Movement Disorder Emergencies

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Robert L. Rodnitzky and Christopher L. Groth

Introduction

Movement disorders can be the source of significant occupational, social, and functional disability. In most circumstances the progression of these disabilities is gradual, but there are circumstances when onset is acute or progression of a known movement disorders is unexpectedly rapid. These sudden appearances or worsening of abnormal involuntary movements can be so severe as to be frightening to the patient and their family and disabling, or even fatal, if left untreated. This chapter reviews movement disorder syndromes that rise to this level of concern and that require an accurate diagnosis that will allow appropriate therapy that is sufficient to allay anxiety and prevent unnecessary morbidity.

Acute Parkinsonism

The sudden or subacute onset of significant parkinsonism, especially akinesia, is potentially very frightening to the affected patient and his/her family members. Of more concern is the potential for severe untreated akinesia to lead to serious complications, such as pulmonary embolism, aspiration, and pneumonia. Seven general etiologic categories of acute parkinsonism can be identified, and the likelihood of arriving at the correct clinical diagnosis can be greatly enhanced by systematically considering which one or combination of these etiologies may be at play in a given acutely parkinsonian patient. The seven etiologic categories of acute parkinsonism are as follows: (1) structural, (2) toxic, (3) impaired levodopa absorption, (4) iatrogenic, (5) infectious, (6) surgery, and (7) genetic.

Structural

The two most common structural causes of acute parkinsonism are stroke and hydrocephalus, although neither is extremely common in an absolute sense. Parkinsonism due to acute hydrocephalus is to be distinguished from the gradually evolving form of parkinsonism that can occur in patients with chronic hydrocephalus, especially normal pressure hydrocephalus. Acute parkinsonism can occur simultaneously with the development of acute hydrocephalus [1] but can also occur after shunt placement [2, 3] or shunt revision [4] in patients with long-standing hydrocephalus. The rapid onset of parkinsonism in acute hydrocephalus is probably due to direct compression or shearing force on the substantia nigra secondary to changing pressure dynamics of the rapidly enlarging ventricles [5]. Parkinsonism

R. L. Rodnitzky (✉) · C. L. Groth
Neurology Department, Roy J. and Lucille A. Carver College of Medicine, University of Iowa, Iowa City, IA, USA
e-mail: robert-rodnitzky@uiowa.edu; christopher-groth@uiowa.edu

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due to shunt revision or placement is due to rapidly shrinking ventricles with subsequent midbrain distortion [2]. The simultaneous occurrence of other signs of rostral midbrain dysfunction, along with parkinsonism, after shunting supports the notion that the postshunting findings are all due to mechanical distortion of the midbrain [6]. In patients whose akinesia appears to be related to acute hydrocephalus with acutely enlarging ventricles, shunting is indicated and could be lifesaving. Parkinsonism might be improved by this intervention or, as mentioned above, could be exacerbated. In parkinsonism related to acute hydrocephalus, persistent hydrocephalus, or shunt revision, levodopa therapy is usually effective both in the short term and over the long term [2, 4–6].

Acute cerebral infarction involving the striatum or the substantia nigra is another structural insult that can result in acute parkinsonism. The common term "vascular parkinsonism," as used today, refers to the gradual appearance of parkinsonian features, usually a parkinsonian gait, due to diffuse, bihemisphere small vessel ischemic disease. Large artery infarctions, on the other hand, produce unilateral or bilateral parkinsonism over a matter of days to months. When a striatal infarction is associated with significant hemiparesis, unilateral parkinsonism typically evolves once the hemiparesis begins to improve [7]. Striatal infarctions are relatively common, but only a small percentage result in parkinsonism [8]. Parkinsonism can also develop after infarction of the substantia nigra [9]. Infarction of the pedunculopontine nuclei in the brainstem can cause acute onset of gait freezing, similar to that seen in Parkinson's disease [10]. Therapy of infarction-related parkinsonism with levodopa is most effective in those cases where the pathology is in, or close to, the substantia nigra [11]. Somewhat paradoxically, stroke involving the tuberothalamic artery can improve parkinsonian tremor, presumably through damage to the ventrolateral thalamic nucleus, similar to the lesion of a therapeutic thalamotomy [12], or deep brain stimulation of this structure. Acute worsening of parkinsonism of any cause is sometimes mistakenly diagnosed as a stroke and in those instances has even been mistakenly treated with intravenous thrombolytic therapy [201].

Toxic

A variety of nonindustrial toxins can also cause acute parkinsonism. The more common toxic exposures that might present to a community emergency department are discussed here. Organophosphate insecticides, either through inadvertent ingestion on food or exposure in an agricultural setting, can cause acute, reversible parkinsonism. In these cases, treatment with levodopa [13] has been less effective than amantadine [14] and dopamine agonists [15]. Carbon monoxide (CO) poisoning results in subacute parkinsonism. In a large series of 242 CO poisoning cases, 10% of the individuals affected developed parkinsonism with a latency of 2–26 weeks (median 4 weeks) after the acute exposure [16]. Imaging of the brain in these patients reveals evidence of bilateral pallidal necrosis with symmetric hypodensity on CT scan and high signal intensity on FLAIR and T2-weighted MRI sequences [17]. There is, however, not a complete correlation between the appearance of pallidal necrosis on CT or MRI and parkinsonism in CO poisoning. Of 17 patients with CO-related parkinsonism in one series, only 47% had abnormal CT scans [16]. In this series, levodopa and anticholinergic drugs were not effective, but 81% of affected individuals recovered gradually over a 6-month period of time. Initial hyperbaric oxygen therapy of CO poisoning in the acute phase may reduce subsequent neurologic sequelae, but controlled studies of this therapeutic approach are still lacking [18]. Long-term exposure to ambient CO in the form of air pollution can also increase the risk of Parkinson's disease [202]. Purposeful or accidental ingestion of ethylene glycol or methanol can result in acute parkinsonian akinesia, often associated with hemorrhagic necrosis of the basal ganglia [19]. Levodopa therapy can improve the rigidity and bradykinesia associated with these two toxic exposures [19].

Impaired Levodopa Absorption

Gastric emptying is commonly slightly delayed in PD patients, but superimposed gastrointestinal disorders can further delay passage of levodopa through the pylorus resulting in a significant decrease in levodopa absorption in its main absorptive site in the jejunum. The consequence of such an acute or subacute decrease in levodopa absorption is an acute increase in parkinsonian symptoms, including akinesia due to delayed-on or no-on [203]. In these cases, identification and treatment of the comorbid gastrointestinal disorder is the first therapeutic measure that should be taken. In a review of 146 non-parkinsonian patients with acute gastroparesis, the 3 most common associated clinical features were abdominal pain, depression on antidepressant therapy, and gastroesophageal reflux [20]. Should recent onset or worsening of any of these comorbid conditions be present in the acutely akinetic PD patient, gastroparesis with resultant impaired levodopa absorption should be strongly suspected. Gastroparesis in PD patients has also been reported in the presence of acute duodenal ulcer and intestinal volvulus [21]. In addition to treating the primary medical cause of delayed gastric emptying, prokinetic agents can be useful to reduce gastric stasis. Domperidone, a peripheral dopamine receptor antagonist, is useful for this purpose but is not yet approved in the USA. Administering levodopa with a carbonated and/or caffeinated beverage may enhance passage of levodopa through the stomach and enhance absorption. Replacing an oral dopamine agonist with a transdermal agent, such as rotigotine [22], would be useful. For very severe absorptive dysfunction with significant akinesia such as after gastrointestinal surgery, subcutaneous apomorphine may prove useful [23], although in this circumstance, some patients become relatively refractory to all dopaminergic agents, including apomorphine [21]. In some PD patients, failure of the pyloric sphincter to relax is the cause of delayed gastric emptying and resultant delayed intestinal absorption of levodopa. A preliminary report of botulinum injection of this sphincter suggested that this therapy may result in several months of symptomatic improvement in reliable "on" responses to each levodopa dosage [204].

Iatrogenic

Extrapontine myelinolysis, typically due to very rapid correction of hyponatremia, can include striatal involvement and an attendant akinetic rigid state which may respond to levodopa therapy [205]. The inadvertent or ill-advised use of drugs that are dopamine receptor blocking agents (DRBA) can rapidly result in a severely exacerbated parkinsonian state in PD patients. Occasionally, non-PD patients or PD patients not yet known to have clinically apparent PD can be rendered acutely or subacutely akinetic by the administration of DRBAs, particularly if used at a high dosage. Among DRBAs, the typical antipsychotic agents, such as haloperidol, have the greatest potential to cause significant akinesia, but other classes of dopamine antagonists, including most of the atypical antipsychotic agents and the DRBA antiemetic drugs, such as prochlorperazine and metoclopramide, have this potential as well [24]. The most serious iatrogenic forms of acute akinesia are neuroleptic malignant syndrome (NMS) and the closely related condition known as parkinsonism-hyperpyrexia syndrome (PHS), as these conditions, left untreated, can result in major disability and are potentially fatal. Serotonin syndrome shares some clinical features with NMS, including some parkinsonian phenomena.

Neuroleptic malignant syndrome is an acute reaction that can occur either as a result of treatment with a dopamine-blocking agent [25] or after rapid withdrawal or reduction of one or more dopaminergic drugs in a Parkinson's disease patient, in which case it is referred to as parkinsonism-hyperpyrexia syndrome (PHS) [26]. Although discontinuance of any Parkinson's drug can result in PHS, stopping levodopa is the most common cause. PHS can also occur in other forms of parkinsonism, such as progressive supranuclear palsy or multiple system atrophy (MSA) [27]. The onset of NMS is usually within

a month after beginning DRBA therapy or an increase in dosage, but as many as 16% of cases of NMS begin within the first 24 h of therapy and 30% by 2 days [25]. PHS developing in Parkinson's disease patients usually presents shortly after the discontinuance or reduction of a dopaminergic medication [26]. In one series, PHS occurred at a mean of 93 h after medication withdrawal [28]. All neuroleptic drugs can cause NMS, as can all atypical antipsychotic agents [29–32]. The overall incidence of NMS appears to be lower in patients receiving atypical antipsychotic agents, and at least in the case of clozapine [33], olanzapine [34], and risperidone [31], a milder syndrome with less prominent fever or rigidity [35] and less elevation of creatinine kinase may develop. However, in one recent review of the literature [36], 68 reported cases of NMS were related to atypical antipsychotics, and in this survey, clozapine was associated with NMS as often as other atypical agents, suggesting that low extrapyramidal syndrome-inducing potential does not necessarily reduce the occurrence of NMS. Aside from the possible lower incidence of NMS associated with lower-potency neuroleptic agents, one study suggested that NMS mortality may also be lower in cases associated with these less potent agents [206]. Antiemetic DRBAs, such as metoclopramide and prochlorperazine, can also result in NMS [37]. Antidepressants, including tricyclics [38], selective serotonin reuptake inhibitors [39], and lithium [40], either alone or in combination, have all been reported to cause a syndrome resembling NMS, but such cases are uncommon, and often the clinical presentation is atypical or indistinguishable from serotonin syndrome. NMS is more likely to occur in young patients, in males, and in patients who are agitated and dehydrated, who have received large rapidly administered dosages of the offending drug, or who have had previous electroconvulsive therapy [41, 42]. Elevation of serum creatine kinase during a previous psychotic episode unassociated with NMS may be a risk factor for NMS developing during future administration of DRBAs [43].

In addition to dehydration, risk factors for PHS include several characteristics of the underlying parkinsonism. Thus, more severe parkinsonian symptoms, longer disease duration, a history of "wearing off," and a history of an early age of parkinsonism onset are risk factures for PHS [44]. Serious PHS has occurred after perioperative withdrawal of antiparkinsonian medications [45]. PHS has also been reported in Parkinson's patients who abruptly discontinued fava bean ingestion, which was being taken for its levodopa content [46]. The syndrome has also occurred in Parkinson's patients during extreme periods of ambient heat even in the absence of medication withdrawal [47]. Acute akinesia related to levodopa resistance after a surgical procedure resembles PHS [21].

The cardinal clinical manifestations of NMS and PHS are virtually identical and include fever, muscular rigidity, autonomic instability, and confusion or alteration in consciousness [37]. Among autonomic symptoms, tachypnea, tachycardia, labile blood pressure, diaphoresis, and urinary retention are most common [48]. The most frequent movement disorder in NMS is rigidity, which is often preponderantly axial. Other movement disorders are possible, including dystonia and chorea. Fever is typically at least 38 °C and often higher. Creatine kinase levels are usually above 2000 IU/L and often in the range of 15,000–20,000 IU/L [49, 50]. The white blood cell count is often elevated, but usually without a left shift. Milder or atypical forms of the syndrome without one of the classic features, such as muscle rigidity [51] or fever [31, 52], may exist. Cases without rigidity may simply present as a fever of unknown origin [53]. PHS is especially likely to present with fever as the first symptom [27]. An international expert consensus (IEC) panel created a diagnostic score based on a weighted list of these symptoms [207], and the resultant use of this score was shown to have 91% specificity for the diagnosis of NMS [208].

The treatment of NMS and PHS should be considered emergent, especially in cases in which all of the clinical criteria are fulfilled or in patients with extremely high fever and rhabdomyolysis. In these cases, there can be serious morbidity and occasionally a fatal outcome. The most common complications affecting the prognosis are cardiac

failure, cerebellar degeneration, respiratory disturbances, and renal failure, the latter of which can be associated with disseminated intravascular coagulation and rhabdomyolysis [54, 55]. The first therapeutic measure that must be taken is discontinuing the offending neuroleptic or another causative dopamine-blocking drug, or in Parkinson's patients with PHS, replacing a recently withdrawn or altered dopaminergic drug. Supportive measures, such as hydration and lowering of fever, must be started early. Anticholinergic drugs should be discontinued in Parkinson's disease patients, since they inhibit heat dissipation. Tapering anticholinergics is advised rather than abrupt cessation to avoid rebound rigidity. Respiratory support may be needed because of severe rigidity of respiratory muscles. Cardiac arrhythmias and blood pressure abnormalities must be treated [56]. In patients with dangerously high body temperature, antipyretics such as aspirin are usually ineffective, but a noninvasive body surface cooling device can be very useful to reverse hyperthermia [57].

The specific first-line medical therapies for NMS include bromocriptine, orally or by nasogastric tube, dantrolene, and amantadine [37]. Bromocriptine is administered in an initial dosage of 2.5 mg every 4 h, being careful to observe for induction or worsening of hypotension. The dose can be increased daily, if required, to as much as 50 mg per day. An alternative dopamine agonist is subcutaneous apomorphine, which can produce a rapid clinical response [58, 59]. Dantrolene can be administered intravenously, if needed, in a dosage of 1–10 mg/kg/day in three divided dosages. Most patients will require dosages in the lower part of this range [60]. Dantrolene is a good choice for initial therapy alone or in combination with bromocriptine when there is severe rigidity and rhabdomyolysis. Carbamazepine is a possible second-line therapy [61]. None of these medical therapies have been proven to be effective by prospective studies but rather derive their reputation for efficacy from case reports and small series culled from the literature. However, a large retrospective review of 734 cases of NMS concluded that treatment with bromocriptine, dantrolene, or amantadine reduced mortality more than supportive care alone [62]. For NMS cases that are refractory to medical therapy, electroconvulsive therapy has been found to be useful in both adults and children [63], as well as in PHS [64].

Recovery from NMS typically occurs over a 1- to 2-week period, but resolution after recovery from the acute phase may be delayed in those having received long-acting depot neuroleptics. Some sequelae, especially neuropsychiatric symptoms, can persist for weeks or months [65]. Pulse methylprednisolone therapy has been reported to significantly shorten the recovery phase in patients with Parkinson's disease [66]. Rechallenge with neuroleptics after recovery results in reoccurrence of NMS in less the 15% of cases. To minimize the likelihood of reoccurrence, rechallenge should be delayed for at least 2 weeks after recovery, and a lower-potency neuroleptic agent or atypical antipsychotic drug should be used.

Serotonin syndrome (*SS*) has become increasingly more common, reflecting the increased number and increased use of serotonergic medications. This pattern of increased use also includes the pediatric population. In a survey of North Carolina Medicaid prescriptions, the prevalence of prescriptions for SSRIs in the 6–14-year-old age group increased sevenfold from 0.2% to 1.5% between 1992 and 1998 [67]. This syndrome, like NMS, includes involuntary abnormal movements, especially myoclonus and tremor, and as such is considered a movement disorder emergency. As the name implies, serotonin syndrome occurs in patients receiving one or more serotonergic drugs. There are two commonly utilized diagnostic criteria for serotonin syndrome, the Sternbach Criteria [68] and the Hunter Serotonin Toxicity Criteria [69]. Using the Sternbach Criteria, there are three requirements:

(a) After the addition of or increase in dosage of a serotonergic agent, at least three of the following clinical features must be present: agitation, mental status changes, myoclonus, hyperreflexia, diaphoresis, shivering, tremor, diarrhea, incoordination, and fever.

(b) Other etiologic causes (infectious, metabolic, substance abuse, or withdrawal) have been ruled out.
(c) An antipsychotic has not been started or increased in dosage before the onset of the symptoms.

To fulfill the Hunter Serotonin Toxicity Criteria, the patient must have taken a serotonergic agent and meet one of the following requirements:

(a) Exhibit spontaneous clonus
(b) Have inducible clonus plus agitation or diaphoresis
(c) Exhibit ocular clonus plus agitation or diaphoresis
(d) Have hypertonia
(e) Have a temperature greater than 38 °C plus ocular clonus or inducible clonus

Both sets of criteria are useful, but a comparison of their utility in patients with an established serotonin syndrome diagnosis suggested that the Hunter Criteria was more sensitive than the Sternbach Criteria (84% vs. 75%) and minimally more specific (97% vs. 96%) [69].

The clinical signs of serotonin syndrome resemble those of NMS, and in many cases the two syndromes appear to overlap in the same patient [70]. For determining proper therapy, distinguishing the two syndromes from one another is very important, since their respective medical therapies are distinct. Both syndromes include mental status changes, fever, autonomic dysfunction, and a variety of movement disorders, but the relative severity of these signs in the two syndromes can be a differentiating factor. Compared to NMS, in serotonin syndrome, fever, elevation of creatine kinase, and alteration in sensorium are generally less prominent, while myoclonus, gastrointestinal symptoms, a shivering-type tremor, hyperreflexia, clonus, and pupillary dilatation are more prominent. Among these differences, hyperreflexia with clonus, the presence of otherwise unexplained myoclonus, and a rapid onset (within hours of the offending pharmacologic event) are among the most useful clues that the patient is suffering from serotonin syndrome rather than NMS. A comparison of common features of serotonin syndrome, NMS, and features that most accurately discriminate the two syndromes from one another is shown in Table 14.1.

Misdiagnosis, especially early in the course of serotonin syndrome, is common. For example, the presence of hyperreflexia and clonus can lead to the false impression of a pyramidal syndrome, and the presence of diarrhea plus fever can lead to the incorrect diagnosis of an infectious gastroenteritis [71].

The offending therapies that have the potential to contribute to serotonin syndrome fall into one of the following seven pharmacologic categories (Table 14.2). Although serotonin syndrome is thought to result from stimulation of 5-HT_{1A} and 5-HT_{2A} receptors [73], some drugs that stimulate other classes of receptors, such as most triptan agents, probably can contribute to the development of serotonin syndrome.

Although any of these drugs and treatments taken alone can cause serotonin syndrome, the risk is greatest when two or more serotonergic therapies are administered simultaneously [74, 75]. The greatest risk is in those receiving a nonselective MAO inhibitor along with a potent serotonin reuptake inhibitor [76]. Higher dosages of these medications also increase the risk and the

Table 14.1 Serotonin syndrome. Comparison with neuroleptic malignant syndrome

	SS	NMS
Mental status change	+	++
Fever	++	+++
Tachypnea/tachycardia	++	+++
Diarrhea	+++	0
Diaphoresis	++	+++
Rigidity/bradykinesia	0	+++[a]
Stupor	+	+++[a]
Tremor	+++[b]	+
Shivering	+++[b]	0
Myoclonus	+++[b]	+
Hyperreflexia/clonus	+++[b]	0
Elevated CK	+	+++[a]
Pupillary dilation	++	0
Acute onset	+++[b]	+

[a]Important differentiating feature of neuroleptic malignant syndrome (NMS)
[b]Important differentiating feature of serotonin syndrome (SS)

Table 14.2 Agents that can cause serotonin syndrome

1. Inhibitors of serotonin reuptake: all of the SSRIs, SNRIs, several tricyclic antidepressants, dextromethorphan, amphetamine, cocaine, MDMA (ecstasy), St. John's wort, lamotrigine
2. Inhibitors of serotonin metabolism: selective MAO-B inhibitors (selegiline or rasagiline), non-selective MAO inhibitor antidepressants, non-selective MAO inhibitor antibiotic (linezolid), methylene blue
3. Agents that increase serotonin synthesis: L-tryptophan
4. Enhancers of serotonin release: amphetamines, cocaine, fenfluramine, MDMA (ecstasy)
5. Serotonin agonists: buspirone, triptans, ergotamines
6. Nonspecific enhancers of serotonin activity: lithium, electroconvulsive therapy
7. Serotonergic effect, mechanism is uncertain: second-generation antipsychotic agents – quetiapine, olanzapine, clozapine, risperidone, aripiprazole

Adapted from Lane and Baldwin [72]

severity of the syndrome. For example, several cases of serotonin syndrome in children have resulted from accidental ingestion of a large and pharmacologically excessive amount of a parent's medication [77, 78]. Methylenedioxymethamphetamine (MDMA), also known as "ecstasy," is an amphetamine-derived street drug that is commonly used by high school and college students, especially while attending drug-inspired dance gatherings known as "raves" [79] during which there is a high ambient temperature and vigorous physical activity leading to dehydration. This drug has serotonergic properties and either alone or in combination with other serotonergic drugs can produce a syndrome with features of serotonin syndrome [70]. Fatalities have occurred due to MDMA-related serotonin syndrome, often associated with delayed diagnosis in part due to unawareness of the history of illicit drug ingestion. Purposefully combining MDMA with an MAO inhibitor to enhance its effect has proven especially lethal [80]. In the UK, 605 ecstasy-related deaths were reported in a 7-year period [81]. Generally, what contributes to a potential fatal outcome in serotonin syndrome is the development of rhabdomyolysis, myoglobinemia, and renal failure. Acute myocardial infarction has also occurred in the setting of serotonin syndrome [82].

Of interest to neurologists are the risks associated with some serotonin-enhancing drugs that are commonly used in neurologic practice, including antimigraine agents, such as triptans and dihydroergotamine, and the selective MAO-B inhibitors, selegiline and rasagiline, used in Parkinson's disease. Serotonin syndrome was reported in only 11 patients receiving a triptan alone in the FDA adverse event reporting system [83]. However, triptans taken along with other serotonergic agents, especially the commonly used SSRIs, have been reported to cause the serotonin syndrome [84]. In 2006, the FDA issued an alert concerning the potential of serotonin syndrome in patients taking triptans and SSRIs or SNRIs, based on 29 reported cases. Subsequent analysis of these cases has suggested that the risk is very small, and in fact not all of the FDA cases may have met the diagnostic criteria for serotonin syndrome [85, 86]. In regard to selegiline, there is concern that this agent could cause the serotonin syndrome in patients also receiving other serotonergic drugs. Despite this concern, there are very few well-documented cases of this interaction, and a similar level of risk seems likely for the newer selective, irreversible MAO-B inhibitor, rasagiline. Recently, it has become apparent that the widely used antibiotic linezolid is an MAO inhibitor that can cause serotonin syndrome when used along with other serotonergic drugs [87]. Another widely used drug with surprising MAO-inhibiting properties is methylene blue which is typically administered after cardiac surgery to combat vasospastic hypotension. Administered along with a serotonergic agent such as an SSRI, methylene blue can result in severe serotonin syndrome, sometimes referred to as "blue coma" [88].

Prevention is very important in the serotonin syndrome. To avoid an interaction leading to serotonin syndrome, there should be a period of at least 2 weeks between stopping an SSRI and starting an MAO inhibitor and approximately 5 weeks after discontinuance of fluoxetine, which has a much longer half-life. Treatment of the acute serotonin syndrome begins with the discontinuation of all serotonergic medications. When the syndrome is relatively mild, consisting

only of hyperreflexia, clonus, tachycardia, and anxiety, this strategy alone will often result in resolution of symptoms within 24 h. When symptoms are particularly resistant or severe, consisting of any or all of severe hyperthermia, autonomic instability, rigidity, rhabdomyolysis, and respiratory distress, direct medical therapy should be begun with cyproheptadine. The most commonly recommended dosage plan is 12 mg initially, crushed and by nasogastric tube if necessary, followed by 2 mg every 2 hours while symptoms persist. Once stabilization is achieved, the regimen can be changed to a maintenance dose of 8 mg every 6 hours until symptoms remit [89]. Chlorpromazine has been suggested as a therapy for serotonin syndrome, but its use depends on absolute certainty that the patient does not have NMS instead, which might be worsened by this therapeutic approach [72]. Rehydration and control of fever are important in the presence of severe hyperthermia. A noninvasive cooling device can be used to lower body temperature similar to its use in NMS [57]. Antipyretic agents, such as aspirin and acetaminophen, are not effective for lowering fever since the fever is not of hypothalamic origin in this condition. In the presence of severe muscle rigidity, dantrolene can be used. In patients with such severe autonomic, respiratory and organ failure symptoms, treatment in an intensive care unit is required.

Drug-induced parkinsonism Administration of dopamine-blocking drugs, including typical antipsychotic agents, atypical antipsychotic agents, and dopamine-blocking antiemetics, can all cause rapid-onset parkinsonism, especially when administered in high dosages [24]. A large number of other drugs that are not primary dopamine-blocking agents, such as selective serotonin uptake inhibitors, valproic acid, amiodarone, and certain chemotherapeutic agents, rarely cause severe de novo parkinsonism and can also occasionally significantly exacerbate parkinsonian symptoms in a known PD patient [90]. The calcium channel blockers, cinnarizine and flunarizine, neither marketed in the USA, can cause parkinsonism due to their significant dopamine-blocking capacity. VMAT2 inhibitors such as tetrabenazine and valbenazine [209], especially the former, can cause parkinsonism. Drug-induced parkinsonism can resemble ordinary Parkinson's disease, although there is a tendency for less tremor and more symmetry in the drug-induced syndrome. Some patients with drug-induced parkinsonism actually have Parkinson's disease that has been uncovered by the administration of the offending drug. These patients may be even more susceptible to drugs that are less obvious dopamine blockers such as selective serotonin uptake inhibitors [91]. SPECT imaging of the dopamine transporter can be used to help determine whether a drug has caused transient parkinsonism or has uncovered latent Parkinson's disease [91]. The initial treatment of drug-induced parkinsonism is to discontinue the offending drug, if medically feasible. Discontinuance may not always be possible in the case of effective antipsychotic agents used to treat a serious psychiatric condition. Even with discontinuance, improvement in drug-induced parkinsonism cannot be expected for days to weeks, occasionally several months, and even, less occasionally, 2 years or more. Once the offending drug has been discontinued, immediate medical therapy can begin with anticholinergic agents or amantadine, although there is uneven evidence that these agents have a major effect. If these are not effective, then a course of levodopa can be considered with appropriate caution regarding the exacerbation of psychosis that this treatment can cause. Identifying patients who might respond to levodopa is greatly enhanced by utilizing a SPECT scan, since most such responders are found to have at least some small component of idiopathic Parkinson's disease [92].

Infection

Any intermittent infection, whether viral or bacterial, can exacerbate ongoing parkinsonian symptoms, especially in moderately or severely advanced PD patients. A recent survey of PD patients admitted to the hospital confirmed that infection was the most common reason for admission, and among infections, pneumonia and urinary tract infection were most common [93].

Occult infection, especially pneumonia or urinary tract infection, should always be considered in PD patients presenting with unexplained worsening of symptoms.

Acute or subacute parkinsonism has been reported as a complication of several different forms of viral encephalitis including encephalitis due to herpes simplex virus-1, West Nile virus, Coxsackieviruses, St. Louis encephalitis virus, and HIV [94–96]. A major clue to this etiology of acute parkinsonism is the recent history or concurrent presence of seizures, fever, or extreme somnolence. Standard antiparkinsonian drugs, such as trihexyphenidyl and carbidopa/levodopa, may improve parkinsonian symptoms during the acute phase of a viral illness [95]. Encephalitis lethargica, which occurred as a pandemic in the early twentieth century, is a well-accepted cause of parkinsonism and, although rare, still does occur [97]. The presence of antineuronal antibodies and the absence of positive viral PCR in parkinsonian patients with encephalitis lethargica suggest that parkinsonism is due to an autoimmune condition rather than an acute viral illness and may require immunomodulatory therapy [98]. Another form of infection that can lead to autoimmune akinesia is parkinsonism after streptococcal infection with associated anti-basal ganglia antibodies [99].

The treatment of infection-related forms of parkinsonism is to first treat the underlying viral or bacterial infection with appropriate antiviral agents or antibiotics. For the parkinsonian features themselves, standard antiparkinsonian therapy such as levodopa is often effective [95, 100]. Those infections associated with anti-basal ganglia antibodies may respond to immunomodulatory therapy, such as corticosteroids [99].

Surgery

Parkinson's disease patients undergoing major surgery commonly note worsening of their symptoms in the postoperative period. Most often, the degree of worsening is mild or moderate, but occasionally it can be severe and associated with profound akinesia [21]. While any type of surgery can have this effect, joint surgery is one of the more common precipitants of postoperative PD worsening. This syndrome appears to be independent of abnormalities of levodopa absorption and, in its most severe form, is associated with refractoriness to all dopaminergic agents [21]. Despite concern for refractoriness to dopaminergic agents, therapy with oral levodopa or nonoral dopaminergic agents, such as subcutaneous apomorphine or transdermal rotigotine, should be attempted if either is available. Should there be no benefit from these agents, supportive care for the immobilized patient is paramount until responsiveness to medication resumes, often in 2–7 days. It is wise to foreworn PD patients undergoing elective surgery that some worsening is likely to occur in the postoperative period in order to minimize personal and family anxiety over this occurrence.

Another potential cause of acute akinesia in the postoperative period is enteral nutrition [101]. This phenomenon is largely the result of persistent interference with levodopa absorption by the high-protein content of continuous tube feedings. It can be combated by changing from continuous to intermittent bolus enteral feedings and staging levodopa dosages in between and temporally distant from boluses of tube feedings.

For PD patients undergoing planned or elective operations, the surgical team should be forewarned to avoid administering dopamine-blocking antiemetics or antipsychotic drugs in the postoperative period, if at all possible, since these agents can further exacerbate postoperative parkinsonism. In place of the dopamine-blocking anti-nausea drugs such as droperidol, prochlorperazine, metoclopramide, or domperidone (not available in the USA), trimethobenzamide should be used instead.

Acute Genetic Parkinsonism

There is one form of degenerative parkinsonism that typically has an acute or subacute onset. Rapid-onset dystonia-parkinsonism (RDP) is an autosomal dominant condition related to a mutation in the *ATP1A3* gene in in which both dysto-

nia and parkinsonism develop as rapidly as over a few minutes to as long as 30 days [102]. In this condition, parkinsonian symptoms, such as bradykinesia and hypophonia, often, but not invariably, pursue a rostral-caudal pattern of progression. RDP can be differentiated from idiopathic PD by its sudden onset, its initial rapid progression, the rostral-caudal progression, the association with dystonia, and the absence of tremor. Family history, if present, is useful, but the autosomal dominant gene in this condition displays variable penetrance. Another somewhat helpful differentiating feature from PD is that the great majority of patients with RDP are under the age of 30, and in fact, almost half are under the age of 20 [102]. A variety of triggers leading to the initial clinical presentation have been reported in this condition including running, stress, alcohol consumption, fever, trauma, and psychiatric events, the latter sometimes falsely raising the possibility of psychogenic parkinsonism or autoimmune encephalitis. Typically, these patients' parkinsonian symptoms are refractory to dopaminergic therapy. Atypical forms with slower progression and a less apparent rostral-caudal pattern of onset are not uncommon [103]. While pharmacologic therapy of this form of acute parkinsonism is not very effective, patients can be reassured that in the majority of cases most of the symptoms are minimally progressive after the initial presentation, with only a small number of patients experiencing a second later episode of abrupt worsening.

Severe or Acute Levodopa-Induced Dyskinesias

Parkinson's disease patients are susceptible to severe medication-induced dyskinesias that can be choreic, dystonic, or both. These involuntary movements are usually a complication of dopaminergic medications and can be further exacerbated by levodopa enhancing preparations such as COMT inhibitors or MAO inhibitors. Dyskinesias related to levodopa and/or dopamine agonist medications typically remit spontaneously given sufficient time, but if the involuntary movements are of extremely high amplitude or involve many body parts simultaneously, they can prove to be frightening and/or exhausting to the patient and to family members, resulting in an emergency department visit. For example, these movements can be sufficiently prolonged and severe to result in rhabdomyolysis and a significant elevation of plasma creatine kinase [104]. Rarely, involvement of the respiratory muscles can lead to a patient's perception of respiratory distress.

Under these circumstances, the causative medication(s) should be temporarily suspended with a plan to reintroduce them at a slightly lower dosage once the dyskinesias have remitted. It is probably unwise to entirely discontinue chronically administered dopaminergic medicines for any sustained period of time for fear of inducing PHS and to avoid producing severe prolonged akinesia. If there is not an immediate reduction in the severity of the dyskinetic movements, then medical therapy will be required in the emergency room setting. Benzodiazepine preparations such as diazepam, lorazepam, or clonazepam can be very helpful, both in relieving the severity of the dyskinesias and diminishing the associated anxiety that accompany them. Often a parenteral route of administration provides more rapid relief. If swallowing is intact and the patient has already ingested a controlled release levodopa preparation, administration of a high-protein snack can be attempted in the hope of limiting further gastrointestinal absorption of levodopa and inhibiting its passage across the blood-brain barrier through competition for the active transport system for large neutral amino acids [105]. If it is necessary to restart dopaminergic medications at the same dosage to control parkinsonian symptoms, strategies to reduce the potential for recurrent severe dyskinesias should be employed including adding amantadine for its antidyskinesia effect and replacing levodopa partially or completely with a dopamine agonist, since this class of agents has a lower potential to cause dyskinesias.

Acute Behavioral Change in Parkinsonism: Psychosis, Delirium, and Panic Attack

A variety of behavioral abnormalities can occur in PD. The most common, dementia, is gradual in evolution and is not typically viewed as an emergency, but many other behaviors can appear suddenly, especially in the chronically demented PD patient. These conditions can result in emergency room visits, emergency inpatient consultations, or involvement by security or law enforcement officials.

Psychosis

Psychosis in PD commonly results in visual hallucinations, delusional thoughts, and illusory phenomena. Auditory and tactile hallucinations can occur but are much less common. Psychosis typically appears in PD patients with cognitive impairment but can also occasionally be seen in nondemented patients. Psychotic symptoms can be rapid in appearance or escalation, suddenly reaching a critical point in severity and resulting in an emergency presentation. The most common emergency presentations are hallucinations that are frightening to the patient or delusions that are threatening. Both have the potential to result in a state of agitation. In these circumstances, reassurance may be somewhat helpful but in the most severe cases is inadequate. Delusions of harm from family or friends or hallucinations of intruders in the home may result in calls from the patient to police or other emergency responders. Recognizing that medications are often a contributing cause of acute psychosis, the most recent additions or dosage increases in antiparkinsonian drugs, or other medications, particularly those with anticholinergic properties, should be evaluated and at least temporarily discontinued if needed. Pharmacologic therapy will often be required for more immediate relief of psychotic symptoms, especially in the emergency room setting. The atypical antipsychotic agents are useful in reversing psychotic symptoms in PD. Clozapine is the most useful but has potentially serious adverse effects, including agranulocytosis, and should not be administered emergently without a thorough review of possible previous administration and adverse effects, a process that cannot be easily accomplished quickly in the emergency room setting [106]. The next most useful and commonly used atypical antipsychotic agent is quetiapine [107]. Although some studies have questioned its efficacy [108], common experience supports its benefit. The only atypical antipsychotic agents readily available in parenteral form for acute administration are olanzapine and ziprasidone. Pimavanserin, a relatively new novel atypical antipsychotic agent with no dopamine-blocking effect, has been shown to be effective in treating Parkinson's disease psychosis [109] with little risk of worsening motor function [110]. The use of atypical antipsychotic agents should be tempered by the "black box" warning of a slight increased risk of death when used to treat elderly patients with dementia [111].

Panic

Anxiety is common in PD. Most forms such as generalized anxiety or social phobia seldom present as an emergency, but panic attacks, which are not uncommon in Parkinson's disease, may result in an emergency room visit. A study of anxiety disorders in PD found a lifetime prevalence of 49% of all forms of anxiety, whereas the specific prevalence of panic disorders in PD patients was 10% [112]. Panic disorder is more likely to appear in patients with an earlier age of PD onset and in those with a family history of parkinsonism [112].

Typical panic attack symptoms include an intense discomfort or fear with sudden onset of associated symptoms such as a sense of impending death, choking, breathlessness, palpitations, or chest pain. A panic attack sometimes is associated with the "off" state in PD. In that circumstance, pharmacologic measures to reverse the parkinsonian "off" state will also improve the

sense of panic. When readjustment of antiparkinsonian medications to correct the off state does not reverse a panic attack, anxiolytic therapy will be required. A short-acting, rapid-onset benzodiazepine, such as alprazolam, is useful for reducing the intensity of panic-associated symptoms. Selective serotonin reuptake inhibitors are also useful for panic disorders, but the absence of a rapid-onset formulation makes them less useful for acute panic attacks in the emergency setting than for the treatment of an ongoing persistent panic disorder.

Delirium

The most common causes of acute delirium in PD are intercurrent illness (especially infection), or the postoperative state. When an identifiable infection is present, appropriate antibiotic therapy will aid reversal of delirium. Any form of surgery, especially orthopedic procedures, may result in postoperative delirium. The greatest risk for postoperative delirium is preexistent dementia. In anticipation of the possibility that delirium may develop postoperatively in such patients, certain preventative measures are useful. Thus, in PD patients with known dementia, the use of regional rather than general anesthesia and employing less deep levels of sedation, if possible, are useful strategies that can lessen the risk of delirium after surgery [113, 114].

In addition to treating concurrent illnesses, such as infection, environmental methods to reestablish normal day, night, place, and time orientation should be employed. Encouraging a family member to sit with the patient and provide a focus of orientation can be useful in this regard. In the severely agitated patient, pharmaceutical management will more likely be required. Whereas haloperidol is often considered standard therapy for delirium, it cannot be used in PD patients without severely worsening their parkinsonism. An atypical antipsychotic agent, preferably quetiapine, should be used instead [115– 117]. Benzodiazepines are not recommended except in the face of alcohol or other substance withdrawal.

Suicide

One final behavioral emergency in PD is suicidal ideation [118], which has been estimated to occur in as many as one third of PD patients [119]. In some studies the suicide rate was found to be especially high in PD patients having undergone deep brain stimulation of the subthalamic nucleus (STN) [120]. A meta-analysis found that suicide attempts were observed in 1% of STN DBS patients, and successful suicides were documented in 0.5% [121]. A large study, however, found that suicidal ideation and behaviors were not elevated in the 6 months post-DBS period, and furthermore there was no difference in these symptoms between STN and globus pallidus DBS patients [211]. On balance, these data do point out that suicidal thoughts, gestures, and attempts can occur in PD patients, possibly more so in DBS patients, and are true emergencies requiring appropriate psychiatric consultation with consideration of admission to the hospital.

Inspiratory Stridor in Multiple System Atrophy

Multiple system atrophy (MSA) can be associated with inspiratory stridor. Whether stridor in this clinical condition is due to laryngeal abductor weakness or adductor dystonia is uncertain, several, but not all, studies suggest that its appearance increases the potential of an earlier fatal outcome. While stridor is more common in moderately or severely advanced MSA patients, it can occasionally be among the presenting signs of this condition [122]. An early clue to the presence of stridor may be peculiar high-pitched, nonposition-dependent snoring during sleep. Family members should be alerted to the presence of this sound which is clearly different from ordinary snoring. In many patients, this may be the exclusive time of day that stridor occurs. Laryngoscopy is the definitive diagnostic technique for identifying laryngeal abductor dysfunction, and in patients with stridor that occurs exclusively at night, the procedure may have to be performed during sleep to identify the problem. Some

patients experience stridor during the daytime as well as at night, which is even more ominous in terms of the potential for serious respiratory embarrassment. One study suggested that MSA patients who develop daytime stridor have a mean survival of less than 1 year [123]. A recent meta-analysis and consensus statement by an international panel of experts noted that not all previous studies found a relationship between the presence of stridor and survival in MSA, yet they noted that those studies not confirming this correlation used less sensitive measures of identifying the presence of stridor [212]. Since stridor has been associated with sudden death in some MSA patients, it is truly an emergency that requires immediate therapeutic attention. Rarely, stridor can be seen in other movement disorders, including Parkinson's disease, Creutzfeldt-Jakob disease, and Machado-Joseph disease [124].

The simplest therapy for stridor associated with MSA is CPAP [125]. Nocturnal video laryngoscopy has documented that CPAP is capable of producing separation of the adducted vocal cords and improvement of stridor [126]. In more advanced patients, where there may also be central hypoventilation, BIPAP has been suggested as the preferred therapy instead [127]. Should none of these approaches be practical or successful, or if there is daytime stridor, tracheostomy, the most definitive therapy, is required [125]. Precipitation or exacerbation of central sleep apnea has been reported to occur after institution of tracheostomy in some MSA patients, occasionally with a fatal outcome [128]. Some deaths during sleep have also been reported in MSA patients despite adequate CPAP therapy, and in these cases concurrent autonomic dysfunction is suspected to have resulted in a cardiac demise [129].

Acute Dystonic Reaction

Acute dystonic reactions (ADR) typically occur after exposure to DRBA. Neuroleptic agents such as haloperidol, or antiemetic agents such as prochlorperazine, are the most common offending agents, though the newer atypical neuroleptics can also potentially lead to development of ADRs [213]. Over 50% of ADRs occur within 24 h after DRBA exposure and approximately 90% occur within 5 days [130]. In the typical clinical presentation, the muscles of the mouth, face, eyes, and neck are involved resulting in one or more dystonic manifestations such as retrocollis, back arching, lateral flexion of the trunk (Pisa syndrome), trismus, tongue protrusion, or deviation of the eyes [131]. Trismus can be severe enough to dislocate the jaw. A potentially fatal form of ADR is dystonic laryngospasm with compromise of the airway [130, 132]. This must be correctly identified and distinguished from an anaphylactic reaction as the therapy of the two conditions is entirely different. The presence of stridor is an important marker of laryngeal dystonia.

Risk factors for ADR include young age, male gender, a primary psychotic disorder, and prior drug-induced dystonic reactions. Patients with homozygous mutations in the CYPZD6 gene that results in slow DRBA drug metabolism are also at greater risk for ADRs [133]. Drug dosage does not seem to be a risk factor. Children have a greater risk for this adverse effect compared to adults. The incidence of ADR seems to be higher after administration of very potent DRBAs, such as haloperidol [132], but milder DRBA such as metoclopramide [134] and drugs with little effect on dopaminergic transmission, such as selective serotonin reuptake inhibitors [135], are also capable of inducing the same syndrome. Rare cases of ADR have been reported after administration of drugs that have no apparent dopamine-blocking function, and patients with this syndrome exhibit the typical brisk response to anticholinergic therapy [136] discussed below. As an example of this phenomenon, both the antiviral drug foscarnet [137] and the commonly used antihistamine agent cetirizine [137] have been associated with ADR. ADR have also been reported with "ecstasy" (MDMA) use [138]. Although atypical antipsychotic agents have been associated with ADR [139], the incidence is lower than that associated with older neuroleptic agents [140, 141]. For example, a 25% incidence of ADR was reported in autistic children being treated with haloperidol [142], while a more

recent trial of autistic children being treated with risperidone reported that none of 49 children developed ADR [141]. Cocaine used together with a DRBA predisposes to the development of ADR, and cocaine can cause ADR even when used alone [143]. Prophylactic pretreatment with anticholinergic drugs can reduce the incidence of ADR in susceptible individuals [132]. Interestingly, although having significant effects on the dopaminergic system, there are only limited reports of ADR in patients taking tetrabenazine and no reports of ADRs in patients taking the newer VMAT2 inhibitors, valbenazine or deutetrabenazine [214].

Children are not only at risk for ADR as a result of administration of prescribed DRBA but also from secretive (parent's medication) or unwise (excessive dose) ingestion of these agents [144]. In one example, several teenagers and one younger child developed ADR after ingesting a medication they believed was "street Xanax" but actually contained haloperidol instead [145].

The treatment of ADR consists of administering intravenous diphenhydramine (25–50 mg) or benztropine (1–2 mg). Intravenous diazepam, a second-line therapy, is also usually effective. These therapies are extremely effective, and the prompt benefit they produce helps confirm the diagnosis of ADR and, in the case of laryngospasm, may be lifesaving. After initial therapy of an ADR, it is wise to continue oral anticholinergic agents for 2 weeks, especially if a long-acting DRBA was used or in those cases where DRBA therapy must be continued. Premature discontinuance can result in recrudescence of symptoms [146]. Discontinuing anticholinergics should be done with a slow taper to avoid rebound worsening. Rarely, ADR can continue to recur over months despite discontinuance of the offending drug, requiring longer-term anticholinergic therapy [147].

Status Dystonicus

Status dystonicus (SD), also known as dystonic storm, is characterized by an acute onset of severe dystonic spasms or acute exacerbation of preexisting dystonia such that the patient is in extreme pain and/or at extreme risk for life-threatening complications. Status dystonicus can mimic other neurologic emergencies such as status epilepticus, neuroleptic malignant syndrome, serotonin syndrome, acute parkinsonism, intrathecal baclofen withdrawal, etc. and thus needs to be strongly considered as part of a differential [215]. Status dystonicus can develop in patients with primary dystonia (e.g., DYT1 and DYT6 dystonia) or more commonly in patients with secondary dystonia (e.g., Batten's disease or juvenile cerebral palsy) [216]. Acute onset of dystonia can occur in the setting of initiation of a new drug (especially a dopamine-blocking agent), or withdrawal of drugs in a dystonic patient (especially anticholinergic agents or intrathecal baclofen), or may simply be a severe spontaneous progression of a neurological condition for which dystonia is one possible clinical component (e.g., Wilson's disease). More commonly, SD is an event-related exacerbation of preexisting, generalized dystonia such as that associated with the DYT1 mutation or juvenile cerebral palsy. In patients with longstanding dystonia, an acute exacerbation may have an obvious precipitant, such as an intercurrent infection, recent trauma, or a change in medications. Alternatively, there may be no apparent cause for the sudden exacerbation of dystonia. The potential systemic complications of severe sustained dystonia are the main reason to consider this a medical emergency. Much like the systemic complications of NMS, patients experiencing SD can suffer respiratory embarrassment, rhabdomyolysis, and myoglobinuria, potentially leading to renal failure [148]. Because of these potentially life-threatening developments, these patients are typically managed in an intensive care unit.

The circumstances that have precipitated SD in each individual patient are important to understand since they may dictate the therapeutic approach. Infections at the onset of SD potentially account for greater than 50% of all triggers with the next most common etiology being medication adjustments at roughly 30% [216]. Thus, SD related to intercurrent infection requires urgent initiation of appropriate antibac-

terial or antiviral therapy. Similarly, withdrawal of an offending medication or reinstitution of a precipitously withdrawn medication will prove to be the most important therapeutic step in other patients. Notably, though, roughly one third of cases may not have an identifiable precipitating trigger [216].

Once the precipitating circumstance has been identified and neutralized, therapy must be initiated to improve the dystonia itself and the systemic complications that have resulted from it. Medical therapy of dystonia may require any or a combination of dopamine-depleting agents (tetrabenazine), anticholinergic drugs (trihexyphenidyl), and/or dopamine-blocking agent (haloperidol), each titrated to an effective or maximally tolerated safe dosage [148, 149]. Anticholinergic agents may be tolerated at higher dosages in those already receiving this class of medication and are also similarly well tolerated in high dosages by adolescents or young adults [150]. A variety of additional agents have been reported in individual cases to have provided benefit in cases of severe and acute dystonia, including dantrolene, baclofen, levodopa, carbamazepine, and various benzodiazepines. Intrathecal baclofen has been reported to be of benefit in a few patients refractory to medical therapy but is not uniformly beneficial [151]. On the other hand, there are cases in which intrathecal baclofen was ultimately of benefit despite lack of efficacy of a test bolus prior to proceeding to an implantable pump [152]. Despite the most aggressive medical therapy, severe dystonic spasms are likely to continue in upward of 90% of patients [216], raising the possibility that therapeutic paralysis, deep sedation, and ventilation may be required in an intensive care setting [153]. Deep sedation can be successfully achieved with propofol [154] or midazolam [155], both short-acting agents with the additional benefit of having gabaergic properties that might contribute to the antidystonic effect.

While in the intensive care unit, supportive measures will be required, including rehydration, control of fever, and careful monitoring of cardiac function and blood pressure. In patients who are still uncontrolled after a period of paralysis, stereotactic surgery including pallidotomy or bilateral pallidal deep brain stimulation may ultimately be required and is often the most successful strategy for refractory patients [156, 157, 216].

Stiff Person Syndrome

The stiff person syndrome (SPS) is classically associated with autoantibodies directed against glutamic acid decarboxylase (GAD), although newer antibodies have been detected in recent years including anti-amphiphysin, gephyrin antibodies, and gamma-aminobutyric acid type A receptor-associated protein (GABARAP) antibodies, gamma-aminobutyric acid type A receptor ($GABA_AR$) antibodies, glycine receptor antibodies, glycine transporter 2 antibodies, and dipeptidyl-peptidase-like protein-6 (DPPX) antibodies [217]. Although there is controversy about the role of these antibodies, they presumably act by reducing GABA-mediated inhibition of spinal interneurons with resultant axial and limb rigidity [158]. GAD antibodies are also found in patients with type 1 diabetes, but typically at much lower titers. The clinical syndrome consists of profound rigidity of predominantly axial and proximal limb muscles with superimposed, often stimulus sensitive, muscle spasms that can be severe enough to produce long bone fractures. These spasms, and the ongoing rigidity, can occasionally be life threatening, in that they can result in respiratory compromise, autonomic dysfunction, or both [159]. The clinician should be aware that any combination of one, two or three, or all four limbs can be involved separately, giving rise to a variant of the condition termed "stiff limb" syndrome [160].

There is also a paraneoplastic form of SPS, related to anti-amphiphysin antibodies. Unlike ordinary SPS which has a male predominance, the paraneoplastic form, most common in breast cancer, has a female predominance. In SPS the legs and axial muscles, especially the lower paraspinal muscles, are most commonly affected, whereas in amphiphysin antibody SPS, the arms and neck muscles are often most prominently affected [161]. A still more serious, although

rarer, form is progressive encephalomyelitis with rigidity and myoclonus (PERM) which has a mortality rate up to 40% with 25% requiring mechanical ventilation [161]. The autoimmune form of SPS is associated with a high incidence of other autoimmune conditions, such as thyroiditis and systemic lupus and in fact may be the initial manifestation of a systemic autoimmune conditions such as lupus [162]. Similarly, paraneoplastic SPS can be the presenting symptoms of an occult carcinoma [163]. The clinician who is unfamiliar with this syndrome can easily conclude that a patient with SPS is hysterical, as sensory, long tract, cognitive, and coordination deficits are typically absent [164], and on occasion, only one, two, or three limbs are affected.

Symptomatic therapy of the rigidity in this condition consists of administration of gabaergic agents, such as clonazepam, diazepam, and baclofen. A variety of antiepileptic drugs, including vigabatrin, tiagabine, gabapentin, and levetiracetam, are considered to be somewhat beneficial [165]. Recommendations for treatment of the underlying autoimmune condition include IVIg [166], corticosteroids [167], and rituximab [168]. IVIG is the best studied immunosuppressive therapy and is generally considered the preferred agent in this category [164], although newer immunotherapies including rituximab have been shown to be potentially beneficial as well [218]. Although immunosuppressive therapy may be effective, it cannot be expected to have an immediate effect in an emergency room setting. Intrathecal baclofen can result in more rapid clinical improvement [169], but paradoxically any dysfunction in the baclofen pump system, such as pump failure or catheter leakage, can cause a baclofen withdrawal syndrome with an even more severe exacerbation of rigidity [170], making it imperative that both the clinician and the patient be aware of this possibility. Recently, the GABA receptor potentiator, propofol, in modest intravenous dosages, has been used with significant benefit to provide immediate relief of SPS spasms without attendant sedation [171]. In this circumstance it can be used as a therapeutic bridge pending the placement of a baclofen pump or until potent immunotherapy takes effect.

Hemiballism and Hemichorea

Large amplitude, proximally predominant flinging movements are characteristic of ballism. These movements are thought to exist on a clinical continuum with the smaller amplitude, more distally predominant movements of chorea. The fact that these two different types of abnormal involuntary movements are pathophysiologically related is supported by the observation that both may exist in the same individual at the same time, and ballism, as it improves, may evolve into chorea. In those cases in which chorea and ballism coexist or the abnormal movement is in an indeterminate zone between the two, the term hemichorea/hemiballism is often used. Ballistic movements are anatomically classified as monoballism (involving one limb), hemiballism (involving one side of the body), biballism (involvement of both sides of the body), or paraballism (involvement of both lower extremities). In those cases in which hemiballism is due to involvement of the STN, the somatotopic organization of this structure may account for the selective involvement of only one limb on one side of the body [172], and the same could be said of patients with a cortical lesion. Although the STN is a common location of structural pathology associated with hemiballism, modern neuroimaging has proven that it may not be the structure involved in the majority of cases. Other structures in the STN afferent or efferent pathways such as the striatum, thalamus, globus pallidus, and cerebral cortex may also be the locus of pathology [173]. In one of the largest series in the literature with poststroke hemichorea/hemiballism, only 4 of 27 patients had lesions confined to the STN, while 6 of them were in the stratum or cortex, with other isolated lesions being found in the putamen, caudate, or globus pallidus [173].

Ischemic and hemorrhagic strokes are the most common causes of hemiballism. In some cases of apparent vascular hemiballism, neuroimaging is totally normal, and in others, the CT scan is normal but MRI reveals a lacunar infarction in the STN or elsewhere [174]. Hemichorea/hemiballism develops on the day of stroke onset in the vast majority of cases, but in up to 10%, it may

develop a day later and in rare cases as long as 5 days later [173]. Vascular hemichorea can also appear in the form of a TIA, so-called limb-shaking TIAs [175]. Although the prognosis for survival in those with vascular hemiballism was once thought to be worse than other stroke patients, especially in the preneuroleptic era, recent studies suggest that vascular hemiballism patients, many of whom have had lacunar strokes, have a risk of stroke recurrence and death that is similar to stroke patients in general [176]. As in the case with other stroke syndromes, surgical or neurointerventional procedures that improve cerebral circulation may have a salutary effect on vascular hemiballism [177], as discussed below.

A variety of other pathologies including encephalitis, systemic lupus erythematosus, multiple sclerosis, basal ganglia calcification, and nonketotic hyperglycemia can also result in hemiballism [178]. Structural pathologies such as bacterial or tuberculosis abscess, neoplasm, moyamoya disease, HIV-related toxoplasmosis, or arteriovenous malformation have also been associated with hemiballism. Stereotactic ablation of the STN for the treatment of Parkinson's disease can result in hemiballistic movements that are transient and improve in a matter of weeks [179] but can also rarely result in permanent hemiballism [180]. Similarly, therapeutic stimulation of the STN for Parkinson's disease can produce hemiballism that resolves when the stimulation is adjusted below a given threshold voltage [181].

The syndrome of hemiballism-hemichorea and magnetic resonance striatal hyperintensity associated with nonketotic hyperglycemia has been reported increasingly more frequently in recent years [182] and now represents the second most common cause of hemiballism, stroke being the most common. This syndrome appears to be much more common in patients of Asian descent [182]. In these cases, CT scan of the brain typically reveals hyperintensity in the contralateral striatum corresponding to MRI scans that show increased signal intensity on T1-weighted images and a decreased signal on T2-weighted scans. A high signal is occasionally seen on diffusion-weighted imaging [183]. After metabolic correction of the hyperglycemic state, the abnormal involuntary movement usually disappears along with the CT and MRI abnormalities. In some cases, however, hemiballism persists despite disappearance of the MRI abnormality [184, 185]. Interestingly, the same CT and MRI findings have been seen in some hyperglycemic patients with no involuntary movements [186]. The exact nature of the striatal pathology remains unclear. The finding of normal gradient-echo MR images in hyperglycemic hemiballism along with striatal high signal intensity on a diffusion-weighted scan has suggested to some authors that hyperviscosity with associated cytotoxic edema may play a role in this syndrome [183]. However, autopsy and biopsy evaluation of the striatal tissue demonstrating MRI hyperintensity have revealed evidence of multiple foci of recent infarcts and/or gliosis [187, 188]. PET scans performed in the acute and subacute phases have suggested glucose hypometabolism in the affected regions of the brain [189].

The first therapeutic measure in treating hemiballism is to correct the underlying metabolic, infectious, or vascular abnormality to the extent possible. In the circumstance of nonketotic hyperglycemia and ischemic stroke, the two most common causes of hemiballism, this means correcting the hyperglycemia in the former condition and reversing the ischemia in the second condition through methods such as supporting blood pressure, thrombolytic therapy, and endovascular procedures. Acutely reversing ischemia can be effective in hemiballism due to transient ischemia or stroke [175, 177]. Hemiballism related to hyperglycemia may reverse within hours of correcting the metabolic abnormality, but up to 20% of patients continue to have ballism for months. Vascular hemiballism due to a completed stroke improves spontaneously in the majority of patients. In a series of 25 such patients followed for up to 3 years, hemiballism completely disappeared in 56% of cases after a mean duration of 15 days [173]. In another series of the same size, full recovery was noted after 3–15 days in 56% of patients [176].

In the absence of spontaneous or therapeutic reversal of hemiballism, it must then be treated

symptomatically. For control of the abnormal involuntary movement itself, dopamine (DA)-blocking or DA-depleting drugs are the most effective symptomatic therapy. Traditionally, typical neuroleptics such as haloperidol have been used for this purpose, and more recently low-dose clozapine, olanzapine, and other atypical antipsychotic agents have also been found to be effective [190, 191]. Reserpine is an older therapy [192] that has been replaced by recently developed medications. The vascular monoamine transporter 2 inhibitors tetrabenazine [193], valbenazine [209], and deutetrabenazine [210] can improve ballism. Caution must be exercised with any of these agents not to induce hypotension in patients whose hemiballism is due to stroke. This is especially true of tetrabenazine which has the highest side effect profile among these three drugs. Anticonvulsants can occasionally be beneficial, including valproic acid [194], topiramate [195], and levetiracetam [196]. Sertraline (Zoloft) has been reported to result in a prompt and nearly complete improvement of hemiballism in a single case [197]. In vascular hemichorea, physical therapy may speed improvement in the movement disorder [198]. If all these therapies fail and the amplitude of ballism threatens to produce physical injury, extreme exhaustion, or cardiac symptoms, stereotactic surgery consisting of contralateral GPi DBS for hyperglycemic [199] or vascular [200] hemiballism has been shown to be a useful therapy.

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