PATIENT VIGNETTES

Patient 1: A 75-year-old woman with a history of bipolar affective illness dating back to her 20s 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 was at her mental and physical baseline in the recovery room and then on the postsurgical floor. Two days after surgery she suddenly became mute, stiff, and unresponsive. In addition to her usual regimen of 600 mg lithium, 20 mg fluoxetine, and 4 mg trifluoperazine daily, she had received 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 had markedly increased tone and was akinetic. When her arms were elevated, she slowly lowered them. Deep tendon reflexes were normal. Physical examination, vital signs, laboratory tests, including lithium levels and head computed tomography (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 febrile illness with diffuse erythematous, maculopapular rash, conjunctivitis, and headache for 4 days. 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. No ptosis was noted, and her face was expressionless and her mouth held partly open. A mild, intermittent resting tremor was noted in the left hand. No other adventitious movements were noted. She was diffusely rigid with asymmetry. Deep tendon reflexes were normal and plantar responses were equivocal. The remainder of her neurological examination was unremarkable. Medical and family history was noncontributory. Immunizations were complete apart from measles. Her white cell count was 14.0 × 10^9/L with 45% neutrophils and 48% lymphocytes. Cerebrospinal fluid (CSF) analysis showed 20 white blood cells/mm (all lymphocytes), no red blood cells, and normal protein and glucose. Serum measles antibody titers (by complement fixation) 10 days after the rash were 1:160; 3 weeks later, the titer was 1:80. Electroencephalogram (EEG) and CT of the head were unremarkable. She was started on 25/100 mg of carbidopa/levodopa at one-half tablets three times.
per day with significant improvement. Over the next 3 months, her tremor, bradykinesia, and rigidity slowly resolved.

INTRODUCTION

Secondary parkinsonism as a result of an identifiable, nondegenerative disorder is common, primarily occurring following exposure to medications that block dopamine D2 receptors (1). Primary parkinsonism (2) is caused by a variety of slowly progressive disorders, and the date of symptom onset is usually hard to pinpoint. Most secondary forms of parkinsonism, including the drug-induced forms, evolve over weeks, but may develop over hours to days. It is often difficult to recognize akinetic rigid syndromes at their early stages, especially in patients who may be systemically ill.

The broad categories for etiologies of acute parkinsonism are found in Table 1. Parkinsonism may be a relatively minor aspect of a life-threatening disorder, or may be the presenting and most obvious feature. In the latter case, establishing the onset may be problematic, as patients and families often note the 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 earlier than originally reported.

Acute parkinsonism in psychiatric disorders occurs in two settings—catatonia and conversion. Although parkinsonism may be seen with severe depression (3), particularly in the elderly as well as in persons with severe obsessive-compulsive disorder (4), the onset is not usually acute.

NONINFECTIOUS ACUTE PARKINSONISM

Structural Lesions

Obstructive hydrocephalus is a well-known cause of parkinsonism (5). Normal pressure hydrocephalus often mimics parkinsonism, but the onset is insidious. Acute parkinsonism from hydrocephalus may occur in both adults and children, either as a result of shunt obstruction or at presentation. 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. Some cases of obstructive parkinsonism are responsive to levodopa. Obstructive hydrocephalus following meningitis or subarachnoid hemorrhage may also cause parkinsonism.

Vascular parkinsonism, previously called atherosclerotic parkinsonism, usually results from tiny lacunes in the basal ganglia (6). 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 (7–14). Kim described six patients who developed hemi-parkinsonism, three with rest tremor and cogwheeling rigidity (10). Tremor and other signs of parkinsonism developed after weakness improved. Imaging studies revealed large infarcts involving the supple-
Table 1
Etiologies for Acute Parkinsonism

<table>
<thead>
<tr>
<th>Category</th>
<th>Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td></td>
</tr>
<tr>
<td>Postinfectious</td>
<td></td>
</tr>
<tr>
<td>Autoimmune</td>
<td>systemic lupus erythematosus</td>
</tr>
<tr>
<td>Medication</td>
<td>“typical” side effects of dopamine receptor blocker</td>
</tr>
<tr>
<td></td>
<td>idiosyncratic effects</td>
</tr>
<tr>
<td></td>
<td>neuroleptic malignant syndrome</td>
</tr>
<tr>
<td></td>
<td>serotonin syndrome</td>
</tr>
<tr>
<td></td>
<td>chemotherapeutic drugs</td>
</tr>
<tr>
<td>Toxic</td>
<td>carbon monoxide</td>
</tr>
<tr>
<td></td>
<td>cadmium</td>
</tr>
<tr>
<td></td>
<td>MPTP</td>
</tr>
<tr>
<td></td>
<td>ethanol withdrawal</td>
</tr>
<tr>
<td></td>
<td>ethylene oxide</td>
</tr>
<tr>
<td></td>
<td>methanol</td>
</tr>
<tr>
<td></td>
<td>disulfiram</td>
</tr>
<tr>
<td></td>
<td>bone marrow transplantation</td>
</tr>
<tr>
<td>Structural</td>
<td>stroke</td>
</tr>
<tr>
<td></td>
<td>subdural hematoma</td>
</tr>
<tr>
<td></td>
<td>central and extra-pontine myelinolysis</td>
</tr>
<tr>
<td></td>
<td>tumor</td>
</tr>
<tr>
<td></td>
<td>hydrocephalus</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>catatonia</td>
</tr>
<tr>
<td></td>
<td>conversion</td>
</tr>
<tr>
<td></td>
<td>obsessive-compulsive disorder</td>
</tr>
<tr>
<td></td>
<td>malingering</td>
</tr>
</tbody>
</table>

Acute Parkinsonism

mentary motor area or cingulate gyrus. Other frontal strokes have also caused acute parkinsonism (11, 12). As one might expect, strokes in the substantia nigra may cause parkinsonism (7–9), but these are exceedingly rare. Interestingly, strokes in the lenticular nuclei do not cause parkinsonism (13). Acute hemorrhage is a less common cause of acute parkinsonism (14).

Toxic/Metabolic

A number of poisons may induce parkinsonism. Some, like manganese, develop subacutely (15) or over long periods of time (16). Parkinsonism may follow carbon monoxide poisoning after an acute, life-threatening poisoning during recovery from coma (17, 18). Carbon monoxide poisoning is a persistent problem in some coun-
tries, 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 (19) and ethylene oxide (20), disulfiram (used to prevent alcoholics from imbibing) (21), and cyanide poisoning are other uncommon causes (22,23).

1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) has a special place in the history of movement disorders (24). After its identification by Langston and colleagues as the source of a mini-epidemic of severe, acute parkinsonism in intravenous drug abusers in the San Francisco Bay area, MPTP was exploited as a tool for research into Parkinson’s disease (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. This was the first systemically administered drug that selectively targets these cells, and because it has a similar effects 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 but do not simulate the disease itself. The onset of parkinsonism occurs after the first few doses.

Acute parkinsonism is a rare complication of insect stings (25,26). Acute parkinsonism developed within 3 days of a wasp sting (25) associated with pallidal necrosis, followed by acute deterioration 6 months later with degeneration of the nigrostriatal pathway. Bee stings have not been implicated.

Parkinsonism resulting from alcohol withdrawal has been reported rarely (27–29). A follow-up of some of these patients 1 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 1 week (27). 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. Magnetic resonance imaging (MRI) revealed central pontine myelinolysis. She was responsive to very low doses of levodopa, and her parkinsonism gradually resolved (30). Another similar case was also accompanied by pyramidal features (31). Parkinsonism is not typical for central pontine myelinosis (32). Hypoxic insult to the basal ganglia may cause parkinsonism or dystonia (33–35). This is uncommon and typically occurs after a major brain insult. The syndrome has occurred in children (34) 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 fever, alteration of mental status, and rigidity (see Chapter 11 for a complete discussion of NMS) (36,37). Many patients have extreme elevations of creatine phosphokinase (CPK) as a result of rhabdomyolysis, but this is not required for diagnosis. Elevations in the CPK to the 1000 to 2000 range are sometimes seen in otherwise normal, treated psychotic patients, even in the absence of signs or symptoms of muscle or tone abnormalities. The major differential diagnosis is with in-
Infections frequently cause exacerbations of neurological syndromes, including parkinsonism, in people on neuroleptics. NMS may occur at any point once a patient is treated with neuroleptics, but it usually occurs relatively shortly after drug initiation or dose increase. Although 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. The muscle contractions may mimic a tonic seizure. Management of NMS requires excluding infection, stopping the suspected 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 days. 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 to 3 months after transplant (38,39). In addition to parkinsonism, cognitive and mental changes also occurred. No particular medication could be implicated, and one patient had had an autologous transplant eliminating the possibility of a graft-vs-host reaction. MRI revealed demyelination, and brain biopsies revealed regions of variably active inflammatory demyelinating lesions. Severe and persistent neurologic sequelae were seen. Several reports in the literature describe an acute parkinsonian syndrome occurring with a variety of anticancer drugs (40). Some of these were extremely responsive to levodopa, and the parkinsonism was not permanent.

A handful of teenagers with systemic lupus involving the nervous system developed acute onset parkinsonism in the setting of active central nervous system (CNS) involvement (41,42). Chorea is the more common movement disorder, associated both with systemic lupus and with the lupus anticoagulant antibody.

Psychiatric

Catatonia is an important diagnostic possibility to consider in acute parkinsonism (43,44). Catatonia should be strongly considered in any patient with acute-onset akinesia and no 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, Diagnostic and Statistical Manual (DSM) criteria have been revised to recognize it as a manifestation of manic-de-
pressive disorder as well. It is actually more common in the affective disorders. The patient may have had previous spells that may not have been recognized, and therefore resolved, over long periods of time. The patient may have been functioning quite well until recently when behavioral problems began to recur. Catatonia may punctuate a manic spell or follow a bout of catatonic excitement, suggesting a burnt-out excitatory process like encephalitis. A catatonic, unlike someone with parkinsonism, will not attempt to move. The patient will not appear to be uncomfortable or get hungry. All studies will be normal. If there is no organic disorder, then an EEG, if the eyes are closed, will be normal.

Most physicians incorrectly think of catalepsy as the defining characteristic of the syndrome. 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 manifest 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. Because the patient may keep his or her eyes closed, coma and encephalopathy must be excluded. If the patient’s eyes are open, then coma is not a consideration. However, if the eyes are closed and the patient is stiff and unresponsive to deep pain, then 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, and so on.

Psychogenic parkinsonism is not common but should always be considered in acute-onset cases, especially in young patients. In studies of new referrals to movement disorders specialists, about 2–5% have presumed psychogenic diagnoses (45). 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 (46). One characteristic that helps distinguish it from organic disorders (47,48) is the acute onset. In idiopathic PD, tremor tends to vary throughout the day, often prominent in time of stress and absent 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, and excitement—don’t necessarily affect conversion tremor. On exam, tremor resolves with distraction and varies in frequency, whereas tremor of PD is usually no faster than 4 Hz. The slowness of conversion has a more deliberate character, especially during handwriting. Balance impairment is usually
Acute Parkinsonism

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 don’t understand the implications of the diagnosis or as a denial mechanism. Often patients with conversion have experience with the disorder or a background in medicine, including employment as a nurse, medical secretary, or lab technician. The single most common stressor in women with conversion is a history of childhood sexual or physical abuse.

INFECTION 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).

von Economo’s disease (ED) was probably seen prior to his initial description of 13 cases with onset between February and April 1917 in Vienna (49). Urechia (50) probably described the first recorded credible case series of ED with onsets in April and May 1915 in Bucharest. Somewhat later (1915 or 1916), cases were described in the French army (51,52). On the other side of the globe, a massive encephalitic outbreak affecting 65,000 Chinese in the province of Yunnanfou caused devastation from 1917 to 1927 (53). By 1919, cases had been reported throughout the world. The peak incidence in the United States was in 1923, with about 2000 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 as 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 fre-
quently 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” (54).

In the hyperkinetic form, “chorea and hemichorea as well as myoclonic twitches were observed which might 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” (54).

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” (54).

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” (54).

It is estimated that more than 60% of ED patients who survived developed postencephalitic 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% (55). The average age of onset of PEP was approx 27 years. Resting tremor was the presenting symptom in two-thirds of cases while akinetic-rigid features occurred alone in about one-third (56). Symptoms were occasionally unilateral and often asymmetrical (57). 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” (54). 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 (57,58), supranuclear gaze palsy, and eyelid apraxia (59).

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 onset below middle age, symptoms lasting more than 10 years, oculogyric crisis, and history of ED (60).

The course of PEP is unclear. Duvoisin and Yahr (55) followed 49 patients with probable PEP and observed a stable course or very slow deterioration. On the other hand, Duncan (61), who studied 136 PEP inpatients in London, was impressed with the progressive nature of parkinsonian disabilities. Calne and Lees (62) and
Acute Parkinsonism

Viereggel (63) 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 of death at 74.3 years (56).

Although there appears to be general agreement that ED and PEP share a viral etiology, no causative agent was ever identified. Its occurrence around 1918 and 1919 have led some to link ED/PEP to the influenza pandemic that occurred at that time (64). 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 postinfluenzal encephalopathy (54). Since the influenza pandemic affected at least 500 million persons (65) more than one-fourth of the world’s population at that time, it is very possible that many individuals with ED may also have had influenza (66).

Recent 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 (66–70). Similarly, the search for autoantibodies did not support an autoimmune mechanism in PEP (71). Finally, studies on genetic susceptibility of ED/PEP have been inconclusive. Although Elizan (72) saw a highly significant increase in the frequency of HLA-B14 antigen in PEP cases, Lees (73) 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 onset after 1959 (74–80). Aside from one report of positive influenza A antibody titer (1:>160) (79) and another report of CSF cultures yielding coxsackie B4 enterovirus (80), attempts to identify the viral agent in ED-like cases have failed. Nonetheless, clinical presentation, laboratory studies, imaging, and pathological findings are reminiscent of, if not identical to, ED/PEP. To distinguish these cases from parkinsonism associated with viral encephalitides, Howard and Lees (78) proposed major criteria for the diagnosis of ED. The illness should comprise an acute or subacute encephalitic illness with at least three out of seven features: (1) signs of basal ganglia involvement; (2) oculogyric crises; (3) ophthalmoplegia; (4) obsessive-compulsive behavior; (5) akinetiic mutism; (6) central respiratory irregularities; and (7) somnolence and/or sleep inversion.

Parkinsonism may occasionally accompany viral encephalitides. Table 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 parkin-
<table>
<thead>
<tr>
<th>Virus</th>
<th>Parkinsonism</th>
<th>Author (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>California encephalitis (LaCrosse virus)</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Coxsackie virus</td>
<td>Acute</td>
<td>Walters (117)</td>
</tr>
<tr>
<td></td>
<td>Acute, transient</td>
<td>Posner et al. (118)</td>
</tr>
<tr>
<td>Cytomegalovirus</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Eastern equine encephalitis (EEE)</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Herpes virus</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Human immunodeficiency virus</td>
<td>Secondary to opportunistic infection</td>
<td>Nath et al. (81); Carrazana et al. (82); Navia et al. (83); Noel et al. (84); Maggi et al. (85); De la Fuente et al. (96); Singer et al. (97); Werring and Chaudhuri (98)</td>
</tr>
<tr>
<td></td>
<td>Part/feature of HIV encephalopathy</td>
<td>De Mattos et al. (86); Mirsattari et al. (87)</td>
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<tr>
<td>Eptstein–Barr virus</td>
<td>Acute, transient</td>
<td>Hsieh et al. (119)</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Acute, transient</td>
<td>Isgreen et al. (120)</td>
</tr>
<tr>
<td>Japanese B encephalitis</td>
<td>Followed acute phase without interval</td>
<td>Ishii et al. (122); Shoji et al. (123); Pradhan et al. (124)</td>
</tr>
<tr>
<td></td>
<td>Chronic phase with interval</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute, persistent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Acute, transient</td>
<td>Scheid et al. (125); Adair et al. (126)</td>
</tr>
<tr>
<td>Lymphocytic choriomeningitis</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Chronic, persistent</td>
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<tr>
<td>Mumps</td>
<td>Not reported</td>
<td>Bennett et al. (127)</td>
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<tr>
<td>Murray valley encephalitis</td>
<td>Reported</td>
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<tr>
<td>Papovavirus</td>
<td>Not reported</td>
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</tr>
<tr>
<td>Poliovirus</td>
<td>Acute, transient</td>
<td>Bickerstaff and Clarke (128); Thieffrey (129)</td>
</tr>
<tr>
<td></td>
<td>Acute</td>
<td>Barrett et al. (130); Duvoisin and Yahr (35)</td>
</tr>
<tr>
<td></td>
<td>Parkinsonism in late life with history of polio as a child/young adult</td>
<td>Vincent and Myers (131)</td>
</tr>
<tr>
<td>Rubella</td>
<td>Not reported</td>
<td></td>
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<tr>
<td>Rubeola, measles</td>
<td>Postmeasles, transient</td>
<td>Mellon et al. (132); Meyer (133)</td>
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<td>Russian spring–summer encephalitis</td>
<td>Acute, transient</td>
<td>Henner and Hantal (134,135)</td>
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<td>Encephalitis, european tick-borne encephalitis</td>
<td>Tremor only</td>
<td>Radsel-Medvescek et al. (136)</td>
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</table>

(continued)
Acute 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 human immunodeficiency virus (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; or as part of HIV encephalopathy in the absence of opportunistic infections. The parkinsonian syndrome is often unresponsive to levodopa.

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 and mycoplasma infections present with acute onset and improve markedly with appropriate treatment, despite the severity of the initial clinical presentation. Of 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. One case had severe dyskinesias and dystonia with levodopa therapy, but experienced gradual resolution of symptoms.

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, progressive multifocal leukoencephalopathy, and cerebral tuberculosis. 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. There is only one reported case of parkinsonism following herpes ophthalmicus.

A 5-year-old boy developed isolated fever 15 days after a measles vaccine shot and then developed persistent parkinsonism. MRI showed hyperintense signals affecting the substantia nigra bilaterally. He responded to levodopa but dyskinesias

<table>
<thead>
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<th>Virus</th>
<th>Parkinsonism</th>
<th>Author (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. Louis encephalitis</td>
<td>Tremors</td>
<td>Cerna et al. (137); Wasay et al. (138)</td>
</tr>
<tr>
<td></td>
<td>Dystonia with tremor</td>
<td>Finley (139);</td>
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<tr>
<td></td>
<td>as sequelae</td>
<td>Finley and Rigs (140)</td>
</tr>
<tr>
<td>Varicella-zoster virus</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Venezuelan equine encephalitis</td>
<td>Not reported</td>
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<tr>
<td>Western equine encephalitis</td>
<td>Reported</td>
<td>Fulton and Burton (141)</td>
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<tr>
<td></td>
<td>Chronic persistent</td>
<td>Mulder et al. (142)</td>
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appeared even at low doses (100). The only other similar 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 (101).

Neuropathology and Imaging

The pathological features of ED differ from that of other viral encephalitides (usually characterized by diffuse brain congestion and edema). In ED, pathology typically consists of nonhemorrhagic 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 (NFT) within the substantia nigra (SN), associated with severe neuronal loss (60,102,103). Lewy bodies are not present. In the chronic state (PEP), inflammation is often replaced with degeneration of neurons and gliosis throughout the CNS, particularly the midbrain (104). NFTs occur in the absence of senile plaques (56,105). Unlike Alzheimer’s disease, they do not stain for α synuclein or amyloid (106), but similar to progressive supranuclear palsy, they are ubiquinated and τ-positive on immunohistochemistry (107,108).

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 these may also involve the striatum and lenticular nucleus (80,109). 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 (79,110). This may be a result of the more diffuse involvement of the SN pars compacta in PEP compared with the ventrolateral predominance in PD.

Evaluation

A young patient with acute or subacute onset of parkinsonism associated with a febrile illness should have a full blood count and blood chemistries including liver, renal, and thyroid function tests, tests for antinuclear antibodies and erythrocyte sedimentation rate, chest radiography, electrocardiogram, and blood and urine cultures. CSF should be sent for cell count, glucose, and protein, and extra tubes for CSF gram and acid-fast bacilli stain, Venereal Disease Research Laboratory slide test (VDRL), lyme titer, and serologies (for herpes simplex virus, herpes zoster, mumps, measles, adenovirus, enterovirus, cytomegalovirus, Epstein–Barr virus, toxoplasmosis, etc.). Serum ceruloplasmin, 24-hour 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 recently, and her lithium level was not elevated. Because her symptoms occurred 2 days after surgery, it was unlikely a direct result of the surgery. Meperidine may trigger severe reactions with monoamine oxidase 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, and had a nonfocal 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.

Diagnosis of 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 (44), 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, postinfectious 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, because 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, in which case a dopamine agonist is our drug of choice. When levodopa is not helpful, we advocate a trial of 200–400 mg of amantadine per 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. Because 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 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 (111), amantadine (112), bromocriptine, and deprenyl (113) 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. (114) 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 (114) 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 in PD, where patients often chose to be “on” with dyskinesias, PEP patients preferred to be “off” to avoid emotional lability. Similarly, Duvoisin (116) 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 (58). Because parkinsonism in PEP is probably progressive or, at the very least, persistent, and 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, with a variety of causes. Identification of the cause and institution of appropriate treatment can not only improve patients’ outcome, but may even be life-saving.
REFERENCES


Acute Parkinsonism

Movement Disorder Emergencies
Diagnosis and Treatment
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