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Parkinsonian Syndromes

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ABSTRACT

Purpose of Review: The different parkinsonian conditions can be challenging to separate clinically. This review highlights the important clinical features that guide the diagnosis of Parkinson disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), and corticobasal degeneration (CBD). Strategies for treatment and disease management are also discussed.

Recent Findings: Over the past decade there has been an increasing recognition of the broad clinical presentations of the neurodegenerative forms of parkinsonism. Nonmotor symptoms in these diseases, including psychiatric, cognitive, autonomic, and gastrointestinal dysfunction, appear to have a major impact on quality of life and disability. PSP and CBD are now considered pathologic diagnoses, with several different and varied clinical phenotypes, that overlap and share features with PD and frontotemporal dementia syndromes. PD is distinguished by its excellent response to dopaminergic medications that is maintained over many years, in contrast to the response seen in patients with MSA and PSP. New diagnostic criteria have been proposed for CBD. No new therapeutic interventions have emerged for PSP, MSA, or CBD. Infusional therapies and deep brain stimulation surgery are established therapies for advanced PD.

Summary: The ''parkinsonian syndromes'' encompass a number of nosologic entities that are grouped together on the basis of their shared clinical features but are separated on the basis of their different pathologies. Overall, the consideration of clinical signs, mode of disease onset, and nature of disease progression are all important to make a timely and definitive diagnosis.

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INTRODUCTION

The parkinsonian syndromes include idiopathic Parkinson disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy (MSA), corticobasal degeneration (CBD), and vascular Parkinsonism (VaP), among other rarer causes of parkinsonism.

Bradykinesia is the most significant and indeed the essential clinical sign that leads to a diagnosis of parkinsonism. Bradykinesia implies abnormal function of the basal ganglia–cortical neuronal circuits that lead to a disorder of motor function manifest as slowed, small-amplitude movements. The clinical recognition of bradykinesia requires the identification of small-amplitude movements that may affect limb control (eg, reduced arm swing, micrographia, lack of dexterity), speech (eg, hypophonia), swallowing (eg, dysphagia for liquids), gait (eg, shortened stride length), facial expressivity (eg, hypomimia), or posture (eg, stooping or leaning). In addition, parkinsonism typically includes extrapyramidal rigidity, rest tremor, and postural instability, which are also considered features of basal ganglia dysfunction.

Parkinsonism is generally regarded in purely motor terms, but a more helpful approach is to broaden this view to incorporate the nonmotor features that evolve coincident with the progressive motor disability of these diseases.[1]

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KEY POINTS

- Bradykinesia is the clinical sign that must be invariably present for the diagnosis of parkinsonism as a syndrome.
- Progressive decrement in movement amplitude or speed is required for classifying bradykinesia. However, slowed movements without decrement (hypokinesia) may be the only sign of basal ganglia dysfunction in progressive supranuclear palsy.
- Rigidity applies to the velocity-independent abnormal increase in resistance to passive movements, yielding a ''lead-pipe'' or ''cogwheel'' quality. Conversely, spasticity is recognized by the velocity-dependent abnormal increase in resistance to passive movements, yielding a ''clasp-knife'' quality.

These symptoms may be caused by basal ganglia dysfunction or other system degeneration, leading to psychiatric, cognitive, autonomic, cerebellar, or pyramidal dysfunction.

THE CLINICAL EXAMINATION

Bradykinesia

Patients with parkinsonian syndromes may report that they have ''slowed down'' or become clumsier, and family members may report an impression of rapid aging or increased frailty. These observations often relate to the emergence of bradykinesia, which is defined as ''slowness of initiation with progressive reduction in speed and amplitude of repetitive action'' and which must be present in order to make a diagnosis of parkinsonism. In the office, this clinical sign may be tested in a number of ways, including repetitive finger tapping (index finger on thumb for 15 seconds), sequential finger tapping (all fingers on thumb), rapid alternating movements (at the wrist), repetitive hand opening, and foot or toe tapping. During these tasks, progressive diminution of the amplitude of movements is seen but may require more than 15 seconds of observation.[2] In more severe cases, motor blocking (causing pauses or freezing of movement) may occur. Evaluation of the handwriting or drawing of an Archimedes spiral may reveal micrographia with characteristic reduction in amplitude with ongoing actions. Spontaneous movements are often reduced, including muscles of facial expression (hypomimia) and noticeably reduced gesticulation. Patients will appear to move stiffly and lack fluidity (en bloc) when standing from a seated position or when sitting, which can often be the first sign when bringing a patient in from the waiting room.

Although decrement in movement is required for the classification of bradykinesia according to Queen Square Brain Bank criteria, slowed movements without decrement (hypokinesia) may be the only sign of basal ganglia dysfunction in PSP.[2] This may reflect more widespread pathologic involvement in these patients compared to PD and could also be seen in patients with VaP.

Extrapyramidal Rigidity

Patients rarely report rigidity or muscle stiffness as a primary symptom, but it is an important clinical clue when diagnosing parkinsonism. In the early stages of disease, rigidity may manifest as pain, which can obscure the diagnosis of a CNS problem—for example, in the case of frozen shoulder and low back pain.[3]

In the office, rigidity is tested by passively moving the wrists, elbows, neck, knees, and ankles through their complete range of movement, with the patient at rest. Extrapyramidal rigidity is defined by abnormally increased resistance to movement that is independent of the velocity of the movement. This increase in tone can have a ''lead pipe'' quality (ie, consistent throughout the movement) or ''cogwheel'' quality (ie, jerky, inconsistent resistance). In contrast, pyramidal tone (spasticity) is dependent on the velocity of passive movement and is described as ''clasp knife'' in quality because of the higher resistance during early acceleration of the passive movement followed by giving way, such as is seen when opening lock-blade knives.

Tremor

The rest tremor of PD is one of the most characteristic signs in clinical medicine. It is differentiated from other forms of tremor by its asymmetry, speed (4 to 6 Hz), the predominance of the tremor at rest (and attenuation or cessation during action),

the re-emergence of tremor when maintaining a posture, and its increase in amplitude during tasks that require mental concentration.[4]

The tremor is evaluated in the office with the patient seated and the forearms supported on the arms of the chair, on a pillow, or resting in the lap. The patient is advised to keep the arms and hands at rest, and a period of observation of up to 60 seconds may be required to allow the tremor to emerge. Asking the patient to perform cognitive tasks (eg, serial subtraction) may rouse the tremor. The patient's arms are then examined outstretched, with particular attention paid to abnormal, dystonic posturing; action myoclonus; stimulus-sensitive myoclonus; or postural tremor. A re-emergent tremor can be seen in PD, often between 5 and 10 seconds after adopting a new posture. Slow pronation and supination of the forearms would often reduce the tremor in PD, but may accentuate a dystonic tremor. Rest tremor in the hand can also be evaluated with the patient walking. PD tremor in the legs is most visible with the patient seated on the edge of an examination couch, with the legs hanging and feet unsupported. Rest tremor of the jaw can also be seen, particularly when the patient is performing an activity with another part of the body.

Gait Disturbance

Postural instability and gait disturbance are universal features of advanced disease in PD but may be an important early sign in patients with PSP or MSA.[5] Even before falls develop, patients often describe a loss of confidence on their feet, a feeling of imbalance or reduced ability to negotiate uneven terrain or stairs. Speed of walking is slowed, and this may be one of the first signs of parkinsonism noticeable to others.

The office examination of gait requires a space 10 meters in length so that the gait can be fully assessed. The patient is asked to stand out of the chair without support (when safe) and walk 10 meters, then turn and walk back to sit down. To assess for gait freezing, the patient is asked to stop and turn 360° and then repeat the turn in the opposite direction. The Parkinsonian gait is narrow based, with shortened stride length that may become shorter over distance, as well as reduced arm swing.[6] Patients will often take several steps to turn. The patient may show hesitancy at the initiation of gait, or freezing of gait, which is often most prominent when turning or walking through doorways or over verges. In most patients with MSA and PSP, tandem gait is impaired.[7] Often in these patients, the gait becomes broad based and unsteady, resembling an ataxic gait. In PSP, a lurching gait with spontaneous falls is characteristic, so careful monitoring of the patient throughout the examination is important.

THE PURPOSE OF CLINICAL DIAGNOSIS

The diagnosis of the parkinsonian syndromes is entirely clinical, as at the present time no imaging, biochemical, or genetic tests definitively diagnose or separate the different diseases.[8] Diagnosis relies on taking a complete medical history that includes timeline of symptoms, recognition of the important clinical signs, and consideration of the differential diagnoses. Individuals' diagnostic acumen is substantially influenced by clinical experience, and even among movement disorder specialists, the clinical diagnosis can change over time because of emerging clinical signs.[9,10]

While the identification of parkinsonism is an important first step for the consideration of therapeutic options,

KEY POINTS

- Slow pronation and supination of the forearms often reduce the tremor in Parkinson disease but accentuate a dystonic tremor.
- Start hesitation or freezing of gait in Parkinson disease are most prominent when turning or walking through narrow spaces, such as doorways.

KEY POINTS

- Postural instability is not an early feature in Parkinson disease and should alert the clinician of an atypical parkinsonian disorder.
- Younger age at onset in Parkinson disease is associated with longer survival and slower accrual of disability.

the differential diagnosis between PD, PSP, MSA, CBD, and VaP does not often provide for further specific disease-modifying therapy. However, a definitive diagnosis serves to inform patients, caregivers, family, and the broader multidisciplinary care team about prognosis, expected clinical progression, disease course, and potentially useful therapeutic modalities. Furthermore, a definitive clinical diagnosis gives a name for the disease, which is regarded by patients as very important and helpful when coming to terms with a chronic disease.[11] Where possible, it is not recommended to diagnose ''atypical parkinsonism'' or a ''parkinsonian syndrome,'' as these terms are meaningless for patients and their care team and provide no further information about management or prognosis. If a definitive diagnosis cannot be reached, then a hierarchical list of diagnostic possibilities should be discussed. In the case of PSP, CBD, and MSA, diagnostic criteria allow for possible and probable diagnostic categories, according to levels of diagnostic certainty.

PARKINSON DISEASE

Clinical Confirmation of Parkinson Disease

The diagnosis of PD is guided by the Queen Square Brain Bank diagnostic criteria,[12] which require two steps. Step one focuses on the definition of parkinsonism and requires the presence of bradykinesia and of either (1) typical rest tremor, (2) extrapyramidal rigidity, or (3) postural instability (**Case 1-1**). However, postural instability is not an early PD feature and should alert the clinician of an atypical parkinsonian disorder. Step two focuses on features typical of the parkinsonism of PD, such as unilateral onset, excellent response to levodopa therapy, and development of dyskinesia. Exclusion criteria include pyramidal signs, stepwise deterioration of parkinsonism (implying stroke), repeated head injury, history of encephalitis or oculogyric crisis, neuroleptic treatment at the onset of symptoms, strictly unilateral features after 3 years, supranuclear gaze palsy, cerebellar signs, early severe autonomic dysfunction, early severe cognitive dysfunction, negative response to levodopa, and imaging evidence of communicating hydrocephalus.

Natural History

The progression of disease and accumulation of disability in PD is variable, and to some extent depends on patient factors, in particular age. Data from the Queen Square Brain Bank suggest that the mean time from diagnosis to death is around 14 years; however, for patients diagnosed in their forties it is 24 years, and for patients in their seventies it is 9.7 years.[13] The mean age of disease onset is 61 years old.

While the cardinal motor signs of PD commonly bring the diagnosis to medical attention, early disease may also include symptoms of depression, fatigue, REM sleep behavior disorder, anosmia, or constipation that require treatment in their own right.[14] Cognitive dysfunction—in particular, mild cognitive impairment with executive dysfunction characterized by difficulties in multitasking, planning, retrieval, concentration, and attention—and visuospatial dysfunction are being recognized at earlier stages.[15]

Throughout the disease course, all patients experience deterioration in their clinical signs, and an associated increase in impairment and disability, with subsequent decline in quality of life. The later stages of disease are characterized by reduced duration of effect of oral medications, increased medication-related side effects, dysphagia, cognitive dysfunction (eventual conversion of PD–mild cognitive

Case 1-1

A 52-year-old salesman presented with a 2-year history of left hand tremor. He had noted the insidious development of left thumb tremor at rest over the course of 2 years that had lately spread to involve his left hand. The tremor was also present when he held a newspaper and could be so intense that it affected his writing and impaired his functioning at work. Over the previous year, he also developed mild pain in the left shoulder. He had a long-standing history of REM sleep-behavior disorder and anosmia but no other neurologic disturbances or family history of neurodegenerative disorders. On examination, he had a normal mental status examination, mood, cranial nerves, and strength. He demonstrated mild hypomimia, a rest tremor in the left hand, and re-emergent postural tremor (ie, it re-emerged with the same frequency it had at rest a few seconds after he extended his arms, as shown in **Supplemental Digital Content 1-1,** *links.lww.com/CONT/A53*). Significant bradykinesia was present on the left with finger tapping, hand movements, and foot tapping with moderate cogwheel rigidity. His gait was normal but lacked associated movement of the left arm, and he displayed a rest hand tremor when walking. Postural reflexes were normal.

He was clinically diagnosed with idiopathic Parkinson disease. Treatment options were discussed, and because his symptoms affected his job performance, medical therapy was recommended and he was started on pramipexole, a dopamine agonist. His bradykinesia improved, but he developed impulse control disorder characterized by gambling and craving food, gaining 3.6 kg in 2 months. These symptoms subsided with the discontinuation of pramipexole. Treatment with levodopa-carbidopa improved the bradykinesia but did not improve the tremor. Benztropine and amantadine induced memory disturbances and had to be discontinued. After deep brain stimulation of the subthalamic nucleus, his symptom control allowed him to resume work.

Comment. This is a typical presentation of Parkinson disease, with classic resting tremor. A tremulous asymmetric parkinsonism phenotype preceded by REM behavior disorder is the most characteristic presentation of Parkinson disease. The case highlights the challenges of therapy, including the development of an impulse control disorder (with a dopamine agonist) and cognitive impairment induced by drugs with anticholinergic properties (amantadine and benztropine).

impairment to dementia), reduced mobility with increased tendency to fall, and, in many, dependence on others for activities of daily living. The mode of death is most often related to respiratory compromise in the setting of bronchopneumonia or aspiration.

Treatment Paradigm

The active treatment of PD begins at the time of diagnosis but does not necessarily require medical therapies immediately. Much of the early treatment focus should be on information delivery, support, and counseling to facilitate a realistic view of PD, prognosis, and management outcomes. These discussions usually take place over a number of office visits and should include a discussion about the medical therapies that are available for PD (**Table 1-1**).

The timing of initiation of dopaminergic therapies is dependent on patient

TABLE 1-1 Medications Used in Parkinson Disease

Class	Medications	Typical Initial Dose	Maximal Recommended Doses	Important Side Effects
Levodopa preparations	Carbidopa/levodopa	25 mg/100 mg 3 times/d	~1200 mg levodopa/d (selected cases may require up to 2500 mg/d divided in 5 or 6 doses)	Short-term: nausea, vomiting, lightheadedness, orthostasis Long-term: dyskinesia, motor fluctuations, hallucinations
	Benserazide/levodopa[a]	25 mg/100 mg 3 times/d		
	Carbidopa/levodopa/entacapone	25 mg/100 mg/200 mg 3 times/d		
Catechol-O-methyltransferase inhibitors[b]	Entacapone	200 mg 3 times/d	200 mg with each dose of levodopa	Same as for levodopa preparations (maximize levodopa effects) Entacapone: diarrhea, brownish-orange discoloration of urine Tolcapone: risk of potentially fatal fulminant hepatic toxicity, which requires close monitoring of liver function tests; diarrhea; brownish-orange discoloration of urine
	Tolcapone	100 mg 3 times/d	200 mg 3 times/d	
Dopamine agonists	Pramipexole	IR: 0.125 mg 3 times/d	IR: 1.5 mg 3 times/d	Excessive sleepiness, impulse control disorders, leg edema, hallucinations, orthostasis
		XR: 0.375 mg/d	XR: 4.5 mg/d	
	Ropinirole	IR: 0.25 mg 3 times/d	IR: 8 mg 3 times/d	Cabergoline is associated with pulmonary fibrosis and cardiac valvulopathy
		XR: 2 mg/d	XR: 24 mg/d	
	Rotigotine patch	2 mg/24hrs	8 mg/24hrs	Apomorphine is associated with orthostatic hypotension, nausea, lightheadedness, sedation
	Cabergoline[a]	1 mg/d	6 mg/d	
	Apomorphine	0.2 mL (2 mg)	0.6 mL (6 mg)	
Monoamine oxidase-B inhibitors	Rasagiline	1 mg/d	1 mg/d	Nausea, lightheadedness, dyskinesia, hallucinations
	Selegiline	5 mg/d	5 mg 2 times/d	
	Selegiline orally disintegrating	1.25 mg every morning	2.5 mg every morning	
Others	Amantadine	100 mg/d	100 mg 3 times/d	Cognitive impairment, hallucinations, dry mouth, myoclonus, livedo reticularis, leg edema

IR = immediate release; XR = extended release.
[a] Formulation not available in the United States.
[b] Catechol-O-methyltransferase inhibitors are used as adjunct to carbidopa/levodopa therapy.

preference, degree of disability, and potential side effects of therapy. In general, early treatment with dopaminergic therapies is recommended, and the choice, depending on age and overall cognition, is between levodopa preparations, dopamine agonists, and monoamine oxidase inhibitors. Monoamine oxidase inhibitors and dopamine agonists are longer-acting medications and therefore require only one dose per day. Levodopa (in combination with a dopa decarboxylase inhibitor) is more efficacious but requires dosing intervals of 3 times per day initially.[16]

The dose adjustments of dopamine agonists and levodopa preparations are made in response to clinical effect, emerging symptoms, and side effects. The risk of psychiatric side effects and dyskinesias is greater at higher doses, so a rule of thumb is to treat with the lowest dose possible to achieve benefits for the patient in terms of function and quality of life. Furthermore, patients below 50 years of age who take doses of greater than 600 mg of levodopa are more likely to experience dyskinesia.[17]

As the disease progresses, motor fluctuations with end-of-dose wearing-off symptoms or peak-dose dyskinesias are inevitable. Initially, the fluctuations will respond well to medication manipulation. Wearing-off symptoms can be alleviated by the addition of monoamine oxidase inhibitors, catechol-O-methyltransferase (COMT) inhibitors, or dopamine agonists, or with increased levodopa dosing frequency. COMT inhibitors (entacapone and tolcapone) can only be used in conjunction with levodopa to increase the ''on'' time, as they yield no intrinsic antiparkinsonian efficacy on their own.

Dyskinesias develop in about 50% of patients with PD, including patients treated with dopamine agonists, levodopa preparations, or monoamine oxidase inhibitors. They are more likely to develop in patients using higher doses of levodopa preparations, in men, and in younger patients. Often, when mild, they do not need any specific treatment. Where possible, doses of dopaminergic medications should be minimized, and in some patients the addition of amantadine can reduce the dyskinesias.

Treatment of depression will often require the addition of tricyclic antidepressants, selective serotonin reuptake inhibitors, or serotonin-norepinephrine reuptake inhibitors. Constipation may respond to dietary adjustment, but patients often require laxatives.

Advanced Treatments

As PD progresses, the development of wearing-off symptoms and dyskinesias can produce severe, disabling motor fluctuations that are not controllable using oral medications. At this point in the disease, advanced therapies are considered, which include deep brain stimulation (DBS) surgery or infusional therapies such as subcutaneous apomorphine or intraduodenal levodopa gel infusions. These therapies are generally reserved for patients who have failed to substantially improve on all of the available oral and transdermal therapies and who do not have symptomatic cognitive or psychiatric effects of PD.[18]

These advanced therapies are best offered by teams that include specialist nurse support and are experienced in their use. DBS, apomorphine, and intraduodenal levodopa can substantially improve motor fluctuations by decreasing both daily off-time and dyskinesias. The benefits of these therapies are known to continue many years after their initiation, but at the same time the underlying pathology progresses. Even in patients who experience an excellent response, advancing disease can lead to the emergence of postural instability and

KEY POINT

- Although seen more often with levodopa, dyskinesias may develop in Parkinson disease patients with dopamine agonists or monoamine oxidase inhibitors, in a dose-dependent fashion.

KEY POINTS

- Threatening visual hallucinations require a sequential reduction or discontinuation in medications according to their decreasing hallucinogenic potential: anticholinergic medications, amantadine, dopamine agonists, monoamine oxidase inhibitors, and lastly levodopa.
- The diagnosis of progressive supranuclear palsy is considered in cases of poor levodopa responsiveness, early postural instability with falls, early executive dysfunction, slowing of vertical saccades, and supranuclear vertical gaze palsy or early dysarthria/dysphagia.
- Early eye-movement abnormalities in progressive supranuclear palsy–Richardson syndrome include slowing of vertical saccades, square-wave jerks (fixation instability), and eventually supranuclear vertical gaze palsy.

falls, cognitive disturbance, autonomic dysfunction, and swallowing and speech disturbance.

Postural hypotension may respond to a high-salt diet but may also require the addition of mineralocorticoids or midodrine. Visual hallucinations require medication adjustment and may need specific therapies if they are troublesome, threatening, or associated with behavioral change. Medications should be reduced or stopped in order of decreasing hallucinogenic potential: anticholinergic medications, amantadine, dopamine agonists, monoamine oxidase inhibitors, and lastly levodopa. However, levodopa dose can only be reduced at the expense of motor deterioration, in which case clozapine is the most effective antipsychotic strategy. Although quetiapine is of lower efficacy, it may be preferred as initial therapy because of its better side-effect profile. While other atypical antipsychotic medications can reduce acute agitation, they often lead to deterioration in the motor parkinsonism. Cholinesterase inhibitors may improve concentration and reduce the occurrence of hallucinations in PD patients with cognitive dysfunction. Cognitive impairment, autonomic dysfunction, and falls are all features of severe PD that substantially affect function and quality of life and incompletely respond to medication manipulation.[19]

PROGRESSIVE SUPRANUCLEAR PALSY

Clinical Confirmation of Progressive Supranuclear Palsy

The clinical manifestations of PSP-tau pathology are variable, and diagnosis can be difficult at times because of the subtle early signs that may be difficult to discern from other physical or psychological symptoms. The diagnosis of PSP should be considered in all patients presenting with parkinsonism not responding to levodopa therapy; postural instability with falls; executive dysfunction; slowing of vertical saccades/supranuclear vertical gaze palsy; or dysarthria/dysphagia (**Case 1-2**).[20]

PSP can be divided into several clinical subtypes, and this separation provides some guidance on prognosis and natural history. Furthermore, the 10% to 30% of patients with PSP-tau pathology who do not present with the classic clinical form of the disease are not diagnosable using the current research diagnostic criteria.[21] The classic form of PSP is referred to as Richardson syndrome (also known as Steele-Richardson-Olszewski syndrome), and other variants include PSP-parkinsonism, PSP–pure akinesia with gait freezing, and PSP-corticobasal syndrome (PSP-CBS).[22] (**Table 1-2**)

Richardson syndrome. Patients with PSP-Richardson syndrome most often report early difficulties with balance, personality changes, visual disturbances, or a combination of these symptoms. The mean age of onset is around 65 years. Medical attention is first sought when patients experience severe postural instability with tendency to fall, the family notices personality changes (apathy), colleagues report underperformance at work, or the patient reports ''slowing down.''

The characteristic eye-movement abnormalities that help confirm the diagnosis of PSP-Richardson syndrome develop over many months, often initially as slowing of vertical saccades and gradually evolve into hypometric saccades, square-wave jerks (fixation instability), and eventually supranuclear vertical gaze palsy.[23,24] Development of these eye-movement abnormalities is associated with midbrain atrophy, a characteristic imaging finding in PSP-Richardson syndrome (**Figure 1-1**[25]). Testing of saccadic eye movements is performed by asking the patient to

Case 1-2

A 59-year-old right-handed man presented with a 3-year progressive history of problems with gait, falls, and speech and visual difficulties. He reported changes in his gait, including slowing and increased difficulty in turning. He developed increasing falls that had become more frequent, particularly when turning and without any clear precipitant. He developed dysarthria and, later, drooling. He had become slower in performing activities of daily living. Over the previous year, he developed photophobia and eye tearing and had recently noted difficulty reading, specifically following lines on a page. He denied symptoms of autonomic dysfunction but had recently noted urinary urgency.

On examination, he was oriented to person, place, and time. Evidence of executive dysfunction and motor perseveration was present. His visual pursuit movements were full, and he demonstrated slowing of vertical saccadic eye movements and significantly decreased vertical optokinetic nystagmus (**Supplemental Digital Content 1-2,** *links.lww.com/CONT/A108*). Square-wave jerks and decreased blink rate were noted. He had moderate hypomimia and mild frontalis overactivity. He displayed increased tone in the neck but normal tone in the limbs, with mild bilateral bradykinesia (finger tapping and toe tapping). He had a slow and wide-based gait and turned en bloc, with diminished postural reflexes. He was unable to tandem walk.

Comment. This patient presented with classic progressive supranuclear palsy or Richardson syndrome with early falls in the context of saccadic abnormalities and a symmetric parkinsonism with axial-predominant rigidity.

generate rapid eye movements between two targets, one in the neutral position (0°) and the other at between 30° and 40° from neutral. This is repeated in four directions (up, down, left, and right), usually asking the patient to make several attempts so that careful judgment of speed of movement can be made. Over time the speed and range of spontaneous and target-directed eye movements becomes reduced, first in the vertical plane, and eventually the eyes become fixed.

TABLE 1-2 Subtypes of Progressive Supranuclear Palsy Pathology

Main Phenotype	Designation
Classic phenotype	Progressive supranuclear palsy (PSP)–Richardson syndrome (sometimes known as Steele-Richardson-Olszewski syndrome)
Parkinson disease–like	PSP-parkinsonism
Pure akinesia (no appendicular rigidity)	PSP–pure akinesia with gait freezing
Asymmetric parkinsonism	PSP–corticobasal syndrome
Frontal-predominant dementia	PSP–frontotemporal dementia

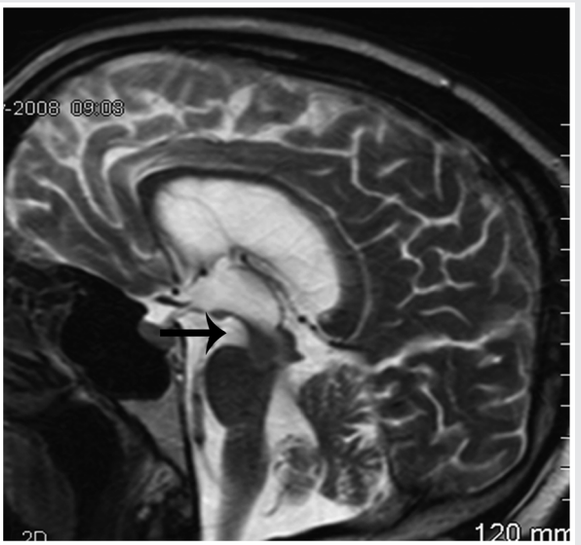

FIGURE 1-1 Sagittal T2-weighted brain MRI of a patient with progressive supranuclear palsy–Richardson syndrome demonstrating substantial atrophy of the midbrain, yielding the ''hummingbird sign'' (*arrow*). Associated frontal-predominant atrophy, as demonstrated by thinning of the anterior portion of the corpus callosum and ex vacuo hydrocephalus is also present.

Reprinted with permission from Biller J, Espay A, Lippincott Williams & Wilkins.[25] © 2013, Wolters Kluwer Health.

KEY POINTS

- Patients with progressive supranuclear palsy–Richardson syndrome do not develop severe autonomic dysfunction, unlike Parkinson disease, dementia with Lewy bodies, and multiple system atrophy.
- Response to levodopa is a feature of early progressive supranuclear palsy–parkinsonism at a stage when postural instability, frontal cognitive impairment, and vertical supranuclear gaze palsy are uncommon.

The cognitive abnormalities that accompany PSP-Richardson syndrome typically affect processing speed and can be tested at the bedside using a frontal assessment battery.[26,27] Memory impairment and severe visuospatial dysfunction are unusual and can be assessed using Addenbrooke's Cognitive Examination, which has characteristic findings in PSP-Richardson syndrome.[28] Ideomotor apraxia and limb dystonia may contribute to impaired limb function in the CBS presentation, also observed in PSP.

Postural instability is usually quite abnormal in PSP-Richardson syndrome, particularly in relation to the relatively mild bradykinesia. It is tested in the office using the pull test, in which the patient stands with feet comfortably apart and is pulled backward by the shoulders sufficiently so that the center of gravity is displaced.[29] This is only performed after the test is explained to the patient, including the instruction that they may take a step backward to steady themselves if required. The examiner will stand less than an arm's length behind the patient and ideally should have a wall less than an arm's length behind the examiner, in case the patient falls backward heavily.

In contrast to PD, dementia with Lewy bodies, and MSA, patients with PSP-Richardson syndrome only rarely develop severe autonomic dysfunction. Cerebellar ataxia, as distinct to gait unsteadiness, is also unusual and is more common in MSA. Patients usually become dependent on others for care 3 to 4 years after disease onset as a result of increasing motor and cognitive slowing.[30] Speech often becomes unintelligible, and recurrent choking can lead to frequent aspiration pneumonia. The mean disease duration from onset to death is about 7 years.[31]

Progressive supranuclear palsy–parkinsonism. In contrast to patients with PSP-Richardson syndrome, PSP-parkinsonism patients develop bradykinesia and limb rigidity at disease onset, which can be asymmetric and, in some cases, associated with a jerky action or rest tremor.[32] Axial rigidity is often a striking early feature, and limb rigidity is more common and severe than in PSP-Richardson syndrome. Parkinsonism in this setting usually improves to some extent after the introduction of dopaminergic therapies, although secondary unresponsiveness occurring over a few years is usual (**Case 1-3**).[33]

Although patients with PSP-parkinsonism appear different from patients with PSP-Richardson syndrome in the first couple of years, over time most will develop severe postural instability, frontal cognitive

Case 1-3

A 58-year-old woman was evaluated 6 years after onset of an asymmetric, levodopa-responsive tremor. Video was taken in the ''on'' state (**Supplemental Digital Content 1-3,** *links.lww.com/CONT/A54*). She showed reduced facial expression, axial-predominant rigidity, and unsteady gait with reduced arm swing and gait freezing during turning. Mild hypometric vertical saccades were present. Eight years after disease onset, she demonstrated mild hypometric saccades on right gaze and moderate hypometric saccadic eye movements in the vertical plane. She had a positive glabellar sign and severe blepharospasm with eyelid-opening apraxia. Her gait had deteriorated with worse postural reflexes, greater difficulty turning, and some mild motor recklessness.

Comment. Progressive supranuclear palsy–parkinsonism is a variant of progressive supranuclear palsy that can be indistinguishable from Parkinson disease at the outset. Early response to levodopa can be robust but wanes over time. Later development of oculomotor dysfunction and blepharospasm are clues that assisted the diagnostic revision in this case.

KEY POINT

- Absence of limb rigidity is a hallmark of progressive supranuclear palsy–pure akinesia with gait freezing.

decline, and vertical supranuclear gaze palsy as the disease progresses.[32] These markers of disease severity emerge later in PSP-parkinsonism than in PSP-Richardson syndrome, and disease duration to death is about 3 years longer in PSP-parkinsonism. PSP-parkinsonism is difficult to differentiate from PD in the earliest stages, but helpful pointers for PSP-parkinsonism may include rapid progression, prominent axial symptomatology, and suboptimal response to levodopa despite typical clinical features of PD.[33] Drug-induced dyskinesias are extremely unusual in PSP-parkinsonism.

Progressive supranuclear palsy–pure akinesia with gait freezing. In this small group of patients, isolated bradykinesia, predominantly affecting gait and leading to gait freezing, is the only initial manifestation of underlying PSP-tau pathology.[34] Patients present to medical attention following the slow emergence of gait difficulties and unsteadiness that may develop for up to 2 years after the freezing of gait and gait-initiation failure develop. Characteristically, these patients also develop early hypophonia, hypomimia, and micrographia. Axial rigidity with increasing neck stiffness in the absence of limb rigidity is a distinctive feature.[35] A supranuclear vertical gaze paresis and blepharospasm develop late in the majority, and in contrast to PSP-Richardson syndrome, cognitive deficits and bradyphrenia are not prominent, although they may occur late in the disease, which has a median duration of more than 10 years.[34,36]

Progressive supranuclear palsy–corticobasal syndrome. CBS has typically been associated with CBD but has been increasingly recognized with several underlying pathologies, including PSP. CBS is characterized by lateralized motor (unilateral ideomotor apraxia, nonlevodopa-responsive parkinsonism, myoclonus, dystonia) and nonmotor features (aphasia, cortical sensory and/or visuospatial deficits). Patients with PSP-CBS are at present almost undistinguishable from those with other underlying pathologies, including corticobasal degeneration.

Progressive supranuclear palsy–frontotemporal dementia. A small number of patients with PSP-tau pathology develop behavioral variant

KEY POINT

- The phenotype of progressive supranuclear palsy may occur as part of the spectrum of frontotemporal lobar degeneration due to tau deposition. This can be suspected in the setting of marked personality changes and/or language abnormalities (usually, nonfluent aphasia).

frontotemporal dementia (progressive personality change including disinhibition, loss of empathy, change in eating patterns, ritualized or stereotypical behavior, and apathy) or progressive nonfluent aphasia (predominant apraxia of speech), which are both considered among the frontotemporal dementia (FTD) syndromes.[37,38] These patients usually develop typical motor symptoms of PSP (ophthalmoplegia, postural instability, rigidity, hypokinesia), although typically more than 5 years after presentation.

Natural History of Progressive Supranuclear Palsy

The progression of disease and accumulation of disability in PSP is more rapid and severe than in PD, even given the variability described among the different clinical subtypes. The mean age at diagnosis is 65 years.[32] Frequent falls, causing fractures and head injuries, contribute substantially to morbidity and may be minimized by physical therapy, use of a weighted walker, and eventually wheelchair use. The terminal stages of disease are characterized by severe communication difficulties, immobility, severe axial rigidity, severe dysphagia and complete ophthalmoplegia (particularly in PSP-Richardson syndrome). As in PD, the mode of death is most often related to respiratory compromise in the setting of bronchopneumonia.

Treatment Paradigm

The active treatment of PSP is directed at optimizing function and alleviating suffering. Supportive therapy using pharmacologic approaches and rehabilitation by a multidisciplinary team is usual. Information delivery, support, and counseling are particularly important in PSP because of the expectation of deterioration and increase in care needs over a short period of time.[39]

The specialist neurologist has a role to help coordinate the multidisciplinary team, educate the patient and caregiver, and clarify the role of medications and interventions in management of the disease. This will include the trial of different medications to improve parkinsonism, affective or adjustment disorders, pain, and sleep disturbance. Physical, occupational, and speech therapy have a crucial role in managing the various progressive symptoms by instituting strategies to overcome impairment and optimize function. Decisions whether to proceed with interventions such as gastrostomy tube insertion to manage dysphagia are made in consultation with the neurologist and speech therapist.

The multidisciplinary team should include the following:

1. Physiotherapist—to assess mobility, with a view to prescribing gait aides when necessary, and instruct on techniques for safe transfers
2. Occupational therapist—to perform an environmental assessment, including the need for lifting devices or wheeled mobility aides, and optimize upper limb function
3. Speech pathologist—to treat difficulties with communication (eg, speech amplifiers or communication boards) and monitor swallowing (modified barium swallow test), with a view to prescribing increased consistencies of food when required
4. Nurse or social worker—to provide support and liaison for strategies to manage medication delivery and coordinate the provision of home care and support as required

Other aspects of care that should be considered include counseling (to assist in coming to terms with the diagnosis

of a neurodegenerative condition and end-of-life decision making) and palliative care (for appropriate nursing near the end of disease).

Medical intervention has a limited role in alleviating symptoms. Unfortunately, the dopaminergic medications do not improve symptoms in PSP to the same extent as in PD, except in PSP-parkinsonism, where the effect often diminishes over months or years. Levodopa responsiveness can be tested by administering escalating doses (with a peripheral decarboxylase inhibitor) up to 1200 mg/d for at least 1 month (if necessary and if tolerated). Dopamine agonists are less effective than levodopa and are not often used in PSP because of their side effects. Amantadine is occasionally helpful in improving motor symptoms, including gait freezing and dysphagia, and may be helpful when sialorrhea is severe. Anticholinergics should be avoided as they may worsen cognition. Antispasmodics for the treatment of the overactive bladder (eg, solifenacin)—ideally those that cross the blood-brain barrier less—may improve the neurogenic bladder symptomatology (urgent micturition). Botulinum neurotoxin is used for treatment of blepharospasm and apraxia of eyelid opening, painful dystonic postures that can affect the neck or limbs, and, more recently, neurogenic bladder.

MULTIPLE SYSTEM ATROPHY

Clinical Confirmation of Multiple System Atrophy

In patients with MSA-parkinsonism, the slow evolution of apparently unrelated symptoms often leads to early misdiagnosis. It is not unusual for a gastroenterologist, cardiologist, sleep medicine physician, and urologist to be involved in the care of patients by the time the neurologic diagnosis is made.

The classic and striking clinical characteristic of MSA is the progressive autonomic dysfunction that often dominates the early clinical picture and precedes the evolution of motor symptoms by up to several years. The diagnosis of MSA is usually considered in patients who develop parkinsonism in the presence of increasing urinary urgency, constipation, postural hypotension, and erectile dysfunction in men.[40] A neuroimaging feature supportive of MSA-parkinsonism is the subtle slitlike signal abnormality of the posterolateral putamen, bilaterally or only contralateral to the more affected side, due to atrophy and excessive iron deposition at the putamen (**Figure 1-2**[25]). A proportion of patients with MSA develop a predominantly cerebellar phenotype with no or only very subtle parkinsonism (MSA-cerebellar),

KEY POINT

- Multiple system atrophy is invariably associated with progressive and severe autonomic dysfunction that often dominates the early clinical picture and precedes the evolution of motor symptoms by up to several years.

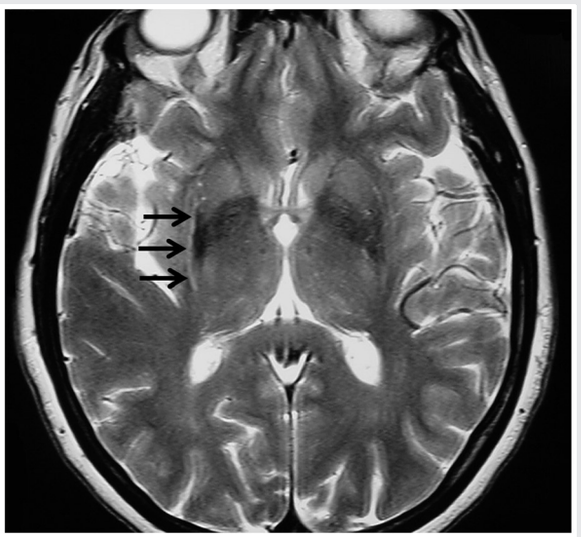

FIGURE 1-2 Axial T2-weighted brain MRI of a patient with multiple system atrophy–parkinsonism demonstrating a slitlike area of hyperintensity bordered by hypointensity (from iron deposition) in the putamen, worse on the right (*arrows*). The putaminal atrophy is always greater on the opposite side of the more affected hemibody.

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KEY POINTS

- Action spontaneous and stimulus-sensitive distal myoclonus is more common than rest tremor in multiple system atrophy–parkinsonism.
- Early autonomic failure, older age of onset, and short interval from disease onset to motor milestones (particularly, frequent falling, unintelligible speech, and severe dysphagia) are predictors of a more aggressive disease of multiple system atrophy.

usually in association with autonomic dysfunction.[40]

The parkinsonism of MSA is usually symmetrical and classically responds poorly to dopaminergic therapies (although in approximately 30% of patients the response is good), and drug-induced dyskinesias can develop, particularly axially. Bradykinesia and rigidity progress somewhat faster than in PD, and as a consequence, postural instability and falls usually emerge within the first 3 years of disease onset. Rest tremor can be present, but stimulus-sensitive myoclonus is more frequent. The gait disturbance of MSA may be purely parkinsonian, purely cerebellar (broad based, unsteady, with truncal and upper limb ataxia giving an appearance of flailing), or a combination of both.

To aid in the clinical diagnosis, in addition to the bedside assessment of parkinsonism, postural blood pressure recordings should be taken. The patient should be assessed after lying supine for several minutes. The blood pressure and pulse rate should be taken, after which the patient stands and blood pressure and pulse is recorded after 2 to 3 minutes of standing. When autonomic failure is present, the blood pressure will fall by more than 20 mm Hg systolic and/or 10 mm Hg diastolic on standing, with no reactive increase in pulse rate (**Case 1-4**).[40]

Natural History

The median survival of patients with MSA with either the parkinsonism or cerebellar phenotype is approximately 8 years, but the range is large.[31] Motor and autonomic features lead to major disability. Early autonomic failure; older age of onset; short interval from disease onset to frequent falling, cognitive disability, unintelligible speech, severe dysphagia, dependence on wheelchair for mobility, and urinary catheter use; and lack of admission to a nursing home facility independently predict short disease survival.[31]

Treatment Paradigm

The appropriate management of patients with MSA requires a multidisciplinary team approach, as for patients with PSP.

Dopaminergic medications. Approximately one-third of patients with MSA-parkinsonism benefit from dopaminergic medication, and 10% may improve more than 50% of their motor symptoms after levodopa therapy. However, in general, the benefits of levodopa in MSA are less gratifying than in PD because they are not as significant and long-lasting. Despite this, an adequate trial of levodopa should be attempted in MSA patients who exhibit parkinsonism. The treatment should be initiated with carbidopa/levodopa 25/100 and could be started at a lower dose than usual (eg, one-half tablet with an increase in dose every other day as tolerated to 3 times a day, and thereafter a weekly increase of one-half tablet per dose to a total dose of up to 1200 mg/d, according to best response or emergent side effects. The use of dopaminergic medications requires caution, as it may worsen orthostatic hypotension and REM sleep behavior disorder.

Autonomic dysfunction. Monitoring and management of comorbid orthostatic hypotension is critical in MSA. It is important to reduce or discontinue any concurrent antihypertensive medications. Other strategies are increasing dietary salt and noncaffeinated fluids, getting up slowly, and wearing thigh-high compression stockings.

Pharmacologic strategies are necessary when the above measures fail. These include increasing the patient's blood volume through the use of fludrocortisone or increasing the peripheral

Case 1-4

A 50-year-old man presented with a 2-year progressive history of gait slowness and instability. He reported frequent falls, was slow in performing activities of daily living, and had noted some jerkiness in his upper limbs as well as progressive dysarthria and lately dysphagia for liquids. Levodopa was started, and the patient showed a moderate improvement in bradykinesia and rigidity but soon developed dyskinesia.

He had a 5-year history of progressive erectile dysfunction and urgent micturition, with occasional episodes of incontinence. He also reported severe constipation.

On examination, his blood pressure was 150/70 lying down, 90/50 standing immediately, and 89/60 at 3 minutes. He denied symptoms of lightheadedness. He had hypermetric saccades, but otherwise his cranial nerves, strength, and sensation were normal. Moderate bradykinesia was present in the upper and lower extremities, with moderately severe axial rigidity and moderate rigidity in the limbs (**Supplemental Digital Content 1-4,** *links.lww.com/CONT/A55*). He showed no tremor at rest, but distal postural and stimulus-sensitive myoclonus was present in the upper extremities, as was minimal dysmetria. His gait was slow and slightly wide-based, and he demonstrated freezing and postural instability, particularly when turning. He progressed significantly, developed stridor, and required a tracheostomy 1 year later.

Comment. This case illustrates a number of key features pointing to multiple system atrophy–parkinsonism despite a falsely reassuring early response to levodopa. Importantly, myoclonus should not be part of the phenomenology of Parkinson disease and was a red flag against this diagnosis. The prominent dysautonomia—including neurogenic bladder, orthostatic hypotension, and the almost-diagnostic inspiratory stridor—were also critical elements supporting the diagnosis of multiple system atrophy–parkinsonism.

KEY POINT

■ Pharmacologic strategies to treat orthostatic hypotension include increasing the blood volume (fludrocortisone) or increasing the peripheral vascular resistance (midodrine or, if midodrine is ineffective, indomethacin or pyridostigmine).

vascular resistance via midodrine or, if midodrine is ineffective, indomethacin or pyridostigmine.

Urologic symptoms. Urinary incontinence or retention are usually present early in MSA. Urodynamic studies are helpful to determine the type of neurogenic bladder. The principal problem is often bladder spasticity, which responds to peripherally acting anticholinergic agents or botulinum toxin. Occasionally, intermittent catheterization or transcutaneous suprapubic catheterization may be required.

Supportive therapy including allied health care team. Considering the limited pharmacologic benefit, it is crucial that MSA patients be treated by a multidisciplinary team as described above for PSP. Because of the occurrence of cervical, laryngeal, and pharyngeal dystonia that can cause upper airway obstruction, tracheostomy and gastrostomy tube may be considered in selected patients. The advisability of either gastrostomy or tracheostomy should be approached on an individual basis with a realistic appraisal of the patient's general quality of life.

CORTICOBASAL DEGENERATION

Clinical Confirmation

CBD usually develops in the fifth to seventh decades of life and presents with various phenotypes that include CBS, FTD, progressive nonfluent aphasia, and

KEY POINT

- Corticobasal syndrome applies to an asymmetric progressive parkinsonism with ideomotor apraxia, rigidity, myoclonus, and dystonia, often associated with an alien limb phenomenon. The pathology can be diverse, including corticobasal degeneration, progressive supranuclear palsy, Alzheimer disease, and frontotemporal lobar degeneration.

Richardson syndrome, which make it a very challenging disorder to diagnose (**Table 1-3**). None of these phenotypes is sufficiently specific to unequivocally diagnose CBD. New diagnostic criteria have been recently developed that include all these phenotypes.[41] These criteria are a step forward regarding identification of possible CBD, but they will need to be validated and may require further refinement. Definite diagnosis of CBD requires autopsy confirmation.

Corticobasal degeneration–corticobasal syndrome. CBS is the classical presentation of CBD; however, CBS can be due to PSP (as described above), a focal form of Alzheimer disease, or FTD.[42] The CBS usually presents with an asymmetric progressive ideomotor apraxia that frequently affects the hand and is associated with rigidity, myoclonus, and dystonia (**Case 1-5**). These symptoms spread to the lower extremity and eventually affect all four extremities but remain asymmetric. The myoclonus is frequently stimulus sensitive but not always present. Dystonia and myoclonus are less frequent than the akinetic-rigid syndrome and apraxia.[43] Alien-limb phenomenon is seen in some patients and identified by involuntary grasping, purposeless movements, or levitation in an apraxic limb. When CBS affects the right extremities, it is more likely to be associated with a nonfluent aphasia, whereas, when affecting left extremities, it may associate at onset with visuospatial and visuoconstructive deficits. Eventually, patients may develop both language and visuospatial deficits, as well as a cortical sensory syndrome and an alien limb. CBS less frequently affects lower extremities first.

Patients with CBS can also manifest oculomotor disturbances. They may present with oculomotor apraxia (delayed latency of saccades with normal optokinetic nystagmus) that frequently would affect horizontal and vertical gaze. However, they can also develop, usually later, vertical supranuclear gaze palsy.

Newly proposed diagnostic criteria for CBD-CBS include two levels of clinical confidence, possible and

TABLE 1-3 Phenotypes Associated With Pathology-Proven Corticobasal Degeneration

Main Phenotype	Key Features
Asymmetric parkinsonism, ideomotor apraxia, dystonia, myoclonus (classic phenotype)	CBD-CBS: 50% of all pathologic diagnoses of CBS
Symmetric parkinsonism, postural instability, oculomotor disturbances (PSP-like)	CBD-PSP: More executive and behavioral abnormalities than in pathology-proven PSP patients
Posterior cortical atrophy (PCA) syndrome (visuospatial disturbances, apraxia, myoclonus)	CBD-PCA: More frequent myoclonus than in other CBS phenotypes (more common Alzheimer disease pathology)
Frontotemporal dementia (FTD) (behavioral, visuospatial, and language disturbances)	CBD-FTLD: Sporadic and familial FTLD-Tau and FTLD-TDP pathologies (see **Figure 1-5**)
Progressive nonfluent agrammatic aphasia (PNFA)	CBD-PNFA: most common aphasia subtype in CBD, but other pathologies are also found in PNFA

CBD = corticobasal degeneration; CBS = corticobasal syndrome; PSP = progressive supranuclear palsy; FTLD = frontotemporal lobar degeneration; TDP = TAR DNA-binding protein (*TARDBP*) coding for TDP-43.

Case 1-5

A 75-year-old woman presented with a 3-year history of progressive loss of control of her right hand. Initially, she noted difficulties with writing, which evolved to a more pervasive loss of dexterity. Performing activities with her right arm became difficult, and she felt that the right arm became ''useless.'' She developed myoclonic jerks and progressive dystonic posturing of the hand and arm. She reported her arm as ''having a mind of its own,'' exhibiting levitation. She also became slower, particularly when getting out of a car and performing activities of daily living. Her speech became slow and dysarthric but without language difficulties. On examination, she was found to have ideomotor apraxia and sensory neglect in the right upper extremity. She exhibited a dystonic right arm and hand myoclonus, with greater bradykinesia and rigidity in the right compared to the left limbs (**Supplemental Digital Content 1-5,** *links.lww.com/CONT/A56*).

Comments. This example of markedly asymmetric parkinsonism with a ''useless'' dystonic and apraxic limb, exhibiting alien-limb phenomena and myoclonus, is the classic presentation of corticobasal syndrome.

KEY POINT

■ Criteria for probable corticobasal degeneration requires an asymmetric presentation of two of the following three symptoms: (1) limb rigidity or akinesia, (2) limb dystonia, (3) limb myoclonus, plus two of the following: (1) orobuccal or limb apraxia, (2) cortical sensory deficit, (3) alien limb phenomena.

probable (**Table 1-4**).[41] Imaging studies often demonstrate asymmetric parietal or frontoparieto-occipital atrophy (**Figure 1-3**[25]).

Corticobasal degeneration–progressive supranuclear palsy. Infrequently, CBD can present with a PSP phenotype that is hard to differentiate from PSP-Richardson syndrome, but in CBD usually there are more cognitive and behavioral frontal disturbances.[44] CBD-PSP patients tend to be more disinhibited than PSP-Richardson syndrome patients.

TABLE 1-4 Clinical Criteria for the Diagnosis of Corticobasal Syndrome[a]

Category of Certainty	Features Required Besides Asymmetric Onset
Probable	**Two of these three:** 1. Limb rigidity or akinesia 2. Limb dystonia 3. Limb myoclonus **Plus two of these three:** 1. Orobuccal or limb apraxia 2. Cortical sensory deficit 3. Alien limb phenomena
Possible	**At least one of these three:** 1. Limb rigidity or akinesia 2. Limb dystonia 3. Limb myoclonus **Plus at least one of these three:** 1. Orobuccal or limb apraxia 2. Cortical sensory deficit 3. Alien limb phenomena

[a] Adapted with permission from Armstrong MJ, et al, Neurology.[41] © 2013 American Academy of Neurology. *www.neurology.org/content/80/5/496.abstract?sid=44cb8cff-d094-4df2-9de1-29b9ebcd2ba3*.

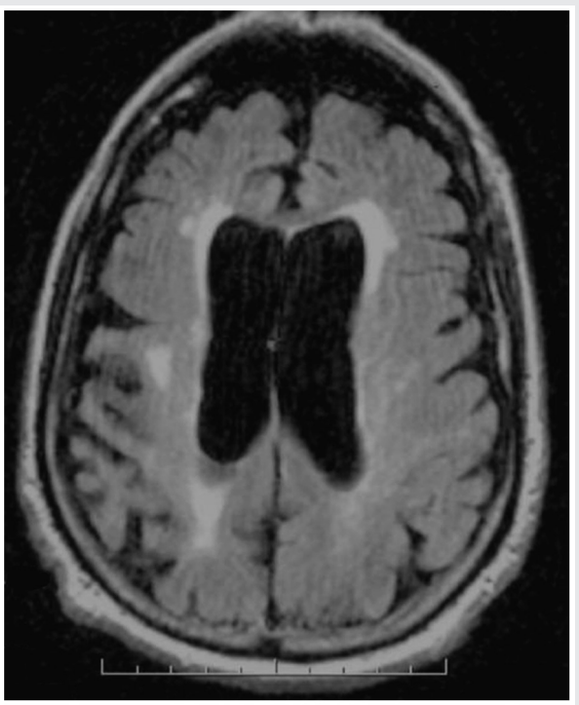

FIGURE 1-3 Axial fluid-attenuated inversion recovery (FLAIR) brain MRI showing asymmetric hemispheric atrophy, predominantly right parietal, in a patient with corticobasal syndrome due to Alzheimer disease pathology.

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KEY POINT

■ The presence of pyramidal signs supports the diagnosis of vascular parkinsonism and excludes Parkinson disease.

Natural History

Patients with CBD may exhibit more than one phenotype during life. Symptoms are relentless and survival is usually 7 to 8 years.

Treatment Paradigm

Pharmacologic therapies are usually of no benefit. The parkinsonism usually does not benefit from dopaminergic therapy, although it is always useful to attempt treatment with levodopa for at least 1 month with the maximum tolerated dose (900 to 1200 mg/d). The most useful symptomatic therapies are those targeting myoclonus (eg, valproic acid, clonazepam, levetiracetam, and piracetam) and dystonia (eg, botulinum toxin) when they affect the patient's quality of life. Treatment of dystonia is indicated when the contractures cause pain or impede hygiene.

Supportive therapy including an allied health care team is important and should follow the principles described above. Patients with CBD benefit from rehabilitation services more than pharmacologic approaches.

IMPORTANT DIFFERENTIAL DIAGNOSES

Vascular Parkinsonism Versus Primary Neurodegeneration

VaP is suspected in the setting of a lower body–predominant parkinsonism and a brain MRI showing extensive subcortical white matter lesions (**Figure 1-4**[25]) (**Case 1-6**).[45] Only around half of patients with VaP develop pyramidal signs, but when present, according to diagnostic criteria, they exclude PD. In a minority of cases, a history of stepwise deterioration will be present, which suggests a large-vessel infarct, and in these patients MRI should demonstrate a vascular lesion involving the globus pallidus externa, substantia nigra, ventrolateral nucleus of the thalamus, or frontal lobe contralateral to the side of parkinsonian symptoms.

If a VaP-suggestive history is not associated with a brain MRI demonstrating leukoencephalopathic changes, a diagnosis of primary neurodegeneration (eg, PD, PSP, MSA, or CBD) should be preferred.

Dystonia Versus Parkinson Disease

Patients with segmental dystonia can develop asymmetric slow movements and rest tremor in the absence of PD neurodegeneration. In these patients, the clinical signs do not progress, or progress extremely slowly, and medications are often not required because of the mild symptoms. Other clinical signs that might suggest dystonic

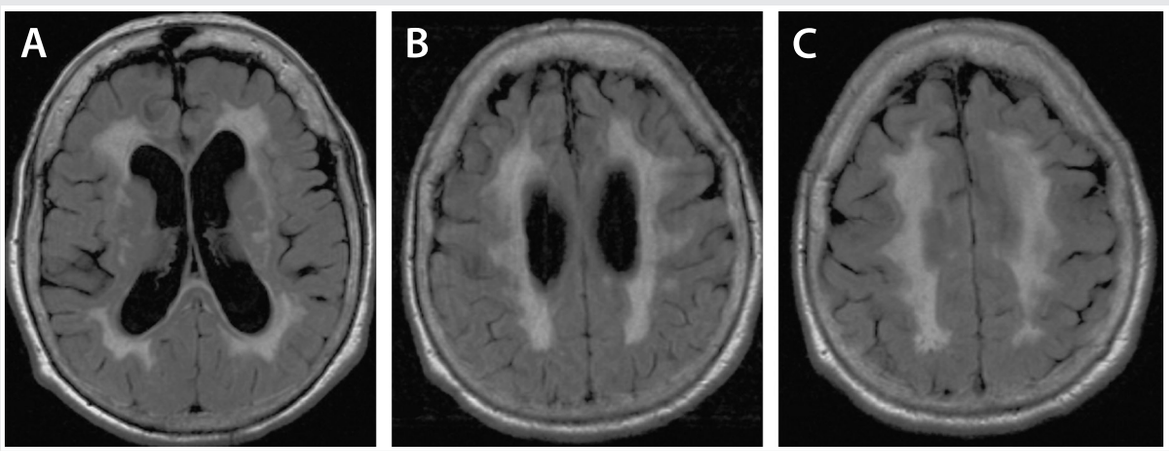

FIGURE 1-4 Axial fluid-attenuated inversion recovery (FLAIR) brain MRI of a patient with vascular parkinsonism demonstrating moderate confluent periventricular and cotton-shaped deep white matter hyperintensities, with associated enlargement of the lateral ventricles and moderate cortical atrophy.

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tremor over PD in this scenario include the presence of hypokinesia (rather than bradykinesia with decrement of movement), position-specific tremor, and the co-occurrence of dystonia in the affected limb.[46]

Frontotemporal Dementia Syndromes

Patients with FTD can develop parkinsonism before, during, or after the development of the frontal cognitive or behavioral disturbances. The spectrum of FTD includes the behavioral variant FTD, primary progressive aphasia, and FTD with ALS. These phenotypes can present as sporadic (tauopathies: PSP and CBD; TAR DNA-binding protein-43 [TDP-43] proteinopathies with or without ALS) or familial diseases (FTD with parkinsonism linked to chromosome 17; TDP-43 proteinopathies due to

Case 1-6

A 75-year-old woman had an 11-year history of gradually progressive slowness in walking and spontaneous falls, with poor responsiveness to levodopa (less than 30% improvement). Brain MRI showed ''age-related vascular changes.'' Muscle stretch reflexes were not exaggerated, and tone was mildly increased, but no clonus was evident. She showed difficulty standing from a chair, start hesitation, and an unsteady short- and wide-stepped gait requiring the use of a four-wheeled walker (**Supplemental Digital Content 1-6,** *links.lww.com/CONT/A57*). Pathologic findings at autopsy confirmed vascular changes within the basal ganglia and no other pathologic abnormalities to account for her clinical signs.

Comment. Patients with vascular parkinsonism most often present with an insidious onset of bilateral parkinsonism with rigidity and bradykinesia, often with an early onset of gait disorder.

progranulin or *C9ORF72* mutations) (**Figure 1-5**[47]).

Niemann-Pick Disease

Patients with Niemann-Pick type C may occasionally present with an akinetic-rigid syndrome, tremor or ataxia, and supranuclear gaze palsy, usually without hepatosplenomegaly. One should suspect this disorder in young patients, usually also when in the presence of seizures and dementia.

Prion Disease

Patients with prion disease can develop a clinical picture that resembles Richardson syndrome or corticobasal syndrome.[48] In general, the progression of disease is fast (months rather than years). Diagnostic MRI, EEG, or

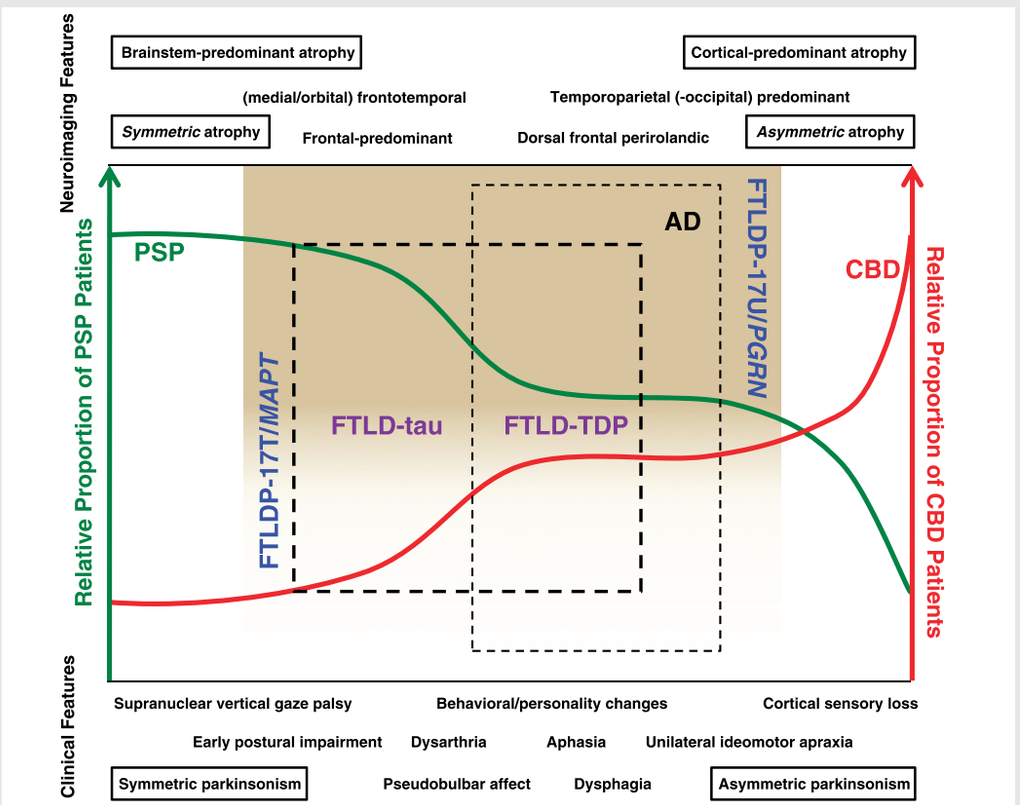

FIGURE 1-5 The pathologic (progressive supranuclear palsy [PSP], corticobasal degeneration [CBD], frontotemporal lobar degeneration [FTLD]–tau, FTLD–TAR DNA-binding protein [TDP], and Alzheimer disease [AD]), genetic (frontotemporal dementia with parkinsonism-17 [FTDP-17]/FTLD with progranulin mutations [FTLD-PGRN], FTDP-17T/FTLD with microtubule-associated protein tau mutations [FTLD-*MAPT*]), clinical (*bottom*), and neuroimaging (*top*) overlap between motor and cognitive disorders. Classic PSP (*green*) is predicted by the presence of symmetric parkinsonism and brainstem predominant atrophy, among other features (*left end of the diagram*; relatively few pathology-proven CBD cases). Conversely, classic CBD (*red*) can be predicted by a markedly asymmetric parkinsonism with cortical-predominant atrophy (*right end of the diagram*; relatively few pathology-proven PSP cases). Less characteristic presentations with co-occurrence of behavioral or personality changes or bulbar/pseudobulbar features fall within the spectrum of FTLD (*purple*)—most often FTLD-tau when PSP-like features are associated, or FTLD-TDP when corticobasal syndrome (CBS)–like or language abnormalities are associated. AD is the most common non-CBD etiology in the CBS spectrum (*also right end of the diagram*).

Modified from Espay AJ,Litvan I, J Mol Neurosci.[47] © 2013 with permission from Springer Science + Business Media. *link.springer.com/article/10.1007%2Fs12031-011-9632-1*.

Case 1-7

A 74-year-old woman was seen 2 months after the onset of clumsiness of the left hand. She was observed to have left-sided dystonia, apraxia, and myoclonus (action and stimulus sensitive) (**Supplemental Digital Content 1-7,** *links.lww.com/CONT/A58*). She also had alien limb phenomenon, rigidity, and cortical sensory loss. She died 3 months later, and a pathologic and immunohistologic diagnosis of prion disease (Creutzfeldt-Jakob disease) was made.

Comment. In patients in whom the clinical syndrome is rapidly progressive, primary neurodegeneration must not be assumed. Prion disease should be suspected in very rapidly progressive Richardson syndrome or corticobasal syndrome.

CSF findings are supportive, but definitive diagnosis remains pathologic (**Case 1-7**).

SUMMARY

The different parkinsonian syndromes are separated by subtle but definite signs and symptoms that can be recognized through careful evaluation. Consideration of the differences, particularly in the mode of presentation and disease progression, may lead to an earlier diagnosis and more certain treatment and greater understanding of the disease for patients, their caregivers, and other health care professionals. Recognition of these different syndromes will become increasingly important in the era when disease-specific treatments emerge.

VIDEO LEGENDS

Supplemental Digital Content 1-1

Idiopathic Parkinson disease. Video shows the patient with clinical diagnosis of idiopathic Parkinson disease described in **Case 1-1**. He shows left hand resting tremor with reemergence on posture and exacerbation during walking. Decrement of amplitude and speed can be seen during performance of rapid alternating movements.

links.lww.com/CONT/A53

Supplemental Digital Content 1-2

Progressive supranuclear palsy. Video shows the patient clinically diagnosed with progressive supranuclear palsy described in **Case 1-2**. The oculomotor examination shows preserved horizontal pursuit. Vertical pursuit is interrupted by square-wave intrusions. Convergence is absent. Square-wave jerks are present in primary gaze. Optokinetic nystagmus is horizontally preserved and vertical optokinetic nystagmus is reduced, with observation of square-wave jerks. He also shows poor blink rate.

links.lww.com/CONT/A108

Supplemental Digital Content 1-3

Progressive supranuclear palsy–parkinsonism. Video shows the patient with early clinical diagnosis of Parkinson disease described in **Case 1-3**, who progressed to a progressive supranuclear palsy phenotype between 6 and 8 years after symptom onset (both time points shown in the video). Later development of oculomotor impairment and blepharospasm with apraxia of eyelid opening were clues regarding the revised diagnosis.

links.lww.com/CONT/A54

Supplemental Digital Content 1-4

Multiple system atrophy, parkinsonian type. Video shows the patient in **Case 1-4** who has been clinically diagnosed with multiple system atrophy, parkinsonian type. He is shown to have a tremorless parkinsonism with axial-greater-than-appendicular rigidity, distal-arm postural and stimulus-sensitive myoclonus, and slow, slightly wide-based gait with freezing and postural instability when turning.

links.lww.com/CONT/A55

Supplemental Digital Content 1-5

Corticobasal syndrome. Video shows the patient clinically diagnosed with corticobasal

syndrome described in **Case 1-5**. Among other features, she illustrates an asymmetric parkinsonism with a markedly dystonic right arm, myoclonus, ideomotor apraxia, and cortical sensory loss.

links.lww.com/CONT/A56

Supplemental Digital Content 1-6

Vascular parkinsonism. Video shows the patient with a pathologic diagnosis of vascular parkinsonism described in **Case 1-6**. The patient demonstrates severe gait impairment with start hesitation, short- and wide-stepped gait, and reliance on a walker for ambulation.

links.lww.com/CONT/A57

Supplemental Digital Content 1-7

Creutzfeldt-Jakob disease. Video shows the examination of the patient in **Case 1-7** who shows left-sided dystonia, rigidity, apraxia, myoclonus, and cortical sensory loss. Pathologic diagnosis confirmed Creutzfeldt-Jakob disease.

links.lww.com/CONT/A58

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