about 1/5 of patients
Athetosis	Present in about 1/10 of patients
Signs are listed roughly in the order of frequency in the authors' experience	

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

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

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

Finally, some patients will be diagnosed in what we call the "presymptomatic" state. This will usually occur when siblings of a newly diagnosed case are screened. Each sibling is at 25 % risk for having the disease genotype, but has not yet become clinically ill. The disease is believed to be almost 100 % penetrant, so it is important

that these patients be diagnosed and treated prophylactically. At the time of diagnosis, these patients have usually suffered some liver damage and may have mildly elevated serum transaminase enzymes and/or exhibit evidence of hypersplenism, such as leukopenia or thrombocytopenia. They may also have Kayser–Fleischer rings. Occasionally, presymptomatic patients will come to attention because of a chance observation, such as the presence of Kayser–Fleischer rings.

Recognition, Screening, and Definitive Diagnosis

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

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

With regard to neurological presentations, any patient under the age of 50 years who develops one or more signs or symptoms of a movement disorder (see Table 23.1) should be screened for Wilson's disease unless there is *positive* information providing for an alternate diagnosis. In particular, *any* patient under age 50 who is considered for a diagnosis of essential tremor or Parkinson's disease should be screened for Wilson's disease (patient 1). There may already be clues in the patient's laboratory tests to bolster the neurologist's decision, such as mildly elevated transaminase enzymes (in about 50 % of neurological patients) or leukopenia or thrombocytopenia (in about 35 % of neurological patients); however, this should not be the determining factor in ordering screening tests. Because a slit lamp examination is required for a diagnosis to be definitive, it doesn't hurt to take a peek at the patient's eyes (although again, this should not be a determining factor). If the eyes are the right color (such as blue), Kayser–Fleischer rings may be readily visible.

Screening for Wilson's disease in the neurological (and psychiatric) presentation is easier than in the hepatic presentation and in presymptomatic patients (Table 23.2).

Table 23.2 Tests for screening and definitive diagnosis in the neurological and psychiatric presentation of Wilson's disease

Procedure	Interpretation	Comment
Ophthalmologist slit lamp examination for Kayser–Fleischer rings	99+% of these patients are positive	False positive and false negatives are extremely rare. See text regarding obstructive liver disease
24-h Urine copper	Symptomatic patients always have values over 100 μg (normal 20–50)	Presymptomatic patients over 100 μg only about ½ of time. Heterozygous carriers may have values up to about 65

This is because first, over 99 % of such patients have Kayser–Fleischer rings on slit lamp examination by an ophthalmologist (178 out of 179 patients, in our series); and second, 100 % of such patients (90 out of 90, in our series) have diagnostic elevations (>100 μg/24 h, with normal less than 50) of urine copper (Table 23.2). The combination of tests is not only adequate for screening but also for definitive diagnosis in this type of patient, obviating the need for a liver biopsy. I recommend using both tests, because a rare neurological Wilson's patient may not have the rings, and because laboratories can make mistakes in measuring urine copper. If the two tests are concordant (either both diagnostic or both normal), further work-up is not needed. If discordant, both should be repeated, with different operatives. False positives and negatives for Kayser–Fleischer rings are quite rare. However, if the patient has obstructive liver disease of a year's duration or longer, Kayser–Fleisher rings, elevated urine copper, and elevated liver copper can occur in the absence of Wilson's. The serum ceruloplasmin can be helpful in affecting index of suspicion, but should not be used as a definitive test. It is low in 80 % of patients with Wilson's disease, including those with neurological disease, but is normal in 20 %. Furthermore, carriers of one copy of the Wilson's disease gene have low ceruloplasmin values 20 % of the time. If a liver biopsy is done, it should include measure of copper quantitatively and will always show values of 200 μg/g dry weight of liver, or higher (normal 20–50).

The same screening guidelines apply to psychiatrically presenting patients as apply to neurologically presenting patients (Table 23.2). However, patients with Wilson's disease presenting with liver disease have Kayser–Fleisher rings only about one-half of the time. Their 24-h urine copper will always be elevated, but the presence of active hepatitis or chronic obstructive liver disease can elevate urine copper in the absence of Wilson's disease. A liver biopsy with measurement of copper is usually required with the liver disease presentation.

Presymptomatic affected patients present with Kayser–Fleischer rings about one-third of the time, and diagnostically elevated urine copper about half the time. If the urine copper is clearly normal (below 55 μg/24 h), and the measurement is valid, Wilson's disease is excluded. If the urine copper is in the gray zone (between 55 and 100 μg), the person may be just a heterozygous carrier, who can have mild elevations of urine copper but not require treatment, or a presymptomatic patient, who does require treatment. In this case, a liver biopsy should be

done with quantitative assay of copper. Patients are always over 200 μg/g dry weight, whereas carriers are 125 μg or less.

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

Anticopper Drugs

The anticopper drugs available are shown in Table 23.3, and include TM, which is not yet commercially available. The earliest drug available was penicillamine, which is a chelator that acts by increasing urinary excretion of copper [12]. It is effective at producing a negative copper balance, but has numerous side effects [27, 30] that are rapidly decreasing it use, given the advent of newer, effective, and safer drugs. Penicillamine also has the severe disadvantage in newly diagnosed neurologically presenting patients of making about 50 % of them neurologically worse, and only one-half of that number recover to their pre-penicillamine baseline [32]. Thus, penicillamine makes 25 % of neurologically presenting patients permanently worse (as with patient 2). The second oldest drug is trientine, which is also a chelator that increases the urinary excretion of copper [13]. Trientine is also uniformly effective, has a much better safety profile than penicillamine, although it has some of the same side effects as penicillamine and makes neurologic patients worse 26 % of the time [33].

The third drug is zinc. Zinc acts by inducing intestinal metallothionein, which blocks intestinal absorption of copper [34]. Zinc is uniformly effective and has only one side effect—that of causing mild epigastric burning pain in a significant number of patients [16]. The fourth drug is TM [17, 18], which acts by forming a tripartite complex with copper and protein. Given with food, it prevents copper absorption. Given between meals, TM is well absorbed and causes the available copper in the blood to combine with serum albumin in a very stable complex. In this way, the potentially toxic copper of the body can be quickly titrated and safely complexed. Side effects that we have observed with TM are discussed later.

Here, we focus on the initial treatment of the neurological presentation followed by maintenance therapy. References for treating hepatic and presymptomatic patients are readily available [29–31, 35]. The initial treatment of the neurologically presenting patient is problematic because the drug used most often by physicians, penicillamine, is contraindicated in these patients (patient 2). Penicillamine has an approximately 25 % chance of making the patient permanently, and often disastrously, worse neurologically, as it did with patient 2 [32]. The problem of initial treatment of these patients is compounded by the fact that the excellent maintenance

Table 23.3 Anticopper drugs

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

drug, zinc, acts too slowly, in our opinion, for this type of acutely ill patient. Prior to our work (discussed later), trientine had been untried in this setting, but because it shares penicillamine's mechanism of action, it was suspected of also causing initial neurological worsening.

Because of the therapeutic need of these patients, TM was developed [17, 18, 36, 37]. TM is very fast acting and, based on animal studies, appears to be a very safe drug. Over a period of years we have treated 55 neurologically presenting patients with an 8-week course of TM [18]. To evaluate possible neurological worsening, we developed a semiquantitative neurological examination (scored 0–38, with 0 normal) and a semiquantitative speech examination (scored 0–7, with 0 normal). Criteria for worsening included a consistent deterioration of five or more points in the neurological test and three or more points in the speech score. Only 2 of the 55 patients (3.6 %) reached our criteria for neurological worsening in the open-label study [18], compared with an estimated 50 % who are initiated on penicillamine [32].

Subsequently we (together with Dr. Michael Schilsky and his group at New York's Mount Sinai) initiated a double-blind study comparing TM and trientine for initial therapy. The results [33] confirm TM's low rate of neurologic deterioration and showed that trientine-treated patients had neurologic deterioration 26 % of the time, a value about halfway between penicillamine (50 %) and TM (4 %). Trientine patients who deteriorated did not do well [33].

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

get the regular 120 mg dose for 2 weeks, then drop down to half the regular dose (60 mg) for an additional 14 weeks. This approach greatly reduced the two side effects, so this is the regimen now recommended [38].

Anticopper Drug Treatment Recommendations

Given the above background, our recommended first drug for initial therapy is TM (Table 23.4). TM is not currently commercially available because of holdups in meeting FDA requirements. In the meantime, our second choice would be zinc therapy, and our third would be trientine. Monitoring recommendations for the three drugs are given in Table 23.5.

Our first choice for maintenance therapy is zinc. Zinc is fully effective and has many fewer side effects than penicillamine or trientine [16]. Monitoring zinc therapy (Table 23.5) is also easier than with the other drugs [16, 29–31]. Because zinc does not directly affect urine copper, the 24-h urine copper becomes a good reflector of the body status of copper. In untreated Wilson's disease, the urine copper may be quite elevated, up to several hundred micrograms per 24 h (normal 20–50 μg). With zinc therapy, this will gradually come down so that by the end of the first year it is usually less than 125 μg. We view anything below 125 μg as indicating adequate control. Minor fluctuations over time are to be expected, but major increases (30 % or more) suggest noncompliance. Another way to monitor patients is to measure 24-h urine zinc, using the same sample. In an adequately treated patient, the urine zinc should be 2 mg or higher per day. If levels fall below that number, it gives an early warning signal of noncompliance. Twenty-four-hour urine zinc levels will decrease within 2–3 weeks of significant noncompliance, whereas it takes 2–3 months for urine copper to increase. Urine copper and zinc should be monitored every 3 months early during maintenance therapy, and as the patient exhibits good compliance, the frequency decreased to every 6 months and then to annually. Every patient should be monitored at least annually. If the urine copper gets down into the normal range, overtreatment and copper deficiency may follow. At this point, it is a good idea to begin backing off on the zinc dose. At the time of urine evaluation, blood counts and liver function tests should also be carried out.

The second choice for maintenance therapy is trientine. Trientine can cause side effects such as proteinuria, bone marrow depression, and an autoimmune disease. Patients should be monitored by blood and urine studies, as well as asked about side effects, every week for 4 weeks, biweekly for 2 months, monthly for 6 months, every 6 months for 2 years, and then annually (Table 23.5). Copper status can be evaluated at 1, 3, 6, and 12 months for the first year, and then at least annually in complicated patients. Urine copper, blood copper, and blood ceruloplasmin should be used. The 24-h urine copper will start out at about 1 mg, and go down to 200–300 μg by 1 year of adequate treatment. The problem with interpreting this value in terms of compliance is that it represents both the action of the drug and body loading

Table 23.4 Recommendations for Anticopper drug therapy in neurologically presenting patients with Wilson's disease

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

Table 23.5 Monitoring recommendations for the anticopper drugs

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

of copper. The best that usually can be done is to take note of any sudden significant increase and ask the patient about compliance. With trientine, it is more important to concomitantly measure blood copper and ceruloplasmin than it is with zinc. The copper in ceruloplasmin can be subtracted from the blood copper to determine the nonceruloplasmin plasma copper, often called the free copper (this is done by subtracting 3.0 μg of copper for every milligram per deciliter of ceruloplasmin, and subtracting that number from the serum copper in microgram per deciliter). This number is normally 10–15 μg/dL of serum and may be very high (50 μg or so) in untreated patients. It should come down to 25 μg or less during the first year of therapy and remain there. If it bounces up, it suggests noncompliance.

Penicillamine is the third choice for maintenance therapy and is not highly recommended because of its long list of side effects. These include an initial hypersensitivity reaction in about 25 % of patients, proteinuria, bone-marrow suppression, autoimmune disturbances, skin wrinkling and other skin side effects, and possible vascular wall deterioration. It is monitored much in the same manner as trientine (Table 23.5).

Assuming that the patient does not suffer initial neurological deterioration, the prognosis is quite good for substantial neurological recovery [18, 27–31]. This usually begins about 5–6 months after initiation of therapy and is relatively complete by about the 2-year mark. Generally, symptoms and disabilities remaining at that time will be permanent. During the initial 2-year period, it is important for the patient to try to maintain whatever compromised functions he or she has. The patient

should participate in speech therapy, or at least continually work at speaking if he or she has dysarthria, and the patient should remain physically active, trying to maintain as much function as possible in the face of dystonia and incoordination. Physical therapy should be used for this purpose if available. Botulinum toxin injections may be useful to relieve dystonia in key areas. All the medications normally employed for relieving tremor or dystonia can be used [39], with the one caveat that drugs that have major hepatic toxicity should be avoided. If the patient has dysphagia that is causing aspiration, he or she should have a gastrostomy placed and receive tube feedings. The tube can be pulled when swallowing normalizes.

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

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

Conclusion

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

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Chapter 24
Dopa-Responsive Dystonia

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This chapter contains video segments that can be found on the accompanying DVD.

Abstract Dopa-responsive dystonia (DRD) is a clinical syndrome characterized by childhood-onset dystonia and a dramatic and sustained response to low doses of levodopa. There are two known causative genes for DRD: (1) the *GCH1* gene, coding for the enzyme GTP cyclohydrolase I (GTPCH) that catalyzes the rate-limiting step in the biosynthetic pathway for tetrahydrobiopterin (BH4, the essential cofactor for tyrosine hydroxylase [TH]), and (2) the *TH* gene, coding for the enzyme TH in the catecholamine biosynthesis. Many patients with DRD have shown dominantly inherited *GCH1* mutations (GTPCH-deficient DRD, the major form of DRD), whereas a relatively small number of DRD patients have demonstrated recessively inherited *TH* mutations (TH-deficient DRD, the mild form of TH deficiency). Notwithstanding the discovery of these causative genes for DRD, a therapeutic trial with low-dose levodopa is still the most practical approach to the diagnosis of this treatable disorder, and the trial should be considered in all children with dystonic and/or parkinsonian symptoms or with unexplained gait disorders. This chapter summarizes clinical features as well as recent advances in the genetics and biochemistry of DRD.

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Patient Vignettes

Patient 1

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

Patient 2

A 45-year-old woman states that her long-standing foot dystonia has deteriorated over the last year. She also describes that she has developed a tremor involving her right arm in the last few months. She manifested her dystonic posturing (inward turning) at age 7 and the initial treatment strategy has been beneficial, until recently, with trihexyphenidyl. She noticed that her foot dystonia was worse in the late afternoon and evening. She discloses a family history of overt dystonia in her brother, father, and paternal grandfather. Her two daughters (identical twins) have occasionally manifested mild dystonic posture of the foot after extreme exercise. On examination she showed dystonia of the feet, with the right being worse. She had increased tone in her right leg and arm. Rapid alternating movements were slow in the right foot and hand and in the left foot to a lesser extent. She had a mild postural tremor of her right hand. Her walking revealed dystonic posturing of the right foot. Investigations included normal brain CT and copper metabolism studies. She was successfully switched from trihexyphenidyl to levodopa with a DCI and has had no dystonia and parkinsonism on examination. The diagnosis of DRD was confirmed by genetic analysis [3] (Video 24.1).

Introduction

DRD is a clinical syndrome characterized by childhood-onset dystonia and a dramatic and sustained response to low doses of levodopa [4–7]. This clinical syndrome typically presents with gait disturbance due to foot dystonia, later development of some parkinsonian features, and diurnal fluctuation of symptoms (worsening of symptoms toward evening and their alleviation in the morning after sleep) (Table 24.1). The sustained levodopa responsiveness without motor adverse effects of chronic levodopa therapy such as dopa-induced dyskinesias distinguishes DRD from early-onset parkinsonism (EOP) with dystonia [2, 8]. Because DRD responds so well to treatment with levodopa, and because failure to recognize this disorder causes unacceptable morbidity, we choose to classify DRD as a movement disorder emergency.

DRD is differentiated from primary dystonias and is classified under the dystonia-plus category [9]. There are two known causative loci for DRD (locus heterogeneity): (1) the *GCH1* gene on chromosome 14q22.1-q22.2, which encodes GTP cyclohydrolase I (GTPCH), the first enzyme in the biosynthetic pathway for BH4 (Fig. 24.1), and (2) the *TH* gene on 11p15.5, coding for the enzyme TH that catalyzes the rate-limiting step in catecholamine biosynthesis (Fig. 24.1) [10–15]. Many patients with DRD have demonstrated dominantly inherited *GCH1* mutations (GTPCH-deficient DRD, the major form of DRD) [15], whereas a relatively small number of DRD patients have shown recessively inherited *TH* mutations (TH-deficient DRD, the mild form of TH deficiency) [12, 15–19]. Because no

Table 24.1 Clinical characteristics of classic dopa-responsive dystonia (DRD)

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

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

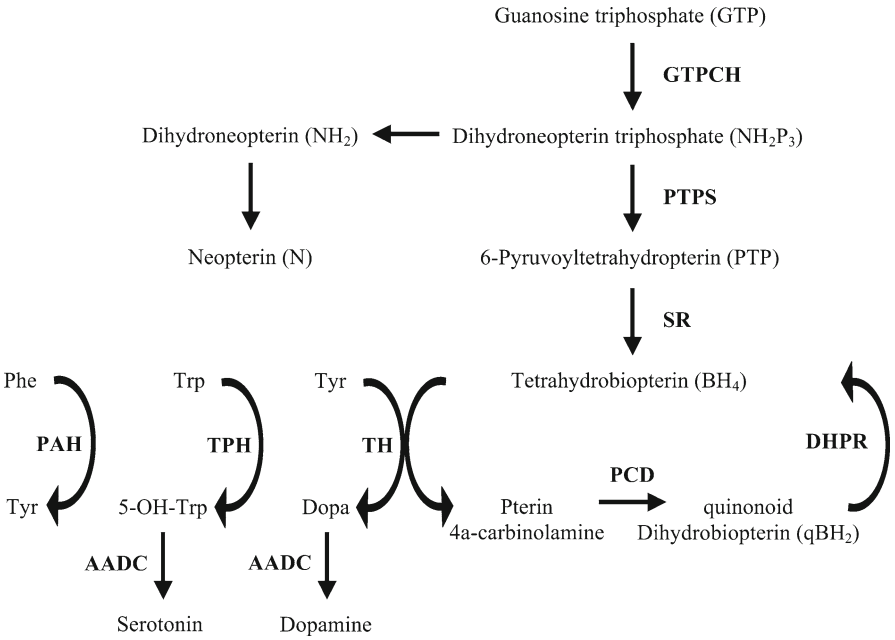

Fig. 24.1 Tetrahydrobiopterin (BH4) biosynthetic pathway and BH4-dependent hydroxylation of aromatic amino acids. *GTPCH* GTP cyclohydrolase I, *PTPS* 6-pyruvoyltetrahydropterin synthase, *SR* sepiapterin reductase, *PAH* phenylalanine hydroxylase, *TPH* tryptophan hydroxylase, *TH* tyrosine hydroxylase, *PCD* pterin-4a-carbinolamine dehydratase, *DHPR* dihydropteridine reductase, and *AADC* aromatic L-amino acid decarboxylase

mutations in either *GCH1* or *TH* were identified in some patients with DRD, a therapeutic trial with low-dose levodopa is still the most practical approach to the diagnosis of this treatable disorder. Since clinical suspicion is a key to the diagnosis, physicians should know not only the classic phenotype of GTPCH-deficient and TH-deficient DRD but also the broad phenotypic spectrum (allelic heterogeneity) in GTPCH and TH deficiencies.

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

Clinical Observations

Classic DRD

In 1971, Segawa [20] and Castaigne [21] independently reported clinical characteristics of one family each with DRD, which they called at that time “hereditary progressive basal ganglia disease with marked fluctuation” and “progressive

extrapyramidal disorder," respectively. Advances in the genetics and biochemistry of DRD have demonstrated that the former had autosomal dominant GTPCH deficiency and the latter had autosomal recessive TH deficiency [11, 22, 23]. In both families, a dramatic and sustained response to low doses of levodopa without motor side effects during chronic levodopa treatment had been confirmed [5, 20–25]. In patients with DRD, there is no abnormality in the perinatal and postnatal period. Early motor development (e.g., sitting and crawling) is normal (Table 24.1). The average age of the onset of typical DRD is approximately 6 years [5, 6].

Initial symptoms in most patients with childhood-onset DRD are gait difficulty due to dystonia in the leg, typically flexion–inversion of the foot (pes equinovarus). Because of this dystonic posturing, patients often wear the outer-side of their shoes down easily. A relatively small number of patients have onset with arm or neck dystonia, tremor (mainly postural), or slowness of movements. In childhood-onset patients, gradual progression to generalized dystonia occurs but dystonia is typically more pronounced in the lower limbs throughout the disease course. There is a tendency to fall, and standing position with equinovarus posturing of the feet can induce increased lumbar lordosis, flexion of the hip joints, and hyperextension of the knee joints. A variable degree of rigidity and slowness of movements is recognized in the affected limbs. Rapid fatiguing of effort with repetitive motor tasks (e.g., foot tapping) is often observed. On neurologic examination, in addition to dystonic and parkinsonian elements, some clinical findings suggestive of pyramidal signs in the lower extremities (brisk reflexes, ankle clonus, spasticity, and/or [intermittent] extensor plantar responses) are detected in many patients. Normal efferent cortical spinal activity using magnetoelectrical stimulation of motor cortex has suggested a non-pyramidal basis for these findings [26]. Dystonic extension of the big toe in DRD (the striatal toe [27]), which occurs spontaneously or is induced by plantar stimulation, may be misinterpreted as an extensor plantar response. Diurnal fluctuation of symptoms occurs in approximately 80% of patients. The degree of fluctuation is variable, with some patients being normal in the morning, whereas others are only less severely affected in the morning when compared to later in the day. Some patients only show exercise-induced exacerbation or manifestation of dystonia, or complain of prominent stiffness and fatigue after exercise. The magnitude of diurnal fluctuation often attenuates with age and disease progression.

A predominance of clinically affected females is observed in autosomal dominant DRD. The female-to-male ratio has been reported to be 2:1 to 6:1 in childhood-onset patients [5, 6]. No increased prevalence of DRD is evident in any ethnic group. Estimates suggest that the prevalence in both England and Japan is 0.5 per million and that 5–10% of dystonia patients in childhood or adolescence have DRD [4, 27]. In general, the severity of gait disturbance and dystonia in adolescent-onset patients is milder than that in childhood-onset patients. Patients with adolescent-onset DRD seldom develop severe generalized dystonia. However, dystonia in female patients can be markedly exacerbated after taking oral contraceptives [28, 29]. Teenage-onset patients with slow progression may become more symptomatic in mid-adulthood due to development of overt parkinsonian features [30].

Phenotypic Heterogeneity

A wide range of symptoms and signs has been reported in patients with DRD due to *GCH1* mutations. An earlier linkage study demonstrated "benign" adult-onset parkinsonism (showing slow progression and no motor adverse effects of levodopa) as a phenotypic expression of autosomal dominant DRD [10]. Patients with this phenotype manifest no dystonic symptoms prior to the onset of their parkinsonism, including resting tremor, in mid- or late-adulthood [10, 31, 32]. In contrast to patients with Parkinson's disease (PD), adult-onset parkinsonian patients in DRD pedigrees markedly respond to low doses of levodopa and remain functionally normal for a long period of time without developing motor response fluctuations, freezing episodes, or dopa-induced dyskinesias under treatment with optimal doses of levodopa. In some of these DRD pedigrees, heterozygous *GCH1* mutations have been identified [29, 33–38]. An age-related decline of striatal biopterin during adulthood could contribute to this parkinsonian phenotype [16, 39].

There have been some DRD patients who were initially misdiagnosed as having cerebral palsy (the spastic diplegic form) or spastic paraplegia (the familial or apparently sporadic form) because of hyperreflexia, clonus, spasticity, and/or extensor plantar responses in the legs [34, 37, 40–44]. As mentioned, a non-pyramidal basis for these findings in DRD has been suggested [26]. An extensor plantar response observed in DRD often disappears after starting levodopa administration, suggesting that the previous finding may be a dystonic phenomenon (the striatal toe) rather than a Babinski response. Mutations in *GCH1* and *TH* have been identified in patients with DRD simulating cerebral palsy (including other forms) or spastic paraplegia [34, 37, 42–44]. Thus, although the differential diagnosis of cerebral palsy and of spastic paraplegia should include DRD, this appears to be still underappreciated.

The clinical phenotype of DRD associated with heterozygous mutations in *GCH1* has been extended to include various types of focal dystonia (e.g., adult-onset guitarist's cramp) and spontaneous remission of dystonia and/or parkinsonism (sometimes with a relapse in the later course of illness) [29, 33, 34, 45–47]. However, in our experience, pure writer's cramp and isolated scoliosis were not always associated with *GCH1* mutations found in the probands with the classic phenotype [16, 37, 48]. In some families with DRD due to *GCH1* mutations, psychiatric and behavioral symptoms (depressive disorders, panic attacks, obsessive–compulsive disorder, etc.), sleep disorders, migraine, and/or restless legs syndrome were reported [23, 29, 49–51]. In rare instances, exaggerated startle responses, involuntary jerky movements, or cerebellar signs were observed in GTPCH-deficient DRD [51–53].

Molecular Genetics

GTPCH-Deficient DRD

The enzyme GTPCH is encoded by a single copy gene, *GCH1*, which is composed of six exons spanning approximately 30 kb [54]. This enzyme catalyzes the rate-limiting step in the biosynthesis of BH4 (Fig. 24.1). BH4 is the natural cofactor not only for TH but also for phenylalanine hydroxylase and tryptophan hydroxylase, and most patients with autosomal recessive GTPCH deficiency (usually homozygotes) have BH4-dependent hyperphenylalaninemia (HPA) and severe neurologic dysfunction [54–56]. In contrast to these patients, GTPCH-deficient DRD patients (usually heterozygotes) never develop HPA. There is another phenotype of GTPCH deficiency, dystonia with motor delay, associated with compound heterozygosity for *GCH1* mutations [28, 29, 36, 57, 58].

In patients with these GTPCH deficiencies, more than 150 independent *GCH1* mutations have been identified. The reason why many different mutations occur throughout all of the exons of *GCH1* is unknown, and no clear correlations between specific clinical features and types of mutations are established. In reports on DRD, in which conventional genomic DNA sequencing of *GCH1* was conducted in a relatively large number of families, mutations in the coding region (including the splice sites) of this gene were found in approximately 60% of pedigrees with DRD [59]; the *GCH1* mutation detection rate by this sequence analysis ranged from 20% [60] to 80% [16, 23, 61]. For *GCH1* "coding region mutation-negative" DRD families, including pedigrees that have an apparently sporadic patient or only a few affected siblings, possible explanations (as suggested [7, 16, 59]) are the following: (1) a large deletion of one or more exons of *GCH1* [3, 14, 38, 44, 47, 61–63]; (2) a mutation in noncoding regulatory regions of *GCH1* [34, 44, 45, 58]; (3) an intragenic duplication [51] or inversion of *GCH1*; (4) a recessively inherited mutation in *TH* ([12, 18, 19, 22, 42, 64, 65]; see below); and (5) a mutation in, as yet undetermined, regulatory genes having an influence on *GCH1* expression or other genes, the products of which interact with GTPCH and can modify the enzyme function. Since our first report of a large heterozygous *GCH1* deletion in the four-generation DRD family (shown in the Vignettes section) [3], a variety of methods, including multiplex ligation-dependent probe amplification (MLPA), have been used to detect an exon deletion in *GCH1* [14, 38, 44, 47, 61–63]. Such a large genomic deletion is an important subtype and should be analyzed in all of the patients with coding region mutation-negative DRD; in fact, after conducting additional *GCH1* analysis, Furukawa [59], Hagenah [61], and Clot [44] found *GCH1* mutations in 80–90% of their DRD pedigrees. When Wider [14] restudied a Swiss family with DRD, which Grötzsch [66] had mapped to a locus named DYT14 on chromosome 14q13 (outside the *GCH1* gene on 14q22.1-q22.2 [11]), a heterozygous deletion of exons 3–6 of *GCH1* was identified.

Approximately 30–50% of patients with DRD have been reported to have no family history of dystonia [5, 6]. Some of these apparently sporadic cases can be explained by gender-related incomplete penetrance of *GCH1* mutations (87% and 35–38% in female and male mutation carriers, respectively [23, 67]), different de novo mutations in *GCH1* (suggesting a relatively high spontaneous mutation rate in this gene [67]), and recessively inherited *TH* mutations [18, 19, 42, 65].

TH-Deficient DRD

Human *TH* consists of 14 exons spanning approximately 8.5 kb [68]. The enzyme TH, a BH4-dependent monooxygenase, catalyzes the rate-limiting step in the biosynthesis of catecholamines (Fig. 24.1). In patients with the mild form (TH-deficient DRD) or the severe form (infantile parkinsonism with motor delay or progressive infantile encephalopathy) of autosomal recessive TH deficiency [17, 59, 68, 69], more than 40 *TH* mutations have been identified [18, 19, 70].

Although Bartholomé and Lüdecke [71] have reported that DRD due to *TH* mutations is characterized by leg dystonia (onset approximately 4 years of age), diurnal fluctuation of symptoms, and a good response to levodopa therapy, further accumulation of genetically proven patients is necessary to establish the clinical features of TH deficiency, including those of TH-deficient DRD. This group found a homozygous *TH* mutation in two brothers with DRD [12]. The mutated recombinant enzyme showed approximately 15% of specific activity compared with the wild type in a coupled in vitro transcription–translation assay system [72]. A dramatic and sustained response to low doses of levodopa without any motor side effects for more than 30 years has been confirmed in at least five patients [22, 64], including two affected brothers (onset at age 2 and 5 years) originally reported by Castaigne [21]. These five patients (all males) with the mild form of TH deficiency were compound heterozygotes for *TH* mutations [22, 64]. Another boy, who was also compound heterozygous for mutations in *TH*, developed DRD simulating spastic paraplegia at 13 months of age [42]. Female predominance, which has been confirmed in GTPCH-deficient DRD [23, 67], may not be a clinical characteristic in TH-deficient DRD [59].

Genetically Related Disorders

Severe GTPCH Deficiency

Patients with autosomal recessive GTPCH deficiency usually develop BH4-dependent HPA in the first 6 months of life [54–56, 59]. There was no detectable GTPCH activity in liver biopsy specimens in patients with GTPCH-deficient HPA. This disorder presents with severe neurologic dysfunction, including convulsions, mental retardation, swallowing difficulties, developmental motor delay, truncal hypotonia, limb

hypertonia, and involuntary movements. In the first report of recessively inherited GTPCH deficiency by Niederwieser [55], hyperreflexia with an extensor plantar response was also described. In contrast to GTPCH-deficient DRD patients, BH4 administration and neurotransmitter replacement therapy (levodopa and 5-hydroxytryptophan) are necessary for GTPCH-deficient HPA patients [55, 56].

Moderate GTPCH Deficiency

A phenotype of GTPCH deficiency (dystonia with motor delay), which is clinically and biochemically intermediate between GTPCH-deficient DRD (mild) and GTPCH-deficient HPA (severe), has been found in compound heterozygotes for *GCH1* mutations [28, 29, 36, 57, 58]. This phenotype is characterized by developmental motor delay, limb dystonia (with truncal hypotonia) that progresses to generalized dystonia, and no overt HPA in infancy. Such compound heterozygotes could be misdiagnosed initially as having cerebral palsy [36]. In three compound heterozygotes [28, 36, 58], their mothers and maternal grandmothers (all heterozygotes) developed DRD symptoms, suggesting that these three patients have at least one dominant allele, whereas compound heterozygous genotypes generally involve different recessive alleles at a locus. The finding of compound heterozygotes in these DRD pedigrees also suggests that intrafamilial phenotypic heterogeneity in some GTPCH-deficient DRD families may be explained by an additional *GCH1* mutation [7, 59]. It is worth noting that one compound heterozygote for *GCH1* mutations responded remarkably to low doses of levodopa and made further improvement in motor function when BH4 was chronically added to maintenance levodopa treatment [28, 73]. This observation suggests that early combination therapy of levodopa and BH4 may be suitable for some compound heterozygotes manifesting with dystonia with motor delay phenotype. In rare instances, homozygotes for *GCH1* mutations may develop a similar phenotype [74].

Other BH4-Related Enzyme Deficiencies

Patients with autosomal recessive BH4-related enzyme deficiencies, including recessively inherited severe GTPCH deficiency (see above), develop BH4-dependent HPA; an exception is autosomal recessive sepiapterin reductase (SR) deficiency (in this case, BH4 is synthesized through the salvage pathway in peripheral tissue) [56, 75]. These patients typically present with psychomotor retardation, seizures, microcephaly, swallowing difficulties, truncal hypotonia, limb hypertonia, involuntary movements, and/or oculogyric crises. Diurnal fluctuation of symptoms and dystonia "partially" responding to levodopa can be found in some patients, especially those with SR deficiency [7, 75–77]. Administration of levodopa and 5-hydroxytryptophan is necessary for cases with autosomal recessive SR deficiency. This neurotransmitter replacement therapy and BH4 treatment are indispensable for those with

other autosomal recessive BH4-related enzyme deficiencies. Steinberger [78] identified a heterozygous mutation in the untranslated region of the *SPR* gene encoding SR in 1 of 95 cases, who presented with dystonia responsive to levodopa and did not have a *GCH1* mutation; they concluded that haploinsufficiency of *SPR* can be a rare cause of dominantly inherited DRD [63]. This "autosomal dominant SR-deficient DRD" has not been confirmed by other groups.

Severe TH Deficiency

In contrast to patients with the mild form of TH deficiency (TH-deficient DRD), patients with the severe form of TH deficiency (infantile parkinsonism with motor delay or progressive infantile encephalopathy) usually have the onset of symptoms at less than 6 months of age [18, 19, 59, 68–70]. Most of these patients demonstrate developmental motor delay, truncal hypotonia, rigidity of extremities, and hypokinesia. Ptosis and/or oculogyric crises are often observed. Generally, typical diurnal fluctuation is not recognized. More severely affected cases also develop mental retardation and hyperprolactinemia; although dopamine is a prolactin-inhibiting factor at the hypothalamus level, serum prolactin concentrations are usually normal in patients with GTPCH-deficient DRD [36]. Very severely affected infants have progressive encephalopathy. In one patient, in whom a homozygous *TH* missense mutation was found, the mutant TH revealed only 0.3–16% of wild-type enzyme activity in three complementary expression systems [79]. It is often difficult to increase levodopa doses smoothly in patients with the severe form of TH deficiency, especially at the initiation of treatment, because of the development of intolerable dyskinesias. For these patients, combined administration of levodopa and selegiline (a monoamine oxidase B inhibitor) has been recommended [18].

Laboratory Investigations

Routine blood counts and chemistries, plasma and urine amino acids, serum copper and ceruloplasmin, and brain CT and MRI are normal in patients with DRD.

CSF Pterin Analysis

Before the discovery of *GCH1* mutations, a functional abnormality of brain GTPCH was suggested by decreased levels of CSF total biopterin and neopterin in autosomal dominant DRD [1, 8, 80–82]. Total biopterin (BP) includes BH4, quinonoid dihydrobiopterin, and 7,8-dihydrobiopterin, and total neopterin (NP) consists

of degradation products (dihydroneopterin and neopterin) of dihydroneopterin triphosphate, which is synthesized from GTP by GTPCH [83] (Fig. 24.1). Most of brain BP exists as BH4 and more than 70% of CSF NP exists as the dihydro form [83]. Generally, NP is considered to reflect GTPCH activity, and low levels of both BP and NP in CSF have been demonstrated in genetically proven patients with GTPCH-deficient DRD (including the apparently sporadic patient shown in the Vignettes section), dystonia with motor delay, and GTPCH-deficient HPA [1, 2, 28, 49, 84]. Reduced brain BP and NP concentrations were confirmed in the two autopsied patients with DRD [16, 30].

GTPCH Activity Assay

Ichinose [11] reported that GTPCH activity levels in phytohemagglutinin (PHA)-stimulated mononuclear blood cells were decreased in DRD patients having *GCH1* mutations compared with normal controls. Using cultured lymphoblasts, however, Bezin [85] has suggested that the PHA induction alone misrepresents the actual status of GTPCH activity. Activity of GTPCH in PHA-stimulated mononuclear blood cells was lower in normal females than in normal males in one report [11]. Nevertheless, there was no difference of this activity between females and males in another report from the same group [86]. Unfortunately, non-stimulated GTPCH activity in mononuclear blood cells is too low to be measured. Although measurement of GTPCH activity in cytokine-stimulated fibroblasts was reported to be useful for the diagnosis of DRD, the reason why the activity was lower in most patients with GTPCH-deficient DRD (heterozygotes) than in those with GTPCH-deficient HPA (homozygotes with more severe symptoms) remains to be explained [50, 87]. In coexpression studies, it has been demonstrated that GTPCH with dominantly inherited *GCH1* mutations but not recessively inherited ones inactivated the wild-type enzyme, suggesting a critical role of this dominant negative effect in autosomal dominant GTPCH-deficient DRD [88–90]. However, Suzuki [91] has suggested that such a dominant negative effect is unlikely to explain low enzyme activity in PHA-stimulated mononuclear blood cells from GTPCH-deficient DRD patients (<20% of controls [11]) and that a reduction of the amount of GTPCH protein found in these cells may contribute to the mechanism of dominant inheritance. It is interesting to know brain GTPCH protein levels in patients with dominantly inherited DRD.

Phenylalanine Loading Test

Patients with DRD never develop HPA. However, a subclinical defect in phenylalanine metabolism (due to partial BH4 deficiency in the liver) can often be detected in GTPCH-deficient DRD patients by the phenylalanine loading test, analyzing plasma

phenylalanine-to-tyrosine ratios for 6 or 4 h following an oral phenylalanine load (100 mg/kg) [92–94]. Nevertheless, both false negative and positive results of this test have been reported [93, 94]. The reason for the difference in susceptibility to a BH4-deficient condition between TH and phenylalanine hydroxylase could relate to different Km (Michaelis constant) values of the hydroxylases for BH4 [59].

Neuroimaging Studies

Positron emission tomography (PET) and single-photon emission computed tomography (SPECT) investigations using presynaptic dopaminergic markers, (1) [^{18}F]-6-fluorodopa whose uptake rate constant is an index of dopa uptake, decarboxylation, and storage mechanisms and (2) ligands ([^{123}I]β-CIT and -fluoropropyl-CIT) which bind to the dopamine transporter (DAT), have shown normal or near-normal results in the striatum of DRD patients [32, 95–99]. These PET and SPECT findings are consistent with normal striatal levels of aromatic L-amino acid decarboxylase (AADC) protein and the DAT examined by [^{3}H]WIN 35428 binding in the autopsied DRD patients with GTPCH dysfunction [30]. Using [^{11}C]-raclopride PET, elevated D2-receptor binding has been found in the striatum of patients with DRD [98, 100, 101]. This increased receptor binding could be due to receptor up-regulation and/or diminished competition for the tracer as a consequence of low synaptic dopamine concentration. Network analysis of [^{18}F]-fluorodeoxyglucose PET images has demonstrated that GTPCH-deficient DRD is associated with a specific metabolic topography, which is characterized by increases in the dorsal midbrain, cerebellar vermis, and supplementary motor area and by decreases in the putamen as well as lateral premotor and motor cortical regions [102].

Neuropathology and Neurochemistry

Neuropathologic studies demonstrated no Lewy bodies and a normal population of cells with reduced melanin in the substantia nigra of three DRD patients (Patient 1 [19 years], Patient 2 [68 years], and Patient 3 [77 years]) and one asymptomatic case (55 years) with GTPCH dysfunction [14, 30, 35, 66, 103]. Patient 1 had a *GCH1* nonsense mutation (Glu65Ter) on one allele and a polymorphism in *GCH1* (Pro23Leu [59]) on the other allele [30]. In Patient 2, no mutation in either the coding region or the splice sites of *GCH1* was found [30]. A heterozygous deletion of exons 3–6 of *GCH1* was identified in Patient 3 [14]. The asymptomatic case in a family with DRD (linked to the *GCH1* locus [10]) had a heterozygous missense mutation (Gly108Asp) in *GCH1* [35]. This missense mutation was not found on 150 normal control chromosomes. There have been no reports of autopsied patients with TH-deficient DRD and neurochemical analysis was not conducted in Patient 3.

In the putamen of Patients 1 and 2, BP and NP concentrations were substantially reduced (mean; −84% and −62%) compared with age-matched normal controls [30]. Striatal subregional dopamine data pointed to an involvement of the caudal portion of the putamen as the striatal subregion that was most affected by dopamine loss (−88%) in both patients [30, 103]. Dopamine concentration in this striatal subdivision was reported to be normal in an autopsied patient with *DYT1* dystonia [104]. It is known that the caudal putamen is most affected by loss of dopamine in patients with PD [105–108]. In the asymptomatic case, decreases in BP and NP levels in the putamen (−82% and −57%) paralleled those in Patients 1 and 2 [35]. Dopamine concentration in the caudal subdivision of the putamen was not as severely reduced (−44%) as in the symptomatic cases. Consistent with other postmortem data suggesting that greater than 60–80% of striatal dopamine loss is necessary for overt motor symptoms to occur [106], the maximal 44% dopamine reduction in the striatum of the *GCH1* mutation carrier was not sufficient to produce any DRD symptoms.

In contrast to patients with PD [109, 110], striatal levels of AADC protein, the DAT, and the vesicular monoamine transporter (measured by [^{3}H]dihydrotetrabenazine binding) were normal in Patients 1 and 2, indicating that striatal dopamine nerve terminals are preserved in GTPCH-deficient DRD patients [30]. However, TH protein levels were markedly decreased in the putamen (> −97%) of both symptomatic cases. These biochemical findings have suggested that striatal dopamine reduction in GTPCH-deficient DRD is caused not only by decreased TH activity due to low cofactor concentration but also by actual loss of TH protein. The human brain data are compatible with TH protein loss but preserved AADC activity in brains of BH4-deficient mice [111–114]. In contrast to the symptomatic cases, the concentration of TH protein in the putamen was only moderately reduced (−52%) in the asymptomatic case [35]. Striatal TH protein reduction in GTPCH-deficient DRD may be caused by a diminished regulatory effect of BH4 on the steady-state level (stability/expression) of TH molecules [30]. Because TH protein concentrations in the substantia nigra, where striatal TH molecules are synthesized, were normal in Patients 1 and 2, BH4 could control stability rather than expression of this enzyme [16, 30]. This is supported by reports showing loss of TH protein but not of *TH* mRNA in brains of BH4-deficient mice [112–114]. Alternatively, there might be an abnormality of TH protein transport from the substantia nigra to the striatum due to congenital partial GTPCH deficiency [16, 30]. The neurochemical findings in the asymptomatic *GCH1* mutation carrier suggest that the extent of striatal TH protein loss may be critical in determining the symptomatic state of GTPCH-deficient DRD [35].

Diagnosis

Which laboratory investigations are practical for the diagnosis of DRD? Because not all patients with DRD have detectable mutations in *GCH1* or *TH*, the present genetic testing for DRD is not suitable for routine clinical practice; in our series,

analyses of both *GCH1* and *TH* showed mutations in 86% of families with DRD or dystonia with motor delay [59]. Measurement of GTPCH activity in PHA-stimulated mononuclear blood cells [11, 86] or cytokine-stimulated fibroblasts [87] is technically demanding and is conducted in only a few research laboratories. Moreover, the activity test using mononuclear blood cells should be performed within 20 hours after blood sampling [86, 87]. The enzyme TH is mainly expressed in the brain and the adrenal medulla and direct measurement of its activity is not a diagnostic option. In the phenylalanine loading test [92], a small number of DRD patients confirmed to have *GCH1* mutations showed no abnormality of phenylalanine metabolism [94, 115]. In contrast, there have been no negative reports on the results of CSF NP measurement (low NP concentrations) in genetically proven patients with GTPCH-deficient DRD, dystonia with motor delay, and GTPCH-deficient HPA [1, 2, 28, 43, 49, 87, 97, 116, 117], except for one report showing a borderline value in an atypical case with dominantly inherited GTPCH deficiency [52]. Decreased NP levels in CSF are not observed in other types of BH4 deficiency [16, 75]. Because of the known influence of age and immune status on NP, it is necessary to have age-matched control data and to exclude samples with infections, when a patient is diagnosed as having GTPCH deficiency by reduced concentrations of both NP and BP in CSF [1, 83]. Precise determination of CSF levels of neurotransmitter metabolites (before starting levodopa therapy) has been reported to be useful for the diagnosis of TH deficiency (low homovanillic acid and 3-methoxy-4-hydroxyphenylethyleneglycol associated with normal 5-hydroxyindoleacetic acid) [18, 19, 79]. Thus, although a lumber puncture is invasive, CSF analyses of pterins and neurotransmitter metabolites are informative for the diagnoses of both GTPCH and TH deficiencies [8, 18, 83, 118]. Unfortunately, however, these analyses are available in relatively limited laboratories. Taken together, a therapeutic trial with low doses of levodopa based on clinical suspicion is still the most practical approach to the diagnosis of DRD.

The major differential diagnoses of DRD include EOP, *DYT1* dystonia, cerebral palsy, and spastic paraplegia. Patients with EOP responding markedly to levodopa, especially those with the onset below age 20 years, often develop gait disturbance due to foot dystonia as the initial symptom [2, 8]. Furthermore, these EOP patients can demonstrate mild to moderate diurnal fluctuation (sleep benefit) prior to levodopa administration. Accordingly, the clinical differentiation between EOP patients with dystonia and DRD patients in the early course of disorder is sometimes difficult. The most reliable clinical distinction between EOP and DRD is the occurrence of motor adverse effects of chronic levodopa therapy (wearing-off and on–off phenomena and dopa-induced dyskinesias) in EOP. Under optimal doses, patients with DRD even on long-term levodopa treatment do not develop these complications. However, this is a retrospective difference. An investigation of the nigrostriatal dopaminergic terminals by PET or SPECT can differentiate DRD (normal or near-normal) from EOP (markedly reduced) [95–97, 99], while this investigation probably will not distinguish between GTPCH-deficient DRD and TH-deficient DRD. Measurements of both BP and NP in CSF can be useful for the differential diagnoses of the following disorders responsive to levodopa [2, 7, 8, 15, 30]: GTPCH-deficient DRD (low BP and NP),

TH-deficient DRD (normal BP and NP), and PD or EOP (low BP associated with normal NP), including the autosomal recessive form caused by *parkin* mutations. A "dramatic" (and retrospectively sustained) response to low doses of levodopa in DRD distinguishes this disorder from all other forms of dystonia, including *DYT1* dystonia (typically early-onset limb dystonia spreading to at least one other limb but not to cranial muscles) due to a 3-bp deletion in the *TOR1A* gene, and from cerebral palsy as well as spastic paraplegia.

Treatment

There is general agreement that patients with childhood-onset dystonic symptoms of unknown etiology should be treated initially with levodopa [7, 119]. Initial use of a dose of levodopa with a DCI, carbidopa/levodopa (Sinemet) 6.25/25 mg, 2–3 times a day, and gradual increase to higher doses have been recommended [119]. Although DRD patients may develop dyskinesias (mainly choreic movements) at the initiation of levodopa treatment, such dyskinesias subside following dose reduction and do not reappear with later slow dose increment [5, 6]: note that these transient dyskinesias are different from those with motor response fluctuations observed in PD and EOP patients during chronic levodopa treatment. Because some children with DRD showed remarkable responsiveness to smaller doses and a child with dystonia with motor delay phenotype developed very severe dyskinesia (which lasted 4 days) after receiving a single 50 mg dose of levodopa with a DCI [28, 120], we suggest starting a therapeutic trial using a dose of carbidopa/levodopa 6.25/25 mg, once a day, for dystonia children without developmental motor delay and of 3.1/12.5 mg, once a day, or even less for those with overt motor delay in infancy. In fact, the child manifesting the dystonia with motor delay phenotype was successfully treated with an initial dosage of levodopa (with a DCI) 8 mg/day [28]. For adult patients, we suggest an initial dose of carbidopa/levodopa 12.5/50 mg, once or twice a day. In DRD patients, motor benefit can be recognized immediately or within a few days and full benefit occurs within several days to a few months after beginning levodopa administration. Maximum benefit (complete or near-complete responsiveness of symptoms) is usually achieved by less than 300 mg/day of levodopa with a DCI (carbidopa/levodopa 25/100 mg, 3 times a day) (Table 24.1) or by less than 20–30 mg/kg/day of levodopa without a DCI [5, 6, 119]. Some genetically confirmed patients with GTPCH-deficient DRD needed 400 mg/day or more of levodopa with a DCI [29, 37, 120]. According to Nygaard and Duvoisin [121], no dose of levodopa (with carbidopa) greater than 400 mg/day has been necessary for DRD patients. A continued stable response to levodopa therapy and no complications for more than 30 years have been confirmed in patients with GTPCH-deficient DRD and TH-deficient DRD [5, 20–25, 29, 64]. Even DRD patients untreated for more than 40 years showed a remarkable response at initiation of levodopa treatment [5, 6, 66]. Although patients with DRD can respond to anticholinergics and dopamine agonists, the efficacy of levodopa is generally superior to that of these other drugs [5, 29, 119]. It has been

reported that amantadine suppressed severe dopa-induced choreic dyskinesia, which developed at initiation of levodopa treatment, in two compound heterozygotes for *GCH1* mutations manifesting the dystonia with motor delay phenotype [57].

The limited clinical literature demonstrates that acute BH4 treatment may be much less effective than levodopa therapy for patients with GTPCH-deficient DRD, including the apparently sporadic patient shown in the Vignettes section [2, 80, 122]. In this genetically proven patient, BH4 (40 mg/kg/day) was orally administered for 5 consecutive days [2]. Although the dosage of BH4 should be sufficient to enter the brain [123–125], no functional benefit was found from this acute oral BH4 administration. Even after intravenous infusion of BH4 in GTPCH-deficient DRD patients, CSF homovanillic acid concentrations were unchanged despite marked elevation of BP levels in CSF [122]. The low efficacy of such acute administration of BH4 (adequate to cross the blood–brain barrier) may be explained by striatal TH protein loss (observed in the two autopsied patients with DRD), which would be expected to limit any acute stimulatory effect of the cofactor BH4 on dopamine biosynthesis [30]. In contrast, the remarkable efficacy of levodopa (which bypasses TH in the biosynthetic pathway of dopamine) can be explained by the normal protein levels of AADC, for which levodopa is a substrate. Assuming that BH4 does, in fact, influence the steady-state level of TH protein in the human brain, it could be expected that repeated administration of BH4, if sufficiently prolonged, might up-regulate TH protein concentration in the nigrostriatal dopaminergic terminals in GTPCH-deficient DRD.

Conclusion

Since the discovery of *GCH1* and *TH* mutations responsible for DRD, our understanding of this disorder has greatly increased. However, a traditional therapeutic trial with relatively low doses of levodopa is still the most practical approach to the diagnosis of DRD, as not all DRD patients have *GCH1* or *TH* mutations that are detectable. Because patients with DRD demonstrate complete or near-complete and sustained responsiveness of symptoms to levodopa therapy, the trial should be considered in all children with dystonic and/or parkinsonian symptoms or with unexplained gait disorders. The diagnostic alternatives (e.g., *DYT1* dystonia, cerebral palsy, and spastic paraplegia), except for EOP responding to levodopa, can be distinguished from DRD by this dramatic response at initiation of levodopa treatment. For the differentiation between DRD (metabolic disorder) and EOP (degenerative disorder) in the early course, a PET or a SPECT study of the nigrostriatal dopaminergic terminals can be useful. Analyses of pterins and neurotransmitter metabolites in CSF appear to be useful for the diagnosis of GTPCH-deficient DRD (the major form of DRD) and of TH-deficient DRD (the mild form of TH deficiency). A finding of the precise mechanism of striatal TH protein loss in GTPCH-deficient DRD will better define the pathogenesis of DRD.

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Chapter 25
Whipple's Disease

Eoin Mulroy, John Lynch, and Tim Lynch

This chapter contains video segments that can be found on the accompanying DVD.

Abstract Whipple's disease is a rare multi-system bacterial infection caused by the bacilliform bacterium, *Tropheryma whipplei*. Neurological involvement occurs in up to 50 % of cases. As illustrated by two clinical cases, certain findings can be suggestive of Whipple's disease of the central nervous system (CNS). In particular, pendular vergence nystagmus, oculomasticatory myorhythmia and oculo-facio-skeletal myorhythmia are pathognomonic of the condition. Nearly all patients also exhibit a supranuclear gaze palsy.

Diagnosing the condition remains exceedingly difficult and often relies on identification of the bacterium within cerebrospinal fluid, usually through polymerase chain reaction. In this publication we propose new diagnostic criteria for Whipple's disease of the CNS based on both clinical findings and identification of the bacterium.

Imaging of CNS Whipple's disease has evolved and in particular magnetic resonance spectroscopy and diffusion-weighted MRI have an important diagnostic role and may have a role in monitoring response to treatment.

There are no agreed treatment schedules for Whipple's disease of the CNS but in addition to new diagnostic criteria, we also propose a treatment algorithm based on the most recent clinical evidence.

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Case Summaries

Patient 1

A 55-year-old man developed right facial twitching without other neurological signs. Hemifacial spasm was diagnosed. Carbamazepine (600 mg daily) and baclofen (60 mg daily) had no benefit. Five months later, he complained of somnolence, blurred vision and poor balance. One month later, the facial twitching spread to his neck and tongue, persisting with sleep. He developed dysarthria and complained of poor memory, change in personality, malaise, intermittent fevers, increased sweating, impotence and inability to ejaculate.

One year after the onset of facial twitching, orientation, memory and language were normal. He was intermittently inattentive and had marked dysarthria due to rhythmic lingual retraction and masticatory myorhythmia coinciding with rhythmic contraction of the right side of the face, neck and chest and the right arm. The contractions spread irregularly to the left side of the face and chest and left arm and leg. Vertical gaze was limited, but improved with the oculocephalic manoeuvre. Saccades were slow in all directions. Pendular vergence oscillations of the right more than of the left eye (frequency = 1 Hz) (see Video 25.1) were synchronous with the masticatory and skeletal myorhythmia (i.e. oculofacial-skeletal myorhythmia [OFSM]). Electromyographic analysis revealed 400-ms bursts of bilateral rhythmic activity. This activity originated at the level of cranial nerve VII, and spread rostrally to involve the muscles of mastication, and caudally to involve muscles of the neck, arms and legs.

Muscle tone, strength, sensation, deep tendon reflexes, plantar responses and postural stability were normal. Gait was mildly ataxic.

Serum chemistries; complete blood count (CBC); serum Venereal Disease Research Laboratory test (VDRL) result; serum Lyme titre; thyroid function test (TFT) results; antinuclear antibody (ANA) titre; human immunodeficiency virus (HIV) test result; vitamin B12; folate; CSF protein and glucose levels and cell count; and electroencephalogram (EEG) were normal. Brain magnetic resonance imaging (MRI) with gadolinium revealed a left frontal periventricular punctate hyperintensity. Technetium 99 m hexamethylpropyleneamine oxime (99 m Tc = HMPAO) single-photon emission computed tomography (SPECT) revealed decreased activity in the right cerebellar hemisphere.

A duodenal biopsy specimen obtained 12 months after the onset of facial twitching was initially normal (periodic acid Schiff [PAS] stain negative, electron microscopy [EM] not performed). After 1 month, a repeat biopsy with Crosby capsule revealed foamy macrophages stained positive with PAS and silver stains, and negatively with acid-fast stain. PAS and Grocott methenamine silver stains demonstrated intracytoplasmic granular rod-shaped structures consistent with Whipple's bacillus. Central nervous system (CNS) WD was diagnosed.

Trimethoprim–sulfamethoxazole (TMP–SMX) (1 double-strength [DS] tablet twice a day) resulted in improvement in malaise and the ocular component of the myorhythmia. When diarrhoea developed, TMP–SMX was discontinued, and

intravenous ceftriaxone (2 g daily) resulted in resolution of the diarrhoea and sweating, decrement in the myorhythmia and increase in alertness. After 1 month, he was switched to receive doxycycline monohydrate (200 mg twice a day), with worsening of hemifacial spasms, malaise and lethargy over the ensuing 9 months. Ceftriaxone (2 g/day) was resumed, with improvement in hemifacial spasms, malaise and lethargy over the ensuing 3 months. After 2 years of follow-up, he was taking TMP–SMX (1 DS tablet twice a day). He still had right facial twitching, complaints of poor memory, increased sweating, impotence and inability to ejaculate. There was moderate improvement in limb myorhythmia, malaise and vertical gaze.

Patient 2

A 47-year-old woman developed severe progressive insomnia unresponsive to medication, a 10-lb weight loss, double vision, fevers and submandibular lymph node enlargement. Past history was notable for arthritis. No diarrhoea, steatorrhoea or other gastrointestinal symptoms were noted. She noted spontaneous rhythmic right eye movement whilst looking in the mirror.

On examination, vertical and horizontal saccades were slow, with diminished abduction of the left eye. Downgaze was full; upgaze was mildly limited. There were spontaneous convergent nystagmoid movements in the right eye unaccompanied by miosis (see Video 25.1). These movements increased with downward moving optokinetic stimuli.

Over the ensuing 8 months, a progressive ophthalmoparesis resulted in complete loss of voluntary eye movements except for adduction of the right eye. She developed short-term memory loss, depressive symptoms, difficulty swallowing, blurred vision, intermittent hyper-somnolence and increased postural instability. On re-examination, she was intermittently unrousable, with hypomimia and severe dysarthria. Pendular vergence oscillations of both eyes that were synchronous with the masticatory myorhythmia (oculomasticatory myorhythmia [OMM]) were present. There was mild hypertonia, and normal strength and sensation. Deep tendon reflexes were brisk. Gait was slow, with shuffling, difficulty turning and postural instability. Levodopa–carbidopa and prednisolone (20 mg daily) were without benefit.

Serum chemistries, CBC, serum Lyme titres, coagulation screen results, ANA titre, B12 and folate levels, TFT results, serum protein electrophoresis and VDRL and HIV test results were normal. EEG revealed a mildly generalised slow background. CSF analyses revealed protein levels of 50–55 mg/dl with a normal glucose concentration, and 0–70 PAS-negative mononuclear cells. Brain computed tomography (CT) scans appeared normal and MRI revealed an Arnold–Chiari type 1 malformation with no brainstem compression. Specimens obtained at two duodenal biopsies indicated mild chronic nonspecific duodenitis. No PAS staining or other changes consistent with WD were detected. EM was not performed. PCR was positive even though PAS staining was negative. CNS WD was diagnosed based on clinical findings (i.e. OMM). Intravenous ceftriaxone (2 g daily) for 6 months

resulted in complete resolution of OMM and improvement in the supranuclear gaze palsy and malaise. After switching to TMP–SMX (1 DS tablet twice a day), the supranuclear gaze palsy, lethargy and malaise recurred. After years of follow-up, she was restricted to a wheelchair and fed by gastrostomy.

Introduction

Whipple's disease was originally described as a gastrointestinal disorder associated with arthralgia [1]. It can result in neurological dysfunction [2, 3] and often has a relapsing course. It is caused by a bacilliform bacterium, *Tropheryma whipplei* (formerly named *Tropheryma whippelii*), which is ubiquitously present in the environment. Infection can occur in several organs, including gastrointestinal tract, heart, lungs, kidney, brain and skin. Fewer than 1,000 cases have been reported. It appears to enter via the oral route but this has not been proven.

Tropheryma whipplei

This bacilliform bacterium is found ubiquitously in the environment, and though its natural source has not been identified, its omnipresence in waste waters from rural communities suggests an agricultural origin [4].

Sequencing of PCR-amplified bacterial 16S ribosomal RNA from infected tissue has led to characterisation of the Whipple's disease-causing organism [5]. A *T. whipplei*-specific nested polymerase chain reaction (PCR) targeting domain 3 of the 23S rDNA is a suitable tool for confirming the presence of *T. whipplei* DNA in specimens with inconclusive histopathological findings [6]. Overall, four different rDNA types are recognised in this proposed classification system for molecular variants of *T. whipplei*. Sequencing of its complete genome confirmed its position as a G–C-rich gram-positive actinomycete [7, 8]. The name *Tropheryma whipplei (T. whipplei)* has been given to this organism.

The bacillus has morphologic features of both gram-positive and gram-negative organisms. Determination of the DNA G + C content confirmed that it belongs to the high G + C gram-positive bacteria [9]. It appears both intracellularly and extracellularly; infected macrophages are characteristically present. In most tissues, however, infection is not restricted to macrophages alone. Infected cells stain strongly with PAS. Examination by electron microscopy demonstrates that the areas of intense PAS staining are packed with bacilli, some degenerated. These areas usually have a distinctive sickle shape. Cells containing them are referred to as sickle particle cells (SPCs).

Culturing the bacterium had long been an elusive goal. In 1997, the bacterium was isolated and grown in human macrophages inactivated with interleukin-4 [10]. It has since been cultured from a patient with endocarditis due to Whipple's disease [11].

Epidemiology

The epidemiology of Whipple's disease is poorly understood. There is a predominance of the systemic disorder in elderly men (8:1 in favour of men) and Caucasians, but this is less obvious in the cases reported with predominant CNS manifestations. Farmers and those in regular contact with soil or animals also have a much higher incidence of Whipple's disease [12]. Asymptomatic carriage of the bacterium is common, which suggests that some underlying predisposition may determine progression to a disease state. Certain HLA alleles responsible for defects in cell-mediated immunity [13–16] are linked to progression to chronic illness [17].

Systemic Disease

The symptoms of the systemic disease are weight loss, abdominal pain, diarrhoea (often with steatorrhoea) and migratory arthralgia. Arthralgia often antedates the gastrointestinal symptoms. Malabsorption may be prominent. Low-grade fever, lymphadenopathy, increased skin pigmentation and subcutaneous nodules, which histologically demonstrate septal panniculitis with a large amount of foamy histiocytes [18], also occur. There has been a report of bone marrow involvement [19]. Myocarditis, pericarditis, endocarditis and coronary arterial damage [20] have been described. There have been cases of ocular (keratitis, uveitis, vitreous opacities) and neurologic disease without evidence of systemic infection [2, 3].

Pathophysiology and Immunopathology

The pathogenesis of Whipple's disease appears to be related to underlying macrophage and T-Cell function defects [13, 21]. Indeed, macrophages of patients with Whipple's disease display an impaired ability to degrade intracellular organisms [22] and this, combined with the fact that the bacterium can prevent maturation of phagosomes [23], results in ineffective clearance and massive intracellular accumulation of bacteria (mainly in the small intestinal mucosa, demonstrated by PAS staining).

Abnormalities in interleukin-12 function appear to be central to the process of impaired bacterial degradation [24].

The lack of animal studies hinders the understanding of the pathogenesis of Whipple's disease. Despite this, Moos et al. postulated that primary infection occurs early in childhood, either asymptomatically or manifested by a self-limiting gastroenteritis, fever or cough [15, 25, 26]. Most infected people develop a protective cellular and humoral immune response [14, 26, 27]. In select individuals with some degree of immune deficiency, the bacterium can persist and subsequently undergo

systemic spread to multiple organs over the next decades. The entry of the microorganism into the CNS might be achieved by the pass of infected monocytes across the blood–brain barrier [28].

Neurological Manifestations

The neurologic disorder, which occurs in 6–43 % of patients with Whipple's disease, is usually a progressive encephalopathy, characterised by memory loss, personality change and cognitive dysfunction [2]. Asymptomatic CNS infection may occur, and even in the absence of neurological symptoms, up to 50 % of patients with Whipple's disease are found to have CNS infection by PCR analysis of the CSF [29].

Neurologic symptoms predating other systemic features of Whipple's disease occur in just 5 % of cases. Panegyres et al. [30] have suggested that cases of primary Whipple's disease of the CNS present with two distinct clinical pictures: (1) multifarious neurological symptoms and signs with contrast (CT) or gadolinium-enhanced (MRI) brain imaging showing multiple nodular enhancing lesions or (2) focal neurology secondary to solitary mass lesions. Neurological problems which can occur include seizures, meningitis, strokes, peripheral neuropathy, myopathy, acute intracranial hypertension [31] and rhythmic tremor of the palate and other cranial limb muscles with cerebellar ataxia [32]. In earlier reports, cerebellar ataxia was reported to occur in roughly 20 % of patients with CNS Whipple's disease [2] but more recent evidence suggests that cerebellar ataxia is a common feature which may be present in up to 45 % of cases [33]. There is a novel association of juvenile dermatomyositis and Whipple's disease [34]. Focal findings which may suggest discrete lesions visible on imaging include ophthalmoplegia, motor and sensory signs, ataxia and evidence of hypothalamic dysfunction, including hypersomnolence and hormone deficiencies.

A combination of slow pendular vergence nystagmus (1 Hz), concurrent contraction of the masticatory muscles (OMM) and vertical supranuclear palsy is pathognomonic of CNS Whipple's disease [2, 3, 35]. Pendular vergence oscillations are characterised by continuous smooth, rhythmic convergent eye movements with a frequency of 1 Hz varying from 10° to 25° of amplitude per eye, but never diverging beyond the primary position. The oscillations continue throughout sleep and may be subtle and asymmetric. Convergence and divergence are at the same speed and are not accompanied by miosis or accommodation. The anatomical basis for this apparently unique movement disorder is not known but may originate from the upper brainstem. Rhythmic myoclonus is characterised by repetitive contractions of facial, masticatory, pharyngeal (OMM) and limb muscles (OFSM). It continues throughout sleep and differs from oculopalatal myoclonus which has a frequency of 2 Hz. OMM in association with supranuclear palsy is pathognomonic of neurologic Whipple's disease.

Radiological Findings

The first neuroradiologic descriptions of CNS involvement in Whipple's disease with CT imaging did not demonstrate specific characteristics. Computed tomography can demonstrate focal lesions, particularly in cases diagnosed ante-mortem without obvious systemic findings. These may mimic CNS neoplasms on imaging [36, 37], with the definitive diagnosis only being provided by lesion biopsy.

The role of MRI has been reviewed [38]. Magnetic resonance (MR) imaging is superior to CT for detection of small lesions. These lesions which occur in 53 % of cases [2] consist of T1 hypointensity and T2 hyperintensity, show no mass effect and are located in the medial part of the temporal lobes, hypothalamus and pons. They may enhance after infusion of contrast. There is associated atrophy in 42 % of cases. Biopsy of these lesions has provided the diagnosis in several cases. Multiple mass lesions have rarely been described [39]. There are only four reports in the literature of spinal cord involvement [38, 40–42]. Involvement of the optic chiasm has only rarely been revealed by MRI [43].

Diffusion-weighted imaging is also assumed to have an increasingly important role in both a diagnostic and prognostic sense [44]. Indeed, areas of restricted diffusion are seen in those individuals with CNS Whipple's disease, and these may represent areas of ongoing infection. It has been suggested that regular follow-up with diffusion-weighted imaging may be a means of confirming treatment effectiveness and complete eradication of the causative organism [44].

Mass lesions caused by CNS involvement in Whipple's disease may mimic high-grade neoplasms on conventional imaging. In these cases, dynamic perfusion MRI may be useful in differentiating an infective lesion from an aggressive tumour [44]. In the appropriate clinical setting, this may obviate the need for brain biopsy.

Magnetic resonance spectroscopy (MRS) may also aid in the early and accurate diagnosis of a case of CNS Whipple's disease. There have been numerous reports of the characteristic MRS changes in this disorder, which include decreased *N*-Acetylaspartate and creatine levels and increased choline [44, 45]. The usefulness of Positron Emission Tomography (PET) imaging in the diagnosis of CNS Whipple's disease is still unclear.

Investigations and Diagnosis

General laboratory studies usually reveal steatorrhoea, impaired xylose absorption, anaemia and hypoalbuminemia. CSF examination may be normal or show a moderate pleocytosis (about 200 cells, mostly mononuclear) or protein levels up to 100–200 mg/dl. IgG elevation has been reported in the CSF.

The diagnostic workup usually begins with jejunal biopsy to demonstrate the PAS-staining macrophages. In advanced cases, there may be macroscopic changes in the duodenal mucosa consisting of a pale yellow mucosa with dilated villi and

ectatic lymph vessels. Because PAS-positive macrophages may be found in other diseases and in other tissues of apparently normal individuals, confirmation of the diagnosis is facilitated by detection of the actual bacillus with appropriate stains or electron microscopy or PCR amplification of *T. whipplei* DNA. The use of PCR on blood is very useful given that it is a rapid and minimally invasive procedure. Recent studies have confirmed the sensitivity and specificity of PCR (performed on either intestinal biopsies, CSF, blood stool or saliva) as a diagnostic test for Whipple's disease [46, 47]. PCR can be used for the diagnosis of Whipple's disease in patients with histologically negative jejunal biopsies [48–51].

However, there are two main problems with PCR analysis. Firstly, as asymptomatic carriage of *T. whipplei* occurs, PCR-positive gastrointestinal samples always need confirmation by histology, or a second PCR-positive result from a sterile site, e.g. CSF. Secondly, all diagnostic PCR systems are now DNA based and thus there might still be a signal from dead bacteria even after successful eradication (a problem which can be addressed by using fluorescence in situ hybridisation (FISH) techniques as discussed later).

Specific diagnosis of CNS Whipple's disease is confirmed by finding PAS-containing macrophages in the brain and by demonstrating the bacillus in these cells or demonstrating a positive PCR assay on CSF for *T. whipplei* [2]. Infection of neural cells has not been demonstrated.

In cases where cerebral brain biopsy is necessary for diagnosis, stereotaxy is the preferred option for sampling the deep-seated areas such as the hypothalamus, basal ganglia, cingulate gyrus, insular cortex and cerebellum where the lesions are typically located [52].

Immunohistochemical staining using specific antibodies against *T. whipplei* offers added specificity over PCR for the identification of *T. whipplei* in PAS-negative tissues [53]. This is of special importance in PAS staining of CNS biopsies where the findings may be unspecific and misinterpreted as *T. whipplei* inclusions.

The use of FISH for the diagnosis of Whipple's disease is a very attractive option since it differentiates between contamination and true infection [54]. Also, it targets RNA (rather than DNA as in PCR) and so preferentially shows up live bacteria. This is useful for the confirmation of complete eradication following treatment as well as for the detection of recurrent infection. Unfortunately, FISH is not routinely available outside of specialist laboratories.

Treatment

If left untreated, Whipple's disease is universally fatal. For years, treatment of Whipple's disease was based purely on anecdotal case reports and personal experience. However, sequencing of the organism's genome allowed identification of its antibiotic susceptibility [55, 56]. Doxycycline, macrolides, ketolides, aminoglygosides, penicillin, rifampin, teicoplanin, chloramphenicol and TMP–SMX are active against *T. whipplei*. Prior to this discovery, tetracyclines were long prescribed as

first-line treatment but resulted in high recurrence rates, and the relapse rate tended to be high if treatment was not continued for at least 1 year [2, 57].

The most common complication arising from treatment of Whipple's disease is the development of a non-specific inflammatory syndrome termed immune reconstitution inflammatory syndrome (IRIS) [58, 59]. IRIS may manifest as prolonged fever along with other signs and symptoms of systemic inflammation, e.g. arthritis, orbitopathy and gut perforation after initiation of treatment. It occurs in approximately 10 % of patients and may require the addition of corticosteroids to the treatment regimen.

One randomised prospective treatment trial looked at the effectiveness of initial intravenous induction therapy with either meropenem or ceftriaxone for 14 days followed by oral TMP–SMX for 12 months [58]. They reported this regime to be 95 % effective in curing Whipple's disease and maintaining a sustained remission. A subgroup analysis of patients with CNS involvement in Whipple's disease (defined by positive CSF PCR for *T. whipplei*) showed 100 % clinical and PCR response at 6 months but a relapse rate of 14 % at 3 years. More recently, Lagier et al. examined a cohort of patients treated with TMP–SMX and reported a 100 % relapse rate, even in those who had received prior intravenous ceftriaxone. They postulated that the failure of TMP–SMX treatment is due to the fact that the organism lacks the enzyme, dihydrofolate reductase, which is the target for TMP–SMX.

This disparate data, though not offering any specific guidelines for the treatment of Whipple's disease, confirms again that treatment of Whipple's disease is very difficult, and no specific guidelines exist. Some have suggested that it should be regarded as a chronic disease prone to relapse and that patients should undergo lifelong follow-up in order to diagnose relapses early and institute treatment without delay [57].

Indeed, studies have suggested that neurologic Whipple's disease may require intermittent prolonged intravenous antibiotics (ceftriaxone) to maintain partial remission [2, 3]. Performing *T. whipplei* PCR on CSF is currently the preferred method for confirming treatment efficacy and eradication of the bacterium from the CNS.

Modified Guidelines for Diagnostic Screening, Biopsy and Treatment of CNS Whipple's Disease [2]

Definite CNS Whipple's Disease

Must have any one of the following three criteria:

1. OMM or OFSM and/or pendular vergence nystagmus.
2. Positive brain tissue biopsy.
3. Positive PCR analysis of cerebrospinal fluid.
4. Autopsy confirmed diagnosis.

Probable CNS Whipple's disease

1. Suggestive neurological symptoms and signs (cognitive decline, personality change, supranuclear gaze palsy, etc.).

   AND
   Positive PCR analysis of duodenal tissue.
   OR
   PAS-positive macrophages in duodenal biopsy.
   +/− Supportive Imaging (MRI, MR Spectroscopy, dynamic perfusion MRI).

Possible CNS WD

Must have any one of the four systemic symptoms, not due to another known aetiology:

1. Fever of unknown aetiology.
2. Gastrointestinal symptoms (steatorrhoea, abdominal distension or pain).
3. Chronic migratory arthralgias or polyarthralgias.
4. Unexplained lymphadenopathy, night sweats or malaise.

AND

Also must have any one of the four neurological signs, not due to another known aetiology:

1. Supranuclear vertical gaze palsy.
2. Rhythmic myoclonus.
3. Dementia with psychiatric symptoms.
4. Hypothalamic manifestations.

Suggested Diagnostic Sequence

Clinical presentation suggestive (but not pathognomonic) of Whipple's disease (cognitive dysfunction, personality change, weight loss, diarrhoea, arthralgia)

Proceed to:

1. Detailed neurological examination—including evaluation for rhythmic myoclonus, supranuclear gaze palsy, pendular vergence nystagmus, cerebellar ataxia.
2. Laboratory investigations: Hypoalbuminemia, steatorrhoea, anaemia.
3. Neuroimaging: MRI brain with gadolinium including diffusion-weighted imaging. MRS and dynamic perfusion MRI may be useful in further characterising the lesion.

Suggestive clinical +/− Biochemical and radiological features

Proceed to confirm diagnosis:

1. Small bowel biopsy: PAS-staining of small intestinal mucosal cells and PCR analysis and FISH if available.
2. If first PCR on gastrointestinal tissue is positive, proceed to PCR/immunofluorescence of CSF.
3. If discreet lesion on imaging, proceed to stereotactic biopsy to outrule neoplasm, and confirm diagnosis (if CSF PCR is negative or if patient fails to respond to appropriate antibiotic therapy).

Diagnosis confirmed:

Begin treatment [60]

First line

1. Intravenous Meropenem 1 g TDS for 14 days or Ceftriaxone 2 g OD for 14 days followed by.
2. TMP–SMX 960 mg twice daily by mouth for 12 months.

Second line

If first-line treatments fail to produce adequate clinical response: Doxycycline 200 mg OD PO + hydroxychloroquine 200 mg three times per day PO + TMP–SMX 960 mg twice daily by mouth for 12 months.

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Chapter 26
Driving Risk in Patients with Movement Disorders

Ergun Y. Uc

Abstract Impairments in cognition, visual perception, motor function, and increased daytime sleepiness reduce driving performance and safety in Parkinson's disease (PD). Although drivers with PD perform worse than controls on experimental road and driving simulation studies, there is no well-established epidemiological association with increased crashes in drivers with PD. However, drivers with PD cease driving earlier than controls.

Medical diagnosis or a clinician's assessment alone is inadequate to determine driving competence in drivers with PD. Although testing of motor, cognitive, and visual functions help to understand the mechanisms of driving impairment in PD, there are no established guidelines on assessing driver fitness in PD. There are no evidence based methods for driver rehabilitation in PD.

Patient Vignette

A 90-year-old man with a 5-year history of Parkinson's disease returned to clinic for his routine follow-up visit in the company of his daughter. He displayed mild slowing of arm movements, and moderate slowing of foot tapping while seated in a chair. He was able to arise without assistance, and walked slowly but independently. During the course of the visit, his daughter brought up the issue of driving safety. She stated that she was concerned about his driving, that she had witnessed how slow he was to react to other drivers, and that she and other family members had asked him to stop driving. The patient stated that he thought that his driving had not

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changed, and that he wanted to continue driving. The neurologist discussed the pros and cons of continuing to drive given his age and examination, and given his refusal to stop driving, asked him to undergo a formal driving evaluation at the motor vehicle bureau. He was not keen to agree, fearing the loss of his license if he failed the test, and the neurologist then advised him and his daughter that he should stop driving, documenting this in the medical record.

At his next visit to the clinic 6 months later, his neurologic examination was unchanged. The neurologist inquired whether or not he was still driving. Somewhat sheepishly, he relayed the following story. He had continued driving while wintering in Florida, never travelling more than a couple of miles from his home. Because he never drove on the highway and never went above 30 mph, he was convinced that he was not unsafe. While making a left hand turn, he struck another car that had the right of way. The police were called to the scene, and fortunately no one was injured. On seeing him at the scene, the police officer informed him that he should not be driving, and confiscated his license on the spot. His daughter and family viewed the incident as a near-miss, and his neurologist agreed.

The Scope of the Problem

Driving is an important activity of daily living and is essential for mobility and independence for many individuals. With increased longevity the number of elderly drivers is rising, which will be accompanied by an increase of drivers with neurological diseases of aging such as dementia, stroke, and Parkinson's disease (PD). In addition to typical motor dysfunction, PD also impairs cognition, vision, sleep, and alertness [1], and is associated with lower performance on road tests [2–13] and driving simulator performance [14–23] compared to controls.

One of the most important concerns in drivers with PD is the potential for increased risk for accidents. Motor vehicle crashes are a major public health problem with about 42,000 fatalities and a financial cost of ~$231 billion in 2000 [24]. Indeed driving simulation studies have shown increased crash rates in PD [15, 20, 22] and retrospective surveys have suggested increased crashes in drivers with PD [25, 26]. However, increased real-life crash risk in drivers with PD has not been confirmed by community based prospective controlled studies or epidemiological research [27–29]. Another potential unfavorable driving outcome in drivers with PD is loss of vehicular mobility (driving cessation) as shown on cross-sectional or retrospective [25–27, 30–36] and prospective [28] surveys.

The goal in counseling drivers with PD is to prevent crashes while preserving mobility and independence. The methods for assessing driver safety in potentially impaired persons and requirements for reporting vary across the world [27] and among states within the USA [37], and no clear guidelines have been established for PD [38]. Medical diagnosis or a clinician's assessment alone is inadequate to determine driving competence in those with cognitive impairment [39, 40]. While a proportion of drivers with PD use compensatory strategies such as reduction of driving

exposure, avoidance of difficult driving conditions (inclement weather, darkness, rush hour, difficult maneuvers) suggesting some insight into their limitations [28], both patients [2, 3, 9] and their neurologists [2] have been shown to overestimate the patient's driving ability.

Theoretical Framework to Study Driving

Driving performance is determined by factors related to the driver (e.g., age, medical condition, cognitive, visual, motor or behavioral dysfunction, decreased alertness, substance abuse), environment (weather, road conditions), vehicle (maintenance, presence of warning or safety devices), presence of distractions, and their interactions [41].

Michon proposed a hierarchical model of cognitive control of driving with concurrent activity 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 behavior that 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 [42].

At an operational level, driver actions can be analyzed by information processing models (Fig. 26.1): (1) Perception and attention to stimulus (e.g., visual and auditory inputs) and interpretation of the road situation; (2) Planning a reaction to the

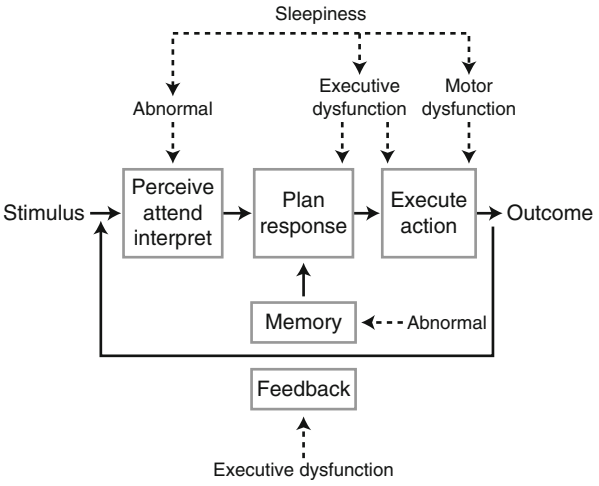

Fig. 26.1 Information processing model for driver error in PD. From Uc and Rizzo [43]

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 and subsequent self correction [43]. 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 (crash) as a result of errors at one or more of these stages [43].

Neural Substrates of Driving

Driving engages parieto-occipital cortices, cerebellum and cortical regions associated with perception and motor control as shown by fMRI studies during simulation [44] or FDG or positron emission tomography (PET) scanning after a road drive [45]. Alcohol degrades driving performance and decreases activation in these areas [46]. Even a simple auditory-verbal distraction such as listening to sentences produces a significant deterioration in vehicle control and is associated with increased activation in temporal regions at the expense of decreased activation of parietal regions, suggesting that language comprehension performed concurrently with driving draws mental resources (spatial processing by the parietal lobe) away from the primary task and impairs driving performance [47]. Alcohol amplifies the negative effects of distraction on brain activation and driving performance [48].

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.

Driving Research in PD

Due to the complexity of the driving task and PD, multiple complementary assessment methods in comparison to a control group need to be studied longitudinally to determine the predictors of driving safety and outcomes. Off-road batteries usually combine questionnaires on general health, mood and sleep, quality of life, driving history and habits, with performance based measures of cognition, vision and motor function. As real life crashes are rare events, driving performance in a simulator and road test in an instrumented vehicle are used as intermediate steps to uncover relationships between cognitive, visual, motor impairments and driving outcomes. While most driving experience consists of uneventful long stretches, there are interspersed segments with multitasking. Some of the secondary tasks are required as part of driving (e.g., following a new route to reach a destination, paying attention to landmarks and traffic signs, listening to radio for weather updates), others may

be discretionary (e.g., speaking on a cell phone, talking to a passenger or eating). The secondary tasks can have a degrading effect on driver safety and performance, especially in drivers with cognitive dysfunction.

Off-Road Battery

Demographics

The patients in reported studies of driving in PD are usually in their 60s or 70s and predominantly male, have mild–moderate disease severity, and live in the community [11]. The male predominance among drivers in PD may reflect that men are at higher risk for PD [26] and that women in this age group have not traditionally been the main driver in the family, and might have more readily relinquished their driving privileges once they developed PD [5].

Driving History and Habits

Questionnaires (e.g., Driving Habits Questionnaire [28]) are used to collect self-report information on driving exposure (e.g., miles/week, days/week), driving history (crashes and citations), perceptions and judgments of impairment and driving ability, and use of compensatory strategies (e.g., no driving at night or in snow). The driving history can be verified by using state records. The caregiver perspective can also give valuable insights on driving ability and deficiency awareness of the patient [10].

Assessments of Cognition, Vision, Motor Function, Indices of Parkinsonism, Sleep, Psychiatric Problems

Although individual tests may differ between batteries used by various research teams, they attempt to probe different aspects of visual perception, cognition (e.g., executive functions, attention, and memory), motor function, mood and sleep. As driving is a primarily visual task, these batteries are rich in visual tests and usually cover all aspects of visual function from the retinal to the cortical level. In most studies, drivers with PD had mild–moderate parkinsonism and performed worse compared to controls on most visual and cognitive abilities, albeit usually showing mild deficits [2, 3, 5–8, 11, 13, 14, 18–20, 22, 23, 27].

Road Testing

In this set of studies (Table 26.1), drivers with PD underwent standardized road tests and various tests of cognition, vision and motor function. Most studies included control drivers with similar demographics. The main outcome measures of these

Table 26.1 Road studies in PD

Reference	Measures	*N*	Outcome	Predictors	Comments
Overall safety					
Heikkila [2]	Expert ratings, Safety errors	20 PD, 20 C	Worse ratings and error counts in PD	Visual, cognitive, age	Neurologists and patients overestimated ability
Radford [77]	Safe/unsafe, driving scores	51 PD	6 PD drivers "unsafe"	Webster's scale predicted "unsafe"	Cognitive and motor tests correlated with driving scores
Grace [4]	Safe/unsafe, safety errors	21 PD, 21 C	PD less safe, more safety errors	Cognitive, axial parkinsonism	Includes comparison to AD ($n=20$)
Wood [3] Worringham [7]	Safe/unsafe, safety errors	25 PD, 21 C	PD less safe, more safety errors	Visual, cognitive, disease duration	Detailed information on error types and locations
Devos [9]	Pass/fail	40 PD, 40 C	PD: 72.5% "pass", 25% "fit with restrictions", 2.5% "unfit"	Visual, cognitive, parkinsonism, simulator score	Post hoc classification into pass/fail, only PD with "minor cognitive deterioration"
Amick [78]	Safe/unsafe	25 PD	11 PD rated marginal or "unsafe"	Visual, cognitive	Uncontrolled study
Cordell [10]	Driving scores	53 PD, 129 C	PD scored worse in all categories	Age, caregiver input, timed walking, UPDRS-ADL	Caregiver questionnaire most predictive; no performance based cognitive test
Classen [12]	Pass/fail, safety errors	19 PD, 104 C	42.1% PD and 21.2% C failed	Visual, cognitive	Cut-offs for UFOV test
Uc [11] (cross-sectional)	Safety errors	84 PD, 182 C	More safety errors in PD	Visual, cognitive, age	Familiarity with driving environment mitigating; IV
Uc [13] (longitudinal)	Change of safety errors over 2 years	82 PD, 110 C	Significant increase within PD and change worse than in C	UFOV, composite cognition score	Only longitudinal study; 38% of PD returned, the returnees had better baseline
Multitasking					
Uc [6] (visual search) Uc [5] (audioverbal distraction) Uc [8] (route following)	Safety errors at baseline and during secondary task; task performance; vehicle kinematics	79 PD, 151 C 71 PD, 147 C 77 PD, 152 C	PD performed worse on secondary tasks; more safety errors in PD during baseline and task, and task degraded PD safety more; PD drove slower	Visual, cognitive Visual, cognitive, age, sleepiness Visual, cognitive	In general, cognitive flexibility (set-shifting) as measured by Trail Making Test (B-A) an important predictor for secondary task performance and safety errors during multitasking. Studies in IV

C control

Table 26.2 Driving safety errors in PD

General classification
Total errors [2–4, 10–12, 20]
Serious/critical errors [3, 11]
Errors during multitasking [5, 6, 8, 14, 19, 23]
Location
Stop signs [10, 11]
Traffic signals [3, 10, 22]
Roundabouts [10]
Maneuver
Turns [2, 3, 10]
Lane changing [3, 10]
Merging [3, 10]
Parking [3, 11]
Vehicle control
Lane observance [3, 10, 11, 20]
Speed control [10, 11]
Blind spot errors [3, 10]

Classification, locations, maneuvers observed to be worse than controls

road tests were pass/fail (or safe/unsafe) ratings by driving experts as categorical measures and/or at-fault error counts as continuous measures. Types and locations of errors were also reported (Table 26.2). Analyses were done within PD group to determine the cognitive, visual, and motor predictors of pass/fail ratings or error counts.

Heikkila [2] assessed the driving ability of 20 patients with idiopathic PD and 20 age- and gender-matched healthy control subjects on the road and showed that patients and their neurologists typically overestimate driving ability. All subjects also underwent a neuropsychological battery (measuring vigilance and concentration, visual perception, choice reaction times, and information processing). The driving abilities of PD patients were estimated by a neurologist and by a psychologist using tests and an interview, by a driving instructor on the basis of a driving test, and by the patients themselves using the same global scale. The patients with PD performed worse than the controls both on neuropsychological tests and on the road test. The driving instructor found 35% of PD drivers unsafe, while none of the patients were rated unsafe by themselves or the neurologist. There was a significant correlation between the driver instructor scores and the psychologist's estimates, but not with the neurologist's estimates. All controls were found safe, and there was agreement between all parties. Drivers with PD committed significantly more at-fault errors, violated the traffic rules more often, and had more difficulty driving in a traffic flow and turning across traffic, especially in urban conditions. In both the patient group and the control group, there was a high correlation between performances in the neuropsychology battery and driving test. Disease duration and the motor stage of the disease, and MMSE were not associated with the driving test scores in PD patients; however, slower information processing correlated with faults observed while driving on the road [2].

Grace [4] compared road safety (error counts and ratings of "safe," "marginal," "unsafe") of drivers with PD ($n=21$), mild Alzheimer's disease ($n=20$, Clinical Dementia Rating scale range 0–1), and controls ($n=21$). Drivers with AD were more impaired on the road than PD. Compared to other groups, drivers with PD had difficulty in maneuvers requiring head turning. Driving performance in PD was related to disease severity (Hoehn-Yahr stage), cognitive measures (Rey Osterreith Complex Figure, Trails B, Hopkins Verbal List Learning Test-delay), and specific motor symptoms (axial rigidity, postural instability), but not to the UPDRS motor total score [4].

Wood [3] assessed driving performance (safety error counts and types, overall pass/fail judgement) of 25 patients with idiopathic PD and 21 age-matched controls on a standardized open road route. The drivers with PD were rated as significantly less safe than controls, and more than half of the drivers with PD would not have passed a state-based driving test. The driver safety ratings were significantly correlated with disease duration but not severity, as indexed by the "on" time UPDRS score. Drivers with PD made significantly more errors than the control group during maneuvers that involved changing lanes and lane keeping, monitoring their blind spot, reversing, car parking, and traffic light controlled intersections. The driving instructor had to intervene to avoid an incident significantly more often for drivers with PD than for controls [3]. Tests of motor performance (Purdue Pegboard test), contrast sensitivity (Pelli-Robson test), and cognitive function (verbal version of Symbol Digit Modalities test) predicted passing the driving test with relatively high sensitivity and moderate specificity [7].

Devos studied 40 patients with PD and 40 healthy age- and sex-matched control subjects in the simulator and administered an off-road test battery [9] to predict the results of driving fitness on a road test administered by an official agency. A "pass" (fit to drive without restrictions) rating was given to 72.5% of PD drivers, and the rest (27.5%) received a "fail" rating, defined as being judged as "fit to drive with restrictions" (25%) or "unfit to drive" (2.5%, $n=1$). A screening battery assessing four clinical variables (disease duration, contrast sensitivity, Clinical Dementia Rating, and motor part of the Unified Parkinson's Disease Rating Scale) provided the best model to predict the pass/fail ratings, correctly classifying 90% of the patients with PD as pass or fail. The Test Ride for Investigating Practical fitness to drive (TRIP) driving simulator score discriminated significantly between drivers with PD and controls [9]. However, only drivers with "minor cognitive deterioration" [9] were enrolled in this study, limiting the generalizability of these results.

Cordell [10] assessed 53 PD subjects and 129 controls in the participant's car along a 15 km route chosen by the participant in his/her neighborhood. Drivers with PD were significantly less competent drivers than controls. The driving performance of the participants declined with age. UPDRS-ADL score and Timed Get Up and Go test correlated with the driving performance. IQ Code (Informant Questionnaire on cognitive decline) was used to assess cognitive status. No other performance based tests to assess cognition or visual perception were reported. In models adjusted for age, gender and disease duration, information provided by caregivers explained 56% of variability in road test scores, whereas UPDRS-ADL and the timed walking test only explained ~30% of variability [10].

Classen [12] compared 19 drivers with PD and 104 controls on a road test and found that 42.1% of PD and 21.2% of controls failed ($p<0.05$). Among several variables that significantly correlated with failing the road test and number of driving errors in PD, The Useful Field of View (UFOV) test was found to have the strongest correlation [12].

Uc [11] compared at-fault safety errors of 84 licensed, active drivers with PD with mild–moderate disease severity (median Hoehn Yahr stage II) and 182 controls on a standardized route across urban and rural settings using an instrumented vehicle (IV) [11]. Overall, drivers with PD had poorer road safety compared to controls, but there was considerable variability among the PD drivers, and some performed normally. Drivers with PD committed significantly more total safety errors compared to controls (41.6 ± 14.6 vs. 32.9 ± 12.3) and 77.4% of PD drivers committed more errors than the median total error count of the controls (medians: PD = 39.5, controls = 31.0). Lane violations were the most common error category, and group differences in some error categories became insignificant after results were adjusted for demographics and familiarity with the local driving environment. Within the PD group, older age and worse performances on tests of visual acuity, contrast sensitivity, attention, visuospatial abilities, visual memory, and general cognition predicted error counts. Measures of visual processing speed and attention (UFOV test) and far visual acuity were jointly predictive of error counts in a multivariate model [11]. An alternative model using CFT-COPY (another strong univariate predictor) resulted in slightly smaller but still significant R-squared value. The advantage of CFT-COPY is that it is a paper-pencil test, which is in public domain and is quick to administer [11]. The follow-up of this cohort [11] showed that 38% of PD drivers and 68% of control drivers returned about 2 years later for follow-up road test [13]. Drivers with PD who returned had fewer safety errors at baseline compared to those who didn't return, whereas no such difference was observed among controls. Compared to controls, the PD group showed a significantly greater increase in total error counts longitudinally (median 13.5 vs. 3.0). Measures of visual processing speed/attention (UFOV) and global cognition predicted decline in driving safety within PD [13].

As part of the road drive in an IV, Uc compared multitasking abilities of drivers with PD and controls by administering tasks (Table 26.1) on navigation (route following) [8], visual search [6], and mental arithmetic (to simulate audioverbal distraction) [5]. Drivers with PD took longer to finish the route following task [8]. A higher proportion of PD drivers made incorrect turns, got lost, or committed at-fault safety errors [8]. Within the PD group, the navigational and safety errors were predicted by poor performance on cognitive and visual tests, but not by the severity of motor dysfunction [8]. During the same IV drive, drivers were asked to report sightings of specific landmarks and traffic signs along a four-lane commercial strip to assess the ability for visual search and recognition of roadside targets [6]. The drivers with PD identified significantly fewer landmarks and traffic signs, and they committed more at-fault safety errors during the task than control subjects, even after adjusting for baseline errors. Within the PD group, the most important predictors of landmark and traffic sign identification rate were performances on visual speed of processing and attention and visuospatial abilities. Trail Making Test (B-A), a measure of cognitive

flexibility independent of motor function, was the only independent predictor of at-fault safety errors in drivers with PD [6]. In another IV experiment in this cohort of PD patients and controls, the effects of auditory-verbal distraction on driving performance in PD were assessed using the Paced Auditory Serial Addition Task (PASAT) [5]. Despite driving slower, drivers with PD were more affected by the distracter task with increased safety errors and higher speed. Decreased performance on tests of cognitive flexibility, verbal memory, postural control, and increased daytime sleepiness predicted worsening of driving performance due to distraction within the PD group [5].

Driving Simulation

Although actual road testing provides richer and more balanced visual, tactile, vibratory, and vestibular cues to the driver [43], road conditions vary between subjects and some maneuvers may be unsafe to test. Driving simulators replicate the experimental conditions for each subject and enable administration of challenging tasks in a safe environment with complete experimental control [49]. Driving simulators may vary widely in their technical characteristics (e.g., motion base vs. fixed base, interactivity, resolution, and field of view). Validation of individual simulators and driving scenarios is needed to derive meaningful conclusions from their administration. Another important concern about simulators is "simulator sickness" (similar to motion sickness), also known as simulator adaptation syndrome, which occurs in a proportion of drivers due to visual vestibular mismatch and can reduce performance or preclude simulation all together [50]. Most studies in the following section (Table 26.3) were performed on medium-high fidelity simulators with a fixed motion base.

Drivers with PD are able to tolerate simulated driving similarly to elderly healthy drivers [20]. Simulator studies in drivers with PD showed impaired steering accuracy, slower driving reaction times, missing red lights [21], impaired land keeping, increased crashes [15] especially rear end collisions [22] and crashes at intersections [20] under low visibility conditions. In these studies, PD driver performance was associated with cognitive and visual dysfunction as well as severity of parkinsonism, especially for reaction times in tasks where speed of response was critical (e.g., reaction to sudden hazard such as an illegal intersection incursion by another vehicle [20]) (Fig. 26.2).

Drivers with PD have difficulty generating internal cues from memory, and rely on external cues such as warnings and signs for better driving performance due to attentional and executive dysfunction [14], akin to the usefulness of visual cues to overcome freezing. Concurrent distracting auditory-verbal [19] or motor tasks [23] take a larger toll on vehicle control and reaction to hazards in drivers with PD compared to controls, although they tend to drive slower and perform worse on the secondary tasks. The impact of these secondary tasks on drivers with PD is associated with an increased severity of their executive and attentional dysfunction.

Table 26.3 Simulator studies in PD

Reference	Scenario	*N*	Outcome	Predictors	Comments
Overall safety					
Madeley [16]	Common driving tasks	10 PD, 10 C	Poor steering, slower RT, signal violation in PD	Parkinsonism (Webster's scale)	Small sample size limited battery
Lings [21]	Common driving tasks	28 PD, 109 C	Poor steering, slower RT, slow speed, signal violation in PD		Controls much younger than PD
Moller [17]	General driving	6 PD	Decreased vigilance and vehicle control in PD	Sleepiness	No formal statistics
Zesiewicz [15]	Collision hazards	39 PD, 25 C	Increased collisions in PD	Parkinsonism, cognitive	Nondrivers included; no visual testing
Uc [20] (low visibility, collisions)	Low vs. high visibility driving; collision hazard due to illegal intersection incursion in low visibility	67 PD, 51 C	PD: Poor vehicle control in both high and low visibility, further worsened by low visibility; increased crashes and prolonged RT at intersection	Visual, cognitive, UPDRS motor, tapping speed	Motor dysfunction becomes also a predictor of performance when response to sudden hazards is required
Uc [22] (rear end collisions)	Approaching intersection where lead vehicle is stopped at green light	83 PD, 52 C	7 collisions in PD, none in controls	Visual, cognitive, rigidity	
Multitasking					
Stolwyk [14]	Driving on curves and approach to traffic signals with or without warning signs	18 PD, 18 C	Drivers with PD had increased SDLP on curves and difficulty with stopping at signals; more dependent on external cues	Visual, cognitive>>motor	"External cues" improved driving performance
Stolwyk [19]	Driving on curves and approach to traffic signals with or without concurrent task	18 PD, 18 C	closer deceleration points in PD drivers before traffic signals with distracting concurrent task		Distraction by an auditory task
Uc [23]	Window rolling during driving	31 PD, 19 C	Worsening safety status in PD due to secondary task, longer task duration	Visual, cognitive, UPDRS-ADL	Distraction by a motor task

RT reaction time, *SDLP* standard deviation of lateral position

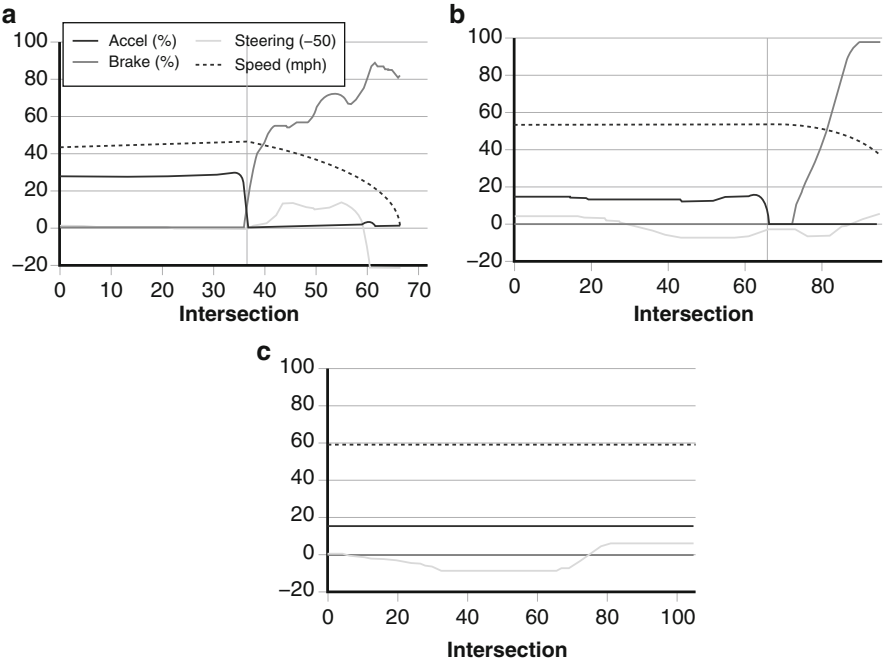

Fig. 26.2 Diagrams of vehicle kinematics and the vehicle path after the intersection incursion was triggered (4.0 s before the intersection as determined by driver speed) in three participants. The common ordinate scale shows the driver's vehicle speed, percentage of pedal application for accelerator and brake, and steering wheel rotations in degrees (upward deflections are counterclockwise rotations). The *x*-axis ends at the expected position of the incurring vehicle. The *upper panel* shows vehicle path inside the lane. (**a**) A control participant able to stop timely before colliding with the incurring vehicle. At 1.83 s after the trigger, he releases the accelerator and starts braking with a smooth deceleration. The brake is applied 82% at the time of stopping. (**b**) The driver with Parkinson disease (PD) reacts late (2.73 s) and collides with the incurring vehicle at 34 mph. (**c**) This driver with PD does not perceive the incurring vehicle, does not react at all, and crashes at 58 mph. Modified from Uc et al. [20]

Real-Life Driving Outcomes

There are no well established epidemiologic data on crash risk in PD [29]. However, a retrospective, cross-sectional questionnaire study from a movement disorders center found that 20% of PD patients had stopped driving due to increased accidents [25]. The frequency of crashes in subjects with more severe PD (Hoehn and Yahr [HY] stage III) was fivefold higher than controls, whereas patients with mild PD (HY I) reported almost twice as many crashes as the controls. An MMSE score of 23 or less was associated with a threefold increased crash rate.

A large mail and phone survey from Germany revealed that 82% of PD patients held a driving license, and 60% of them still actively drove. Of the patients holding

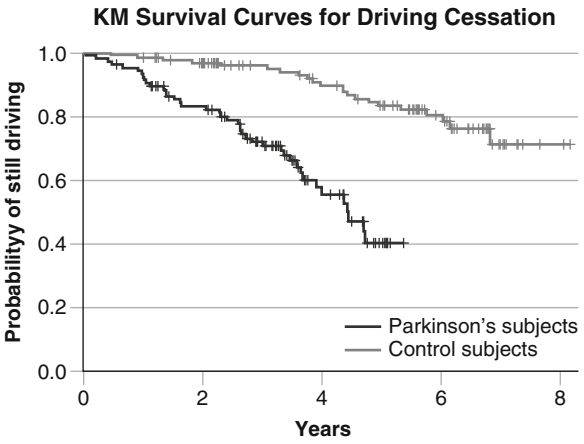

Fig. 26.3 Kaplan–Meier Curves for Driving Cessation (Logrank test $\chi^2 = 37.53$, p-value <0.0001) between subjects with Parkinson's Disease and elderly control subjects. From Uc et al. [28]

a driving license, 15% had been involved in and 11% had caused at least one accident during the past 5 years [26]. The risk of crashes significantly increased for patients who felt moderately impaired by PD, had an increased ESS score, or had reported "sleep attacks" while driving. Female gender, more severe parkinsonism, sleepiness, older age and longer disease duration were associated with driving cessation [26].

In a cross-sectional study among PD patients, Cubo [36] found that compared to current drivers, ex-drivers were significantly older, had longer disease duration, had more overall cognitive dysfunction and greater motor impairment as measured by the CISI (Clinical Impression of Severity Index), HY stage, and the SCOPA (Scales for Outcomes in Parkinson's disease) motor scale and difficulty in activities of daily life. Aging and ADL impairment were the principal clinical predictors that differentiated drivers from ex-drivers [36].

Review of the records of drivers with PD referred to the Scottish Driving Assessment Service over a 15-year period revealed that 66% were able to continue driving, with about half of them receiving recommendations for vehicle modifications. The ability to drive was predicted by the severity of parkinsonism, reaction time, presence of significant comorbidities and poor score on road testing [34].

Our longitudinal, prospective cohort study of 106 drivers with PD and 130 elderly control drivers [28] showed that 40.6% of PD drivers ceased driving compared to 16.9% of control drivers with an estimated HR (95% CI) of 7.09 (3.66, 13.75) for PD, adjusted for age, gender, education and driving exposure at baseline. This was consistent with prior retrospective reports and also consistent with other studies in which PD was found to play a major role in driving cessation but not a significant factor in crashes [35, 51–53]. The Kaplan–Meier plot (Fig. 26.3) shows the probability of still driving (or inversely, the risk of driving cessation) at any particular time point during follow-up, and allows visual comparison between groups for between-group comparisons over time [28]. For example, the cumulative incidence (95% CI) of driving cessation at 2 years after baseline was 17.6% (11.5%,

26.5%) for PD and 3.1% (1.2%, 8.1%) for controls [28]. Significant individual risk factors for driving cessation within PD included older age, decreased driving exposure, poorer ratings of driving ability by self and others, higher number of road errors and past crashes, increased use of compensation strategies, poorer performances in most measures of vision, and higher severity of parkinsonism. A multivariate analysis of risk factors in PD showed a preference to be driven by others, higher UFOV total score, higher UPDRS-ADL scores, and higher daily levodopa equivalent as the most important risk factors for driving cessation [28]. There was no statistically significant difference between groups on crashes; however, the study had limited power to detect differences in crashes due to small number of crashes that occurred. Of note, our results in PD are similar to observations in Alzheimer's disease (AD) by other researchers where driving cessation was the main outcome without showing increased crashes [40]. The likely reasons for these findings may include attrition of potentially unsafe drivers with AD or PD before a potential crash, or restricted driving and strategic compensation [28].

Special Issues Requiring Further Study

Effect of Sleep Related Impairments

Ever since Frucht's [54] observation that PD patients taking the dopamine agonists ropinirole and pramipexole may experience "sleep attacks" leading to car crashes, excessive daytime sleepiness (EDS), or "sleep attacks" have been reported with all dopaminergic medications used to treat PD [55]. About 33% (range 16–74%) of patients with PD suffer from EDS; the estimates for "sleep attacks" are 1–14%, with 1–4% experiencing them during driving [56]. The mechanisms of sleepiness and sleep attacks in PD might include a complex drug–disease interaction with degeneration in sleep centers in the brain and side effects of dopaminergic medications, particularly direct dopamine agonists [56].

Several studies using self-report measures such as the Epworth Sleepiness Scale (ESS, cut-off score 7–10) [11, 20, 26, 33, 57, 58] found a relationship of EDS with driving performance in PD; real sleep attacks without any prior sleepiness were rare. However, the ESS does not correlate well with a more objective measure of sleepiness [55]. Empirical studies using experimental performance measures for driving and physiological measures of sleep while driving are needed to describe the characteristics of sleep related driving problems and predictors of poor outcomes due to wakefulness disorders in PD [17].

Effect of PD Treatment

Road testing in drivers with PD has usually been performed when patients are in the "on" state due to ethical (subject protection) and practical (normally subjects would not start driving without treatment effect) concerns. Thus there are no data on

driving performance comparing "on" and "off" states of PD patients on the road. However, this can be potentially tested in the safe environment of a driving simulator. No significant correlations of dopaminergic medication dosage (levodopa equivalent per day) could be found with empirical driving performance [3, 5–8, 10, 11, 18, 20]. We found that higher levodopa equivalent at baseline predicted earlier driving cessation [28], probably as a surrogate measure of disease severity.

There are limited data comparing the effect of dopaminergic medication class (levodopa vs. direct agonists) on driving. Uc [8] classified PD drivers as being on levodopa, dopamine agonist, on levodopa and dopamine agonist, or other/no treatment, and made formal comparisons among these groups. There was no effect of medication group status on safety errors or performance on the route following task [8].

Guidelines on Driver Fitness Assessment and Reporting to Licensing Authorities

There are no evidence-based practice parameters for driving in PD to date. However, recent National Highway Traffic Safety Administration (NHTSA) [59] and Federal Motor Carrier Safety Administration (FMCSA) [60] 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., compensation strategies to lower risk). A recent evidence based review [61] discusses the role of various cognitive, visual, and motor tests in predicting driver safety in PD.

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" [62].

Interventions to Improve Driving in PD

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 [63–66]. Speed of processing or reasoning training may delay driving cessation in the elderly [67]. There was moderate evidence that educational interventions improve driving awareness and driving behavior, but do

not reduce crashes in older drivers [63, 68–70]. Short-term trials using physical conditioning [71] or classroom and road retraining [72] 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 [73]. However, there was no difference in driving cessation in these stroke patients between the simulator training and control groups at 5 years [74].

To our knowledge, there are no published reports on driver rehabilitation in PD except our pilot studies showing feasibility of simulator training [75, 76]. 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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Chapter 27
Genetics and Genetic Counseling Related Issues

Martha A. Nance

Abstract One would hope that there would be few emergencies related to genetic testing for movement disorders, but we have reviewed below several situations that qualify, including perception of urgency around testing, family conflicts and psychosocial complications related to testing, and problems related to misunderstanding of genetic facts. The physician can minimize the potential for genetic emergencies through proper education of, and support for, patients and their families. The judicious use of genetics specialists, such as genetic counselors, is an invaluable asset to the neurologist.

Vignette 1

The local Huntington's Disease Center of Excellence received a panicked call from a patient, triggering a visit to the center. A 32-year-old woman presented to the clinic in the company of her partner, also 32 years old. She reported that she was 12 weeks pregnant, and her partner reported that he was at risk for Huntington's disease (his mother and uncle had died from the disorder). He had never been evaluated by a neurologist. The pregnancy was desired; however, the partner had not told the woman about his family history until the pregnancy occurred.

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In the office, the woman and her partner met with the social worker and genetics counselor to discuss their options. The woman expressed the desire to continue the pregnancy if she could be assured that the baby would not have Huntington's disease. The partner discussed his fears of the possibility of an HD diagnosis, and also indicated that he was not interested in undergoing predictive testing or a neurologic examination.

After consultation with the woman's obstetrician, a chorionic villus sampling was performed. Testing of the pregnancy revealed that the fetus did not carry a CAG expansion in the IT-15 gene for HD.

Vignette 2

A 34-year-old woman was referred to a local Huntington Disease Center of Excellence after contacting the center in a panicked phone call. She was married, with a 3-year-old son, and attended the appointment without her husband, instead accompanied by her closest friend. She was aware that her father had died of Huntington's disease, and also understood that she was therefore at risk for the disorder.

Her primary care physician had evaluated her 3 months ago for increasing feelings of anxiety and depression. Concerned about her family history, he referred her to a local neurologist. She reported that the neurologist examined her, told her that her examination was normal, and recommended drawing blood for a genetic test for HD "just to be complete." He reassured her that he did not think it was likely that the result would be positive. Formal genetic counseling was not performed. Two weeks later, the neurologist called her on her cell phone while she was driving her son home from day care. He informed her that her genetic test was positive, with 43 CAG repeats, and asked her to come in to the office the following week to discuss the results. Later that day, the patient called the Huntington Disease Center of Excellence, distraught. An immediate appointment was obtained.

In the office, she was tearful and extremely anxious. She reported that she had not informed her husband of the result, citing concerns about the stability of her marriage. Her neurologic examination was completely normal. The center's psychiatrist, social worker, and genetic counselor evaluated her, and the meaning of the result was explained in detail. Her anxiety and depression were treated. She was very angry at the way her results were disclosed, regretted having taken the test, and was fearful that the record of the test might be accessible to her insurance and disability carriers.

Introduction

In the ideal outpatient clinic, diagnoses are provided by caring physicians with an abundance of time and knowledgeable staff, complemented by easy access to educational materials and local support programs. The subspecialties of medical genetics

and genetic counseling have been developed after the realization that genetic disorders present unique diagnostic and management issues. Ideally, these specialists help the neurologist to avoid crises related to the genetic aspects of neurogenetic disorders, or help to manage them if they arise. However, because neurologists are often busy, or may not have specific knowledge or ready access to consultants for an unusual neurogenetic condition, they may unavoidably encounter a neurogenetic emergency. We describe below some problematic situations that can arise related to genetic testing and genetic aspects of neurologic diseases, and suggest strategies to prevent or manage them.

Psychosocial Emergencies Following a Gene Test or Genetic Diagnosis

By definition, genetic disorders are inborn and permanent. If a person is not the first in the family to be diagnosed with a neurogenetic condition, then the diagnosis may confirm the parent or patient's worst fear, a fear that might have been smoldering for years or generations. On the other hand, if the diagnosis is new to the family, the patient may experience guilt, in addition to grief for himself, for having "brought the disease to the family." Most neurogenetic movement disorders themselves have cognitive and behavioral effects that may render a patient ill equipped to cope with a neurogenetic diagnosis.

It is possible that the risk of adverse psychological events following the diagnosis of a neurogenetic condition differs by condition. Suicidal ideation occurs in up to 23.5% of people with "possible" (soft signs suggesting) Huntington's disease and over 15% of those in Stage I or Stage II of the disease before declining in the later stages, suggesting that for this disease, individuals at and around the time of diagnosis are particularly susceptible to suicidality [1]. Suicide has been reported in patients with myoclonus-dystonia syndrome, and following DBS for dystonia [2, 3]. In one review, suicide attempts occurred in 7/45 patients with Wilson's disease [4]. Suicidal thinking was present in 11% of a convenience sample of outpatients with Parkinson's disease [5]. Although suicide has not been reported, depression occurs in about 50% of patients with hereditary spastic paraplegia, and psychosis has also been reported [6, 7]. Although depression is common in Tourette syndrome, suicide appears to be uncommon, and suicide has only rarely been reported in essential tremor or any of the hereditary ataxia syndromes. Whether people with suicidality, depression, or psychosis are more sensitive to the provision of a diagnosis, and whether genetic diagnosis is likely to trigger a less-than-lethal level of depression, are not known.

Huntington's disease presents a somewhat unusual situation in neurogenetics, in which all individuals with the disease have the same mutation in the same location in the same gene (with the minor exception of HD-"lookalikes" such as HDL-2, DRPLA, and SCA17). Because of this, a relatively inexpensive targeted analysis of the CAG repeat expansion can be utilized, and counseling regarding the relationship between the gene mutation and the eventual development of the disease is

relatively straightforward (there can be incomplete penetrance for CAG repeat expansions in the low-abnormal range, but other than that, all patients with CAG repeat expansions will eventually develop HD). The situation is much more complex for the hereditary ataxias, dystonias, and spastic paraplegias, where mutations in several different genes can lead to a similar phenotype, or different mutations in the same gene can lead to different diseases, or disease-causing mutations can be located throughout the gene and may not be detected with the assay used. The clinical genetics of Parkinson's disease is even more complex, as it includes both rare disease-causing mutations and genetic variants in other genes that either increase the risk of the disease, or cause the disease, but with dramatically reduced, age-dependent penetrance. For these other conditions, the clinical significance of either a positive or a negative test result may be quite complicated to explain to the patient, may depend on other factors such as ethnicity, and may change as new knowledge accrues. A genetic counselor can help the neurologist to sort through some of these issues, so as to avoid a later crisis caused by misinterpretation of the significance of test results.

Requests for "Emergency" Diagnostic Testing

While a diagnostic gene test can provide a definitive confirmation of a patient's diagnosis, other than in a child with an acute metabolic crisis due to an inborn error of metabolism, it is rarely an emergency to obtain this confirmation and in some cases, a clinical diagnosis can trump a negative or equivocal gene test result. Unfortunately, both patients and doctors tend to overestimate the importance of the gene test to the diagnosis of a condition, which can create an unnecessary sense of urgency around the use of the diagnostic test. Two cases illustrate these points.

A 40-year-old male asks for an urgent evaluation. He is performing poorly in the workplace, with progressive clumsiness over 3–4 years, change in speech, and ataxia. His deceased mother and grandfather had a similar problem, and his sister has "ataxia." He would like an ataxia gene test, so that he can apply for disability before he gets fired from his job, which seems to be imminent. His evaluation shows dysarthria, gait spasticity and ataxia, limb ataxia, slow eye movements, and hyporeflexia. No additional information can be obtained about the ancestors; he thinks that his sister had gene tests, but does not know what they showed. This patient should be given a working diagnosis of "hereditary ataxia," evaluated for treatable acquired conditions that could cause similar symptoms, and asked to find out the results of his sister's evaluation. An ataxia "gene test panel" can cost $5000–$10,000, which some insurers do not cover and patients often decline to undergo [8]. His need for genetic testing varies significantly depending on whether the sister's evaluation showed that she has (for instance) multiple sclerosis, a positive test for spinocerebellar ataxia type 2, a negative ataxia gene test panel performed 12 years ago (which tested for only 5–6 genes; the current panel tests for many more), or a negative test panel performed this year. The physician's ability to speak to the patient's functional disability

does not depend upon a positive gene test result; if the patient and three other family members have all had similar progressive symptoms, the family has hereditary ataxia, whether or not the gene has been identified and is available for commercial testing. Even without any information about the family (if, for instance, he was adopted and did not have a sister), he can still be diagnosed with a progressive or neurodegenerative ataxia even if the gene test results are all normal.

A different patient, a 35-year-old man, is admitted to the psychiatric crisis unit for the third time in 2 years. He lives on the street in this town in the summertime, but makes his way south in the winter; because he generally appears when he is in a crisis situation, little background information is available. For the first time, a family member appears at his bedside, and indicates that the patient's father and brother both have Huntington's disease. The psychiatry resident, armed with this information, asks for a stat HD gene test and a neurology consult.

Rather than a stat gene test, this patient needs a thorough medical history and neurologic exam. He may benefit, also, from formal neuropsychological assessment. If he has obvious chorea and a decline from his previous function as an architect, then the working diagnosis of HD is evident, and the gene test is not an emergency. If he has no movement disorder, has been on the streets since his 20s, has never worked more than temporary jobs, and carries a diagnosis of paranoid schizophrenia, then the clinical diagnosis of HD is not evident, and this would be considered to be a "predictive" gene test, which should only be done if and because the patient requests it. No matter what the results of the gene test are, the patient needs urgent and ongoing psychiatric care. The gene test can be performed, if at all, at a time when the patient is not in the midst of a psychiatric crisis and is more able to understand and respond appropriately to the results.

Psychosocial Complications of Predictive Testing

Guidelines were written years ago, shortly after the identification of the HD gene made predictive testing for that disease possible, recommending a course of genetic counseling, psychological assessment, and neurologic evaluation prior to the completion of a predictive gene test [9]. The Huntington Disease Society of America maintains a list of genetic testing centers that utilize at least some aspects of these protocols, including, in particular, genetic counseling. A worldwide survey of over 4500 subjects tested at "predictive testing centers" showed that the risk of catastrophic events (defined as suicide, suicide attempt, psychiatric hospitalization) after predictive testing was less than 1% [10]. It is not known whether outcomes are any different for patients who undergo predictive testing in a more casual fashion, through their primary physician or treating neurologist or psychiatrist, without benefit of genetic counseling or psychosocial assessment and support.

It is also not known whether a more abbreviated testing protocol could be used for other neurogenetic conditions. Given that the genetic complexity and heterogeneity of other groups of movement disorders (the ataxias, dystonias, spastic paraplegias,

parkinsonian syndromes) are greater than HD, it seems safest to make use of genetic specialists if a physician is attempting to provide predictive testing, carrier testing, or risk factor analysis for virtually any neurogenetic condition. Knowing that the primary risks of predictive testing are psychosocial, it would also be in the physician's best interest to utilize colleagues who are skilled in evaluating psychosocial risk and treating acute psychological distress, such as a social worker or psychologist, if he intends to order predictive testing for a patient.

An episode occasionally arises in which a third party inappropriately requests an urgent predictive test because of an upcoming event or situation. An employer or an opposing party in a child custody dispute might want to know if a person carries a gene likely to cause HD, or hereditary ataxia, or some other neurogenetic condition. The Genetic Information Nondiscrimination Act of 2008 (GINA), prevents employers from requesting gene tests and provides protection from genetic discrimination in health insurance [11]. In addition, the ethical climate in which predictive testing is performed in the United States strongly incorporates the principle of autonomy, which dictates that predictive testing should be done only at the request of the patient, free of coercion, and with an understanding of the medical benefits (which may be zero) and psychosocial risks and benefits of the test results [12]. An analogous discussion has been applied to the testing of children for adult-onset diseases, although there is ongoing debate as to whether certain children, diseases, or clinical situations, should be exempted [13]. Finally, there is some concern that the use of direct-to-consumer tests by minors could lead to deleterious psychosocial consequences for the children [14].

The potential for genetic discrimination, such as loss of insurance, related to predictive testing of asymptomatic persons for conditions such as Huntington's disease has been discussed for years [15], although there are few detailed case reports of actual such events, and the discrimination, if it exists, can be subtle, perceived only by the patient [16]. A recent study showed that a family history of HD, rather than the gene test itself, presented the greater risk for events perceived as discrimination, and that the events more commonly related to insurance, family, or social settings, and less often to work, health care, or public settings [17]. Nonetheless, the neurologist who treats patients with genetic neurologic disorders should be sensitive to the potential social impact of the diagnosis, the genetic risk status, or gene test results—obtained at any point in the patient's life—on the patient's standing within the family, in the workplace, in the community, and on the ability to obtain or maintain insurance (of many different types).

Prenatal Testing

Prenatal tests for neurogenetic conditions are sometimes requested on an urgent or emergent basis, because of time pressure related to the pregnancy. These requests stem, in general, from a lack of communication. Whether the physician did not provide appropriate information about the genetic aspects of a condition to the

family in the first place, or family members did not hear, understand, or relay the information to other relatives, or individuals married into a family and were not told about the "family disease," or some other breakdown, varies from one patient and family to the next. Although some of these situations are out of the physician's control, the physician can start to improve communication by recognizing that the unit of care in genetics is really the family, and not the individual. This differs from, and can conflict with, the neurologist's usual clinical patient interaction, which focuses almost exclusively on the patient—and which in the HIPAA era, actively rejects interactions with family. The physician who makes a genetic diagnosis, whether by clinical examination or gene test, needs to be aware that this diagnosis has immediate clinical implications for parents, siblings, current and future children, and perhaps more distant relatives. If the physician is not in a position to counsel all of these relatives, he should at least make sure that accurate information is available to the family, and allude to the possibility of predictive, prenatal, or carrier testing if it can be done. As young children or siblings become adults over the course of a patient's illness, genetic counseling may appropriately be reoffered, knowing that parents sometimes do not discuss genetics with their children accurately, if at all.

A pregnant patient requesting genetic testing should always be referred to a genetic counselor or other genetics specialist for a detailed discussion of the situation.

Family Crises Related to a Genetic Diagnosis

Genetic medicine, with its necessary inclusion of family but focus on the individual, is inevitably accompanied by crises related to difficult family dynamics. Particularly common in the Huntington Disease Clinic is a situation in which the family brings a patient, duplicitously, for diagnosis of a condition that the patient is unaware of or believes he does not have [18]. The opposite situation can occur as well; a recent monograph describes in detail many years of physician visits by a depressed and anxious 32-year-old woman at risk for HD who believes that she has been symptomatic since her childhood years [19]. The authors label each visit as "congruent," if the physician performed a neurologic examination, acknowledged the possibility of HD, referred her to a neurologist, or ordered a gene test for HD, and "incongruent," if the physician emphasized the need for psychiatric evaluation or treatment or failed to move ahead with evaluation or testing for HD. It can be very difficult to attend to the needs and desires of the patient and the family when they are in opposition. In the presymptomatic patient, there is no medical benefit to be gained by testing a patient, no matter how many family members request the test. However, in the symptomatic patient, it may be important for legal and psychosocial reasons, to establish a diagnosis. Treatment of symptoms, however, can often proceed with or without a specific genetic diagnosis.

The physician must also be sensitive to the emotional challenges faced by caregivers related to the patient, such as siblings and children, or the special burden

faced by a spouse simultaneously caring for an affected adult and an affected child. We recall the 14-year-old daughter who was called upon by her father to come to her mother's appointment in case the mother needed help with menstrual hygiene in a public restroom. When, at age 16, the daughter refused to be so involved with her mother's care, she required urgent nursing home placement.

Another crisis situation can arise when families are misinformed or have misunderstandings about the genetic aspects of their disease. Assignment of risk by analysis of markers linked to a disease gene is inherently inaccurate, and when genes responsible for HD and SCA1 were first identified, direct testing led to a reversal of risk status for some patients (patients judged to be at low risk were found to carry gene mutations, or vice versa) [10, 20]. Based on observations within their kindred, or misinformation provided decades ago, families sometimes still believe that their disease skips generations, affects only males or females, never affects the second-born child, or is caused by nongenetic environmental influences. Correcting misimpressions is extremely important, but may cause ripples throughout a family. Once again, referral to a genetic counselor, who may be able to take extra time, schedule family conferences, or use visual aids to illustrate various genetic principles, can be extremely helpful to the busy physician. Disease-specific lay organizations often have printed materials about the genetic aspects of the disease, and the online resource, GeneTests [21], provides excellent and detailed information about the genetic aspects of many neurogenetic conditions.

Conclusions

By understanding the unique aspects of genetic medicine, and making use of genetics specialists (geneticists and genetic counselors), the neurologist should avoid most emergencies related to genetic testing for neurogenetic disorders. Most of the crises that arise are psychosocial or family-related, so enlisting the support of social workers, nurse-case managers, psychologists, or psychiatrists, can help the neurologist to defuse crises that do arise.

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Chapter 28
Suicide Risk in Parkinson's Disease

Valerie Voon

Abstract Suicide is a major but possibly preventable public health issue. In Parkinson's disease, the rate of completed suicides is the same as or lower than the general population despite the high comorbid risk factors. Suicide ideation and attempts appear to be more common. Depression is identified as the most common factor associated with suicidal behaviours. Following deep brain stimulation surgery targeting the subthalamic nucleus, the rate of completed suicides increases (Standardized Mortality Ratio 12.63–15.64) in the first postoperative year and remains elevated to the fourth postoperative year. Again depression is the single factor most commonly associated with suicidal behaviours in the postoperative state. Suicidal behaviours in PD demonstrate a clear association with depression, thus highlighting the need to screen for and treat depressive symptoms along with actively screening for suicidal ideation in depressed patients.

Patient Vignette

A 48-year-old man was evaluated in a movement disorders centre for consideration of deep brain stimulation for advanced Parkinson's disease. He developed symptoms of PD at the age of 39, and had received treatment with levodopa and dopamine agonists for 8 years. His current problems included marked motor fluctuations, requiring him to take levodopa every 2 h, and moderately severe peak-dose dyskinesias.

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Neuropsychological testing revealed no cognitive impairment. As part of his preoperative evaluation, psychiatric evaluation revealed an underlying mild to moderate depression and mild anxiety. Social support was limited, as he lived alone with one sibling located in the area. He was currently retired on medical disability.

He underwent successful implantation of bilateral subthalamic deep brain stimulators without incident. Postoperative course was uneventful, and there was substantial improvement in his motor performance, with reduction in his levodopa by 60%. Despite this improvement, his depression worsened postoperatively, and close evaluation by his psychiatrist revealed mild suicidal ideation, with some thoughts of a plan.

He was admitted to the psychiatry service, and a course of antidepressants was begun. Psychotherapy and supportive counselling were also engaged. His depression improved, and he was ultimately discharged home. One year later, his depression remains well controlled.

Introduction

Parkinson's disease (PD) is characterized by a range of disease- or medication-related neuropsychiatric symptoms including depression, apathy, psychosis, anxiety and cognitive and behavioural changes. The risk of completed suicides in PD is remarkably low [1–3] despite the high somatic illness burden and high frequency of psychiatric comorbidities. However, suicidal ideation and attempts appear to be common in PD. Patients who have undergone subthalamic deep brain stimulation surgery (STN DBS) are at greater risk for completed suicides [4]. Suicide is a major but possibly preventable public health issue identified by the World Health Organization as one of the top ten causes of death. Suicide is multifactorial and is associated in the general population with depression, gender, age, marital status, comorbid physical illness and previous suicide attempts [5]. In this chapter, the studies on suicidal behaviours in Parkinson's disease are reviewed and categorized into suicidal ideation, suicide attempts and completed suicides.

Suicidal Ideation and Attempts

Suicidal ideation and suicide attempts appear to be common in PD, although whether they are necessarily more frequent relative to the general population is not clear. In a North American study of 116 PD outpatients, suicide and death ideation assessed using the self-administered Paykel Scale modified to assess the past month, demonstrated current active death ideation in 28%, suicide ideation in 11% and a lifetime suicide attempt in 4% [6]. Death ideation included questions such as "Has there been a time in the last month when you felt that life was not worth living?" and suicidal ideation included questions such as "Has there been a time in the last month

that you thought of taking your own life, even if you would not really do it?" This ideation was associated with increasing severity of depression, impulse control disorders and psychosis. Following logistic regression analysis, depressive symptoms were the primary factor associated with suicidal or death ideation.

Other studies have shown that suicidal ideation is common in PD in cross-cultural settings. In a Brazilian study involving 90 PD patients, suicidal ideation was assessed with three different instruments including a semi-structured clinician interview with the Mini International Neuropsychiatric Interview and a clinician-rated and patient-rated depression scale [7]. Suicidal ideation was present in 14.4% of PD patients associated with younger age, younger PD onset, and psychiatric disorders including major depression, panic disorder and social anxiety disorder. Again, major depression was the primary factor associated with suicidal ideation. Similarly, in a Serbian study involving 128 PD patients, suicidal ideation was documented in 22.7% associated again with major depression, psychosis and high scores on the Beck Hopelessness Scale [8]. Given the lack of a control group, although suicidal ideation and attempts are common, whether the rates are elevated relative to the general population is not known.

Completed Suicides

In contrast, the rate of completed suicides appears to be low, with reports of rates either the same as [2] or as much as ten times lower than the general population [1]. The rates appear remarkably low particularly in the presence of known suicide risk factors including older age, male predominance, chronic medical illness, comorbid psychiatric disorders and psychosocial losses. In a study using the US National Centre of Health Statistics mortality database, from 144,364 patients with PD, 122 (0.08%) had committed suicide, a rate ten times lower than that of the general population (0.8%) [1]. The PD patients with completed suicides had higher rates of depression compared to PD patients who died from other causes, again emphasizing the role of depression. In a smaller study using the Ontario provincial coroner's records with prescription records as a marker of illness, from 1,354 elderly patients who had died by suicide, suicide was not more or less likely to occur with Parkinson's disease (Odds ratio on multivariate analysis: 1.11) as compared to other medical disorders such as congestive heart failure, chronic lung disease and seizures (Odds ratio: 1.30–2.41) and psychiatric disorders (Odds ratio: 2.60–3.94) [2]. Similarly, in a large Finnish database study of 555 hospital-treated patients above the age of 50 years who had completed suicide, only 1.6% of all subjects were PD patients [3]. Previous suicide attempts in PD patients were common, occurring in 44% of cases as compared to other patients in 9.9%. Other associated characteristics including being male, recently diagnosed, living in a rural area and with multiple somatic illnesses. However, in a contrasting Serbian study of 102 PD patients, the suicide mortality rate was 5.3 times higher than the expected mortality rate [8]. This elevated rate may be the result of cross-cultural differences in suicidal behaviours or

may be an issue of reporting bias in a small sample size given the rarity of the behaviour. Taken together, although suicidal ideation and attempts in PD are common, completed suicides are lower than expected in PD. The reason for the low rates has been hypothesized to be related to apathy and the related concept of decreased motor or behavioural initiation [1].

Deep Brain Stimulation and Suicidal Outcomes

This overall low baseline rate of completed suicides stands in marked contrast to the elevated rates reported in PD patients who have undergone STN DBS surgery. In a large international multicentre study involving 55 centres, completed suicides occurred in 0.45% (24/5,311) and attempted suicides in 0.9% (48/5,311) [4]. Suicides occurring in the first postoperative year (0.26%) (263/100,000/year) were higher than the World Health Organization Standardized Mortality Ratio for suicide: age- and gender-matched (SMR: 12.63–15.64; $P<0.001$) and remained elevated to the fourth postoperative year (0.04%) (38/100,000/year) (SMR: 1.81–2.31; $P<0.05$) (Fig. 28.1). The excess number of deaths was 13 for the first postoperative

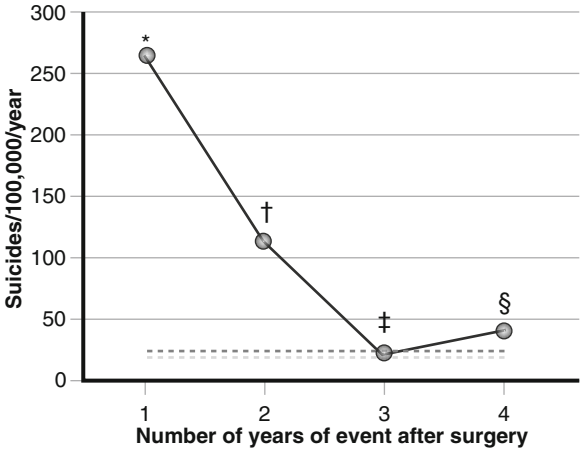

Fig. 28.1 Comparison of the suicide rate per postoperative year following subthalamic stimulation for advanced Parkinson's disease with the baseline suicide rate (printed with permission from Brain). *$P<0.001$, weighted SMR = 12.64–15.64; †$P<0.001$, weighted SMR = 5.13–6.91; ‡$P>0.05$, weighted SMR = 0.91–1.16; §$P<0.05$, weighted SMR = 1.81–2.31. The observed postoperative STN DBS suicide rates per 100,000/year (*solid line*) and the lowest (*grey dotted line*) and highest (*black dotted line*) age-, gender- and country-adjusted WHO expected suicide rates per 100,000/year are reported (Brain 2008;131:2720–8. Used by permission, Oxford University Press)

year. Seventy-five percent of events occurred within the first 17 postoperative months. Postoperative mortality in the first year following STN DBS from other causes (e.g. haemorrhage, infection) has been reported at 0.41%. Thus, postoperative suicidal outcomes represent the highest risk for mortality following STN DBS. In this study, the rates following stimulation targeting the globus pallidus interna (GPi) were not conducted given the much smaller relative sample size. Although these rates were elevated, the rate was much lower than a previous report of 4.3% (6/140) reported following DBS for a range of movement disorders [9]. Similarly, a metaanalysis of the literature demonstrated a rate of completed suicides of 0.16–0.32% and caution of an elevated rate particularly following thalamic and globus pallidus interna surgery [10]. However, it should be emphasized that given the rare nature of suicides, smaller studies should be cautiously interpreted and are likely influenced by reporting bias. The rate of suicide attempts in this PD cohort may also be under-reported or represent a greater proportion of successful attempts. The rates of completed suicides may now be lower given increased awareness of the issue and changes in preoperative and postoperative practices.

The rate of suicide is commonly elevated following any life-altering surgery. For instance, the suicide rate following epilepsy surgery is 1% or 31 times higher than the general population [11]. The baseline rate of suicide in epilepsy is eight times higher than the general population which contrasts with the low baseline rate in PD [12].

The study of associated behaviours allows us to address potentially modifiable risk factors. In a study of 200 STN DBS PD patients, 1/200 (1%) had completed and 4/200 (2%) had attempted suicides [13]. Suicidal behaviours were associated with postoperative depression and impaired impulse regulation in this study. Similarly, the multicentre study compared 27 attempted suicides and 9 completed suicides with 70 STN DBS controls selected from the patients who underwent surgery immediately prior to and immediately following the identified case at the same centre [4]. Postoperative depression ($P<0.001$), being single ($P=0.007$) and a history of impulse control disorders or compulsive medication use ($P=0.005$) were independent associated factors accounting for 51% of the variance of attempted suicide risk. Other associated factors included being younger, younger PD onset and previous suicide attempt ($P<0.05$). A trend was observed associated with greater changes in dopaminergic medications ($P=0.05$). Overall, postoperative depression was the primary factor associated with both attempted and completed suicides after stringent correction for multiple comparisons. See Table 28.1 for a summary of factors associated with STN DBS for PD.

Postoperative depression following STN DBS has been associated with significant decreases in dopaminergic medications [14], a prior history of depression [15], significant psychosocial postoperative changes [16], and has also been linked to serotonergic modulation in an animal model [17]. Possible effects of STN stimulation, dopaminergic medications and the interaction between the two may also play a role in impulsivity.

Table 28.1 Summary of factors associated with attempted suicides following STN DBS for Parkinson's disease

	Probably associated ($P<0.01$)	Possibly associated ($P<0.05$)	Not associated ($P>0.05$)	Unknown
Preoperative ndividual factors	Hx of impulse control disorders or compulsive medication use	Previous attempt Younger age Younger Parkinson's disease onset	Gender Preoperative cognitive status	Family history of suicide
Postoperative state	Postoperative depression[a] Postoperative apathy		Motor efficacy Stimulation parameters Postoperative cognitive changes	Interaction of stimulation with impulse control
Medication		Percent LEDD decrease**		Dopaminergic withdrawal state
Psychosocial factors	Single		Country-specific suicide rates	Expectations Identity changes Relationship changes Supports other stressors

**$P=0.05$

[a]Postoperative depression remains significant following Bonferroni correction (Brain 2008;131:2720–8. Used by permission, Oxford University Press)

Conclusion

Suicidal ideation and suicide attempts are common in PD. However, completed suicides appear to occur much less frequently than expected given the association with comorbidities commonly linked to increased suicide risk. Suicidal behaviours in PD demonstrate a clear association with depression, thus highlighting the necessity to screen for and treat depressive symptoms along with actively screening for suicidal ideation in depressed patients. Other potential associated factors for suicide attempts include psychosis, impulse control disorders, younger age, and anxiety disorders. The postoperative state following STN DBS poses an increased risk of suicide. Preoperative assessment should include a psychosocial assessment focusing on potential risk factors for suicide attempts including being single and a previous history of impulse control disorders. Other possible factors include being younger, younger age of PD onset and a history of previous attempts. Patients at higher risk should be counselled preoperatively along with family involvement and active postoperative follow-up. Preoperative psychotropic medications should be maintained to avoid withdrawal states. Dopaminergic medication titration should be instituted with care given its possible association with suicidal behaviours and potential liability with postoperative depression.

Patients with suicidal ideation or attempts should be referred to a psychiatrist. Issues of safety should be considered if a suicide attempt occurs including the need for certification, hospitalization and observation. The index of suspicion for postoperative depression should be high and those with depression carefully monitored and treated. The aetiology of any postoperative depressive or apathy symptoms should be considered and may require resumption of the dopaminergic medication if related to the withdrawal state, or possibly resumption of a dopamine agonist or an antidepressant with noradrenergic properties. A time-limited confusional state may require careful observation or possibly a low dose of an atypical neuroleptic. Hypomania can be managed with observation, if time limited and mild, or may require changes in dopaminergic medications or stimulation parameters.

Psychosocial issues should be addressed including changes in relationships or identity and may require referrals for counselling or support. Suicidal outcomes in PD represent a potentially modifiable form of mortality. Further studies to address modifiable risk factors would be useful for clinical management.

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