Acute Parkinsonism

4

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Patient Vignettes

Patient 1

A 75-year-old woman with a history of bipolar disease dating back to her twenties was admitted to the hospital after falling and breaking her hip while walking her dog. She had been living alone. She underwent a total hip replacement without incident, and remained at her mental and physical baseline postoperatively in the recovery room and postsurgical floor. Two days after surgery she suddenly became mute, stiff, and unresponsive. In addition to her usual regimen of lithium 600 mg, fluoxetine 20 mg, and trifluoperazine 4 mg daily, she had received a total of five doses of meperidine 50 mg/bolus intravenously for pain control. She kept her eyes open and responded to visual threat and deep pain but not voice. She was akinetic, and tone was markedly increased. When her arms were passively elevated, she very slowly lowered them. Deep tendon reflexes were normal. Vital signs, laboratory tests

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

Immunizations were up to date apart from measles. Her peripheral white blood cell count was 14.0×10^9/L with 45% neutrophils and 48% lymphocytes. Cerebrospinal fluid (CSF) analysis showed 20 white blood cells per millimeter (all lymphocytes), no red blood cells, and normal protein and glucose. Serum measles antibody titer (by complement fixation) 10 days after the rash was 1:160; 3 weeks later, the titer was 1:80. Electroencephalogram (EEG) and computerized tomography (CT) of the head were unremarkable. She was started on carbidopa/levodopa 25/100 mg at 1/2 tablets three times per day with significant improvement in her symptoms. Over the next 3 months, tremor, bradykinesia, and rigidity slowly resolved.

Introduction

There is no universally accepted definition of "acute parkinsonism." We use the term to define a bradykinetic-rigid syndrome developing over minutes to a few weeks. It may be difficult to recognize bradykinetic rigid syndromes early on, especially in patients who are systemically ill. Secondary parkinsonism, defined as an identifiable non-degenerative disorder, often occurs following exposure to medications that block dopamine D2 receptors [1]. In primary parkinsonism [2] the date of symptom onset is usually hard to pinpoint. In contrast, most secondary forms of parkinsonism including drug-induced forms evolve over weeks or even hours.

The major causes of acute parkinsonism are listed in Table 4.1. Parkinsonism may be a relatively minor aspect of a life-threatening disorder, or it may be the presenting and most obvious feature. In the latter, patients and families often note the 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 earlier than originally reported.

Table 4.1 Etiologies for acute parkinsonism

Infectious
Post-infectious
Autoimmune/paraneoplastic
Systemic lupus erythematosus
LGI1 antibodies
IgLON5 antibodies
Dopamine 2 receptor antibodies
Ma2 antibodies
Ri antibodies
Medication
"Typical" side effects of anti-dopamine drugs
Idiosyncratic effects
Neuroleptic malignant syndrome
Serotonin syndrome
Chemotherapeutic drugs
Toxic
Carbon monoxide
Cadmium
MPTP
Ethanol withdrawal
Ethylene oxide
Methanol
Disulfiram
Bone marrow transplantation
Organophosphate exposure
Structural
Stroke
Subdural hematoma
Central and extra pontine myelinolysis
Tumor
Hydrocephalus
Psychiatric
Catatonia
Conversion
Obsessive-compulsive disorder (obsessional slowness)
Malingering

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

Noninfectious Acute Parkinsonism

Structural Lesions

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

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

Acute development of hydrocephalus in patients with aqueductal stenosis can present with levodopa-responsive parkinsonism.

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

Toxic/Metabolic

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

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

Acute parkinsonism is a rare complication of insect stings [28–30]. Acute parkinsonism developed within 3 days of a wasp sting [28] associated with pallidal necrosis, followed by acute deterioration 6 months later with degeneration of the nigrostriatal pathway. Bee stings have not been implicated. Parkinsonism due to alcohol withdrawal has been reported rarely [31–34]. A follow-up of some of these patients one or more years later proved that this withdrawal phenomenon was not a premature unmasking of subclinical PD. Parkinsonism occurred early in withdrawal, and sometimes resolved within a week [31]. The mechanism is postulated to be a metabolic effect of ethanol on striatal dopamine or dopamine receptors. Twelve days after overly rapid correction of hyponatremia, a 66-year-old woman became confused and developed parkinsonism. MRI revealed central pontine myelinolysis. She was responsive to very low doses of levodopa, and her parkinsonism gradually resolved [35]. Another similar case was also accompanied by pyramidal features [36]. Parkinsonism is however not a typical feature of central pontine myelinolysis [37]. Hypoxic insult to the basal ganglia may cause parkinsonism or dystonia [38–40]. This is uncommon and typically occurs after a major brain insult. The syndrome has occurred in children [39] as well as adults, and damage to the lenticular nuclei is clearly visible on magnetic resonance imaging (MRI). Onset is usually delayed, but symptoms may develop rapidly.

Neuroleptic malignant syndrome (NMS) is variably defined, but generally requires the presence of fever, altered mental status, and rigidity [41–43]. Many patients have extreme elevations of creatine phosphokinase (CPK) due to rhabdomyolysis, but this is not required for diagnosis. Elevations in the CPK to the 1000–2000 range are sometimes seen in otherwise normal, treated psychotic patients, even in the absence of signs or symptoms of muscle or tone abnormalities. It is critically important to exclude infection in patients presenting with fever, alteration in mental status, or CPK elevation. Infections frequently cause exacerbations of neurological syndromes, including parkinsonism, and both infection and NMS may occur in the same patient. NMS may begin at any point once a patient is treated with neuroleptics, but it usually occurs relatively shortly after initiation of the offending drug or after a dose increase. While there is general agreement that the newer atypical neuroleptics are less likely to cause NMS, there is as yet little data to support this.

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


The management of neuroleptic malignant syndrome begins with a high index of suspicion for the disorder.

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

Use of typical or atypical neuroleptics (with the exception of quetiapine, pimavanserin, or clozapine) in PD patients is contraindicated.

A handful of children who underwent bone marrow transplantation (BMT) and chemotherapy developed an acute parkinsonian syndrome, sometimes evolving over hours, 2–3 months after transplant [45, 46]. In addition to parkinsonism, cognitive and mental changes also occurred. No particular medication could be implicated, and one patient had an autologous transplant eliminating the possibility of a graft versus host reaction. MRI revealed demyelination, and brain biopsies revealed regions of variably active inflammatory demyelinating lesions. Severe and persistent neurologic sequelae were common. Several reports in the literature describe an acute parkinsonian syndrome occurring with a variety of chemotherapeutic agents [47] and with cyclosporin [48]. Some of these patients responded very well to levodopa, and parkinsonism was not permanent. In a case series of five subjects who were briefly exposed to organophosphate pesticide and developed acute parkinsonism, four recovered completely without treatment (one was lost to follow-up) [49].

Autoimmune/Paraneoplastic

Autoimmune pathology has been demonstrated to be associated with the development of acute parkinsonism. For example, a handful of teenagers with systemic lupus involving the nervous system developed acute parkinsonism in the setting of active central nervous system (CNS) involvement [49, 50]. Chorea, however, is a more common movement disorder associated both with systemic lupus and lupus anticoagulant antibody. Recently, parkinsonism has been reported in a growing number of immunologic processes. Several antibodies have been reported, including Ma2, Ri, IgLON5, and LGI1. Some—but not all—of these antibodies are linked to neoplasms. Paraneoplastic syndromes are a rare cause of movement disorders, including parkinsonism. The most common associated cancers found are small cell lung cancer, breast, gynecological, testicular, lymphoma, and thymoma. Identifying and treating the underlying cancer is critical. If cancer is not identified, immunotherapy is the mainstay of treatment.

Psychiatric

Catatonia is an important diagnostic possibility to consider in the setting of acute parkinsonism [51–53]. Catatonia should be strongly considered in any patient with acute-onset akinesia without an obvious cause such as toxin exposure, hypoxic ischemia, CNS infection, or hydrocephalus. Concurrent use of neuroleptic drugs that may cause parkinsonism may complicate the diagnosis. Although for many decades catatonia was considered a variant of schizophrenia, DSM criteria have been revised to recognize it as a manifestation of manic-depressive disorder as well. It is actually more common in the affective disorders. The patient may have experienced previous spells that may not have been recognized, or resolved over long periods of time. Catatonia may punctuate a manic spell or follow a bout of catatonic excitement. A catatonic, unlike someone with parkinsonism, will not attempt to move. He or she will not appear to be uncomfortable or become hungry. All studies will be normal and an EEG, if the eyes are closed, will be normal. Most physicians incorrectly think of catalepsy as the defining characteristic of catatonia. Not all patients have waxy flexibility or maintain postures that are externally imposed. The hallmark features of catatonia are negativism, a refusal to cooperate generally manifested as mutism or minimal interaction, and lack of movement. Patients may be stiff, or in contrast exhibit "mit-gehen," in which they move with the imposed movement, "helping" the movement. Thus, one sees a patient who is not moving but may not be in the typical flexed posture of parkinsonism. There is no tremor, and, despite an alert status, little interaction with the environment. Patients will not follow commands and may not respond to pain. Since the patient may keep his or her eyes closed, coma and encephalopathy must be excluded. However, if the eyes are closed and the patient is stiff, unresponsive to deep pain, the possibility of coma needs to be considered. If a patient is catatonic, there may be no response to deep pain but cranial nerve reflexes will remain intact. It is unlikely that a catatonic will respond to suggestion, but it is certainly worth trying. "If he is truly comatose/unable to move/stiff/etc., then he will keep his hand above his face when I drop it." If the patient is simply severely parkinsonian from neuroleptics, then he or she should be able to comply with some requests, such as moving the eyes and raising a finger.

Psychogenic or functional parkinsonism is not common but should always be considered, especially in young patients. In studies of new referrals to movement disorder specialists, about 2–5% have presumed functional diagnoses [54]. Acute-onset parkinsonism without a demonstrable cause is not likely organic. The behavioral causes are catatonia, conversion, and malingering. Conversion disorder is a type of somatoform disorder in which patients express mental stress as physical disability [55]. It usually begins abruptly, helping to distinguish it from organic disorders [56, 57]. In idiopathic PD, tremor tends to vary throughout the day, often becoming prominent in time of stress and disappearing during periods of relaxation.

These variations usually occur over minutes, whereas in conversion the symptoms tend to resolve for hours or even days at a time. Factors that typically worsen tremor in PD—cold, heavylifting, excitement—do not necessarily affect conversion tremor. On examination, signs of conversion resolve with distraction and vary in frequency, while PD is usually invariant in frequency. The slowness of conversion disorders has a more deliberate character, especially during handwriting. Balance impairment is usually not present. The presence of a "belle indifference" attitude is often but not always present in conversion. Some patients with bona fide PD will mask their concern, either because they do not understand the implications of the diagnosis or are in denial. Often patients with conversion have a background in medicine, such as nursing, medical secretary, a lab technician, or have experience with the disorder from a relative. The single most common stressor in women with conversion is a history of childhood sexual or physical abuse.

Infectious Parkinsonism

Classification and Clinical Features

Since von Economo first described acute parkinsonism, similar illnesses have been reported with a myriad of infectious agents. In this section, we have divided the infectious causes of parkinsonism into seven categories (Table 4.2).

Von Economo's disease (ED), also called encephalitis lethargica, was probably seen prior to his initial description of 13 cases with the onset between February and April 1917 in Vienna [58]. Urechia [59] probably described the first recorded credible case series of ED with the onset in April and May 1915 in Bucharest. Somewhat later (1915 or 1916), cases were described in the French army [60, 61]. A massive encephalitis outbreak affecting 65,000 Chinese in the province of Yunnanfu caused devastation from 1917 to 1927 [53, 62]. By 1919, cases had been reported throughout 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*: a "prodromal phenomena consisting of general discomfort, shivering, headache and slight pharyngitis. The temperature is generally only a little

Table 4.2 Classification of infectious causes of parkinsonism

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

raised. Within the next few days, somnolence begins to predominate. The patients, when left to themselves, fall asleep in the act of sitting and standing, and even while walking, or during meals with food in the mouth. If aroused, they wake up quickly and completely, are oriented and fully conscious, but soon drop back to sleep. Sleepiness in this form may last for weeks or even months but frequently deepens to a state of most intense stupor. Generally, during the first days of illness cranial nerve palsies appear. Ptosis is one of the first and most frequent symptoms. Rarely observed are supranuclear paralyses, paresis of convergence, nystagmus, optic neuritis, papilledema, pupillary disturbances and even Argyll Robertson's sign" [63]. In the *hyperkinetic form*, "chorea and hemichorea as well as myoclonic twitches were observed which may degenerate into wild jactations. On the other hand, it may find its mental expression in a general, curious restlessness of an anxious or hypomanic type. In most of these cases, there is a very distinct sleep disturbance and generally the condition is one of troublesome sleeplessness" [63]. Von Economo termed the least frequent form *amyostatic-akinetic*. He described it as "a rigidity, without a real palsy and without symptoms arising from the pyramidal tract. This form of encephalitis lethargica is particularly common in the chronic cases, dominating the clinical picture of parkinsonism. I reserve the name 'parkinsonism,' though symptomatically identical with the amyostatic-akinetic form, rather for the chronic cases. To look at these patients one would suppose them to be in a state of profound secondary dementia. Emotions are scarcely noticeable in the face, but they are mentally intact" [63].

ED was a serious, often lethal disease. "The prognosis of clinically well-documented cases of encephalitis lethargica is 40% mortality, 14% complete recovery, 26% recovery with defect, but able to work, and 20% chronic invalidity" [63]. It is estimated that more than 60% of ED patients who survived developed 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% [64]. The average age of the onset of PEP was approximately 27 years. Resting tremor was the presenting symptom in two-thirds of cases while akinetic-rigid features occurred alone in about one-third [65]. Symptoms were occasionally unilateral and often asymmetrical [66]. Other neurological abnormalities besides parkinsonism were present in most patients. One of the most notable features was the presence of oculogyric crises: "they consist of tonic visual convulsions, occurring in fits and generally lasting only a few minutes, during which the patients as a rule look upwards and sideways" [63]. Other features included dystonia (such as blepharospasm, torticollis, cranial, and torsional dystonia), myoclonus (focal or generalized), facial and respiratory tics, choreoathetosis, obsessive-compulsive behavior, pyramidal signs [66, 67], supranuclear gaze palsy, and eyelid apraxia [68]. One study assessing the accuracy of the diagnosis of PEP in pathologically proven cases showed a high reliability and sensitivity in diagnosis. The best predictors for the diagnosis included the onset below middle age, symptoms lasting more than 10 years, and oculogyric crisis [69]. Recent work has suggested that the relationship between ED and PEP is less clear [70].

The course of PEP is unclear. Duvoisin and Yahr [64] followed 49 patients with probable PEP and observed a stable course or very slow deterioration. On the other hand, Duncan [71] who studied 136 PEP inpatients in London was impressed with the progressive nature of parkinsonian disabilities. Calne and Lees [72] and Viereggel [73] both reported deterioration in motor function, generally late in life. The relatively uniform nature of the deterioration exceeded changes in motor function seen in normal elderly subjects and occurred without comparable age-related changes in intellect. In one report, the mean survival from the onset of symptoms was 23.2 years with the mean age at death of 74.3 years [65]. While there appears to be general agreement that ED and PEP share a viral etiology, no causative agent was ever identified. Its occurrence around the time of the influenza pandemic of 1918 and 1919 has led some to link ED/PEP to the influenza pandemic [74]. However, von Economo himself rejected this hypothesis on several grounds: (1) ED appeared prior to the influenza pandemic; (2) ED/PEP was not contagious, whereas influenza was highly so; (3) their clinical presentations were different; and (4) the pathology was different with typical midbrain lesions in ED/PEP contrasting with diffuse brain congestion in cases of post-influenzal encephalopathy [63]. Since the influenza pandemic affected at least 500 million persons [75] or over one-fourth of the world's population at that time, it is very possible that many individuals with ED may coincidentally also have had influenza [76]. Modern studies using immunocytochemistry and immunofluorescence to detect in situ antigens failed to consistently isolate influenza or any other virus in the remaining brain or CSF samples of neuropathologically confirmed ED and PEP [76–80]. Similarly, the search for autoantibodies did not support an autoimmune mechanism in PEP [81]. Finally, studies on genetic susceptibility of ED/PEP have been inconclusive. While Elizan [82] saw a highly significant increase in the frequency of HLA-B14 antigen in PEP cases, Lees [83] could not confirm this in their samples.

ED cases considered to be associated with the 1917–1927 pandemic occurred until the early 1930s, after which the disease disappeared. Thus, assuming up to a 20-year latency, no PEP cases would be expected to appear after the middle 1950s. Several sporadic ED-like and PEP-like cases, unrelated to the pandemic, have been reported with onset after 1959 [84–91]. Other than one report of positive influenza A antibody titer (1:>160) [90] and another report of CSF cultures yielding coxsackie B4 enterovirus [91], attempts to identify the viral agent in ED-like cases have failed. Nonetheless, the clinical presentation, laboratory studies, imaging, and pathological findings are reminiscent, if not identical, to ED/PEP. To distinguish these cases from parkinsonism associated with viral encephalitides, Howard and Lees [88] proposed major criteria for the diagnosis of ED. The illness should comprise an acute or subacute encephalitic illness with at least three out of the following seven features: (1) signs of basal ganglia involvement; (2) oculogyric crises; (3) ophthalmoplegia; (4) obsessive-compulsive behavior; (5) akinetic mutism; (6) central respiratory irregularities; and (7) somnolence and/or sleep inversion.

Parkinsonism may occasionally accompany viral encephalitides [89]. Table 4.3 lists the viruses known to cause encephalitis with or without associated parkinsonism.

Table 4.3 Causes of viral encephalitis

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

In most instances, parkinsonism associated with viral infection occurs during the acute encephalitic phase or shortly thereafter. If the patient survives, the parkinsonism is usually transient, although it can take several months to resolve. Unlike EP or PEP, oculogyric crises, ophthalmoplegia, cranial neuropathies, or psychiatric/behavioral disturbances are rare.

In HIV-infected patients, parkinsonism may develop from exposure to dopamine blockers (such as prolonged use of metoclopramide); secondary to opportunistic infections (toxoplasmosis, progressive multifocal leukoencephalopathy, tuberculosis) affecting the basal ganglia [91–96]; or as part of HIV encephalopathy in the absence of opportunistic infections [97, 98]. The parkinsonian syndrome is often unresponsive to levodopa [99]. Rarely parkinsonism is associated with nonviral infectious agents: spirochetes (neurosyphilis and Lyme disease), mycoplasma pneumoniae, and opportunistic infections accompanying HIV. Most reported cases of parkinsonism from spirochetal [100, 101] and mycoplasma [102–106] infections present with acute onset and improve markedly with appropriate treatment, despite the severity of the initial clinical presentation. Of the five reported cases with mycoplasma, the presenting extrapyramidal features were parkinsonism and/or dystonia, accompanied by seizures in three cases. All patients were children or young adults, and in all cases, MRI revealed selective involvement of the corpus striatum except for one case with concomitant involvement of the substantia nigra and pallidum [103]. One patient [102] experienced severe dyskinesias and dystonia with levodopa therapy, but symptoms gradually resolved.

In patients with acquired immunodeficiency syndrome (AIDS), parkinsonism, hemichorea-athetosis, and ballismus have been described with opportunistic infection. Parkinsonism, in particular, has been reported with cerebral toxoplasmosis [93, 95], progressive multifocal leukoencephalopathy [107, 108], and cerebral tuberculosis [109]. All but one case presented with bilateral lesions in the basal ganglia. One patient with mycobacterium tuberculosis involving the left lentiform nucleus only developed parkinsonism when the right lentiform nucleus was superinfected with toxoplasma [96]. There is only one reported case of parkinsonism following herpes ophthalmicus [110]. A 5-year-old boy developed isolated fever 15 days after a measles vaccine shot and then developed persistent parkinsonism. MRI showed hyperintense signal affecting the substantia nigra bilaterally. He responded to levodopa but dyskinesias appeared even at low doses [111]. The only other reported case was that of a 38-year-old man who experienced fever, sweats, palpitations, diplopia, and leg tremor within hours of receiving the last of three tetanus vaccinations. Within 1 week, he developed severe parkinsonism with resting tremor, generalized rigidity, and bradykinesia, which responded well to levodopa and a dopamine agonist. Unlike the previous case, parkinsonism was transient [112].

Neuropathology and Imaging

The pathological features of ED differ from those of other viral encephalitides (usually characterized by diffuse brain congestion and edema). In ED, pathology

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

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

Evaluation

A young patient with acute or subacute onset of parkinsonism associated with a febrile illness should have a complete blood count, and blood chemistries including liver, renal, thyroid function tests, antinuclear antibodies, erythrocyte sedimentation rate, chest radiography, electrocardiogram, and blood and urine cultures. CSF should be sent for cell count, glucose, protein, and extra tubes for CSF gram and acid-fast bacilli stain, VDRL, Lyme titers, serologies (for herpes simplex virus, herpes zoster, mumps, measles, adenovirus, enterovirus, cytomegalovirus, Epstein–Barr virus, toxoplasmosis, etc.), and state-run encephalitis PCR panels. Serum ceruloplasmin, 24-h urine copper and heavy metals, toxicology, HIV test, tuberculin-purified protein derivatives test, and serum VDRL may be necessary. An EEG may define seizure activity and helps grade the level of encephalopathy. Brain imaging with contrast can define ring-enhancing or granulomatous lesions. Rarely, duodenal biopsy (to rule out Whipple's disease), blood smear (for malaria), and CSF 14-3-3 protein (for prion disease) may be of value.

Treatment

Comments on Patient 1

This patient had been taking trifluoperazine and lithium, both of which may cause parkinsonism, but she had been taking both for many years, had not had an increase

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

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


IV lorazepam may be therapeutic and diagnostic for catatonia.

Toxic, metabolic, infectious, post-infectious, and structural akinetic rigid syndromes are usually not responsive to symptomatic therapies. Levodopa requires conversion to dopamine by intact nigral cells, suggesting that dopamine agonists may be more effective when the nigra is fully depleted. Unfortunately, the general experience with dopaminergic agents in akinetic rigid syndromes is that levodopa works faster and has fewer side effects; we therefore advocate trials of levodopa for all parkinsonian syndromes except NMS, where a dopamine agonist is our drug of choice. When levodopa is not helpful, we advocate a trial of amantadine 200–400 mg/day in patients with normal renal function. Although amantadine has anti-influenza properties, there is no reason to believe it is useful for other viral syndromes. Dopamine agonists should be initiated at low doses and slowly titrated. Since patients with acute parkinsonism may improve on their own, it may be difficult to gauge the response to a slowly increasing dose of dopamine agonists. Once a patient has improved, our general approach is to slowly taper the medicines, as many patients improve spontaneously.

Comments on Patient 2

This 15-year-old girl developed acute parkinsonism immediately following a presumed viral encephalitis. Measles antibody titers suggested a resolving measles infection. Her parkinsonism gradually resolved over 3 months and was not associated with oculogyric crisis, ophthalmoplegia, myoclonus, or other movement disorders. The presentation is therefore not consistent with ED or PEP. In addition to

supportive measures during the acute encephalopathic phase, delivery of the appropriate antibiotic/antiviral agent may suffice to resolve parkinsonism associated with known viral or bacterial encephalitis. When symptoms persist, levodopa alone or in combination with other adjunctive anti-PD agents may be used. Anticholinergic drugs [122], amantadine [123], bromocriptine, and deprenyl [124] have all been reported to augment levodopa response.

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

Conclusion

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

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