Progressive Supranuclear Palsy, Corticobasal Degeneration, and Multiple System Atrophy

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REVIEW ARTICLE

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ABSTRACT

PURPOSE OF REVIEW: **Patients who have parkinsonian features, especially without tremor, that are not responsive to levodopa, usually have one of these three major neurodegenerative disorders rather than Parkinson disease: progressive supranuclear palsy (PSP), multiple system atrophy (MSA), or corticobasal degeneration (CBD). Each of these disorders eventually develops signs and symptoms that distinguish it from idiopathic Parkinson disease, but these may not be present at disease onset. Although these conditions are not generally treatable, it is still important to correctly diagnose the condition as soon as possible.**

RECENT FINDINGS: **In recent years, it has been increasingly recognized that the symptoms of these diseases do not accurately predict the pathology, and the pathology does not accurately predict the clinical syndrome. Despite this, interest has grown in treating these diseases by targeting misfolded tau (in the case of PSP and CBD) and misfolded α-synuclein (in the case of MSA).**

SUMMARY: **Knowledge of the characteristic signs and symptoms of PSP, MSA, and CBD are essential in diagnosing and managing patients who have atypical parkinsonian syndromes.**

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Dr Greene reports no disclosure.

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Dr Greene discusses the unlabeled/investigational use of medications for the treatment of atypical parkinsonism, none of which have been approved by the US Food and Drug Administration.

INTRODUCTION

After the introduction of levodopa to treat Parkinson disease (PD) in the late 1960s, the pathologies and clinical pictures of dopamine deficiency syndromes broadened dramatically. Clinicians identified patients who had signs of dopamine deficiency (masked facies, hypophonia, rigidity, slowness of movement and gait, loss of postural reflexes, and sometimes resting tremor and other features) but, unlike patients with PD, had minimal or no improvement with levodopa. As a group, these patients are said to have atypical parkinsonism. Today, the most common of these disorders are progressive supranuclear palsy (PSP), followed by multiple system atrophy (MSA) and corticobasal degeneration (CBD). The major problem, especially for PSP and CBD, is that patients with typical clinical signs and symptoms of the disease may have very different pathologies, and patients

with the same pathology may have different clinical signs and symptoms. Unfortunately, no definitive diagnostic tests are easily available to distinguish these diseases from each other during life. The gold standard diagnostic test is autopsy, but autopsies are highly selected and may lead to conclusions that do not represent the entire population of a disease.

The history of MSA extends back at least to 1900.[1] In 1900, Dejerine and Thomas[2] described cases of late-onset ataxia and parkinsonism, later termed olivopontocerebellar atrophy. In 1960, Shy and Drager[3] presented two cases of men aged 39 and 49 who developed impotence and urinary disturbance followed by multiple autonomic deficits, parkinsonism, ataxia, and, in one case, lower motor neuron disease, which was referred to as Shy-Drager syndrome.[3] In 1960 and 1961, Adams, van Bogaert, and van der Eecken[4,5] reported four cases of patients with gliosis of the striatum and degeneration of the substantia nigra who had rapidly progressive parkinsonism but also autonomic failure and cerebellar deficits, which they referred to as striatonigral degeneration. Similar cases had been reported before these three reports, but these reports were the first to identify each of these conditions as a syndrome. In 1969, Graham and Oppenheimer[6] reviewed the published literature on patients with autonomic failure and either clinical symptoms or pathology indicating cerebellar and striatonigral involvement. They felt these syndromes overlapped so much that they should all be labeled MSA.[6] In 1998, Lantos[1] described α-synuclein deposits in glia (glial cytoplasmic inclusions) in all three conditions, making it even more likely they were all part of the same spectrum.

In 1964, Steele, Richardson, and Olszewski[7] coined the term *progressive supranuclear palsy* (PSP) after reporting on patients with parkinsonism, loss of postural reflexes, supranuclear gaze palsy, axial rigidity, pseudobulbar state, and dementia who had midbrain and pontine degeneration as well as neuronal loss in the substantia nigra.

In 1968, Rebeiz and colleagues[8] reported on three patients with asymmetric parkinsonism, apraxia, involuntary elevation of upper and lower extremities, and posturing, which would probably now be called dystonia, and a unique pathology involving the cortex as well as the basal ganglia and cerebellum and with neuronal achromasia. They referred to this as corticodentatonigral degeneration with neuronal achromasia, which was later shortened to corticobasal degeneration (CBD).

Although PSP, CBD, and MSA are difficult to accurately clinically diagnose at this time, this article presents the signs and symptoms of these conditions based primarily on clinical experience. Although relatively large series of patients with these conditions have been published based on autopsy, this article bases descriptions primarily on clinical experience. The reason for this choice is that autopsy series have two major shortcomings: (1) autopsies are rarely based on random or consecutive selection, leading to referral bias that is impossible to quantify and (2) the history and physical examinations in most autopsy series are not performed systematically by movement disorder specialists and sometimes not even by neurologists.

For more information on clinical features of autopsy-documented cases of PSP, CBD, and MSA, refer to Respondek and colleagues,[9] Armstrong and colleagues,[10] and Wenning and colleagues,[11] respectively.

PROGRESSIVE SUPRANUCLEAR PALSY

Currently, the most commonly diagnosed of these three syndromes is PSP.

Clinical Symptoms and Signs

The signs and symptoms of PSP vary, probably because different parts of the brain may be affected first and to different degrees. Patients with the classic presentation, also called Richardson syndrome, develop a symmetric akinetic rigid syndrome with axial greater than limb rigidity, lack of resting tremor (although they may have an action tremor), early development of a supranuclear gaze palsy, and lack of response to levodopa.[12] Supranuclear gaze palsy is the inability to look up or down on command, but upgaze is present when the neck is passively flexed, and downgaze is present when the neck is passively extended (ie, the doll's eyes maneuver). Patients may have continuous square-wave jerks and other oculomotor disturbances, early loss of postural reflexes leading to falls, and progressive dementia. Square-wave jerks are involuntary horizontal saccades that go alternately to the right and then to the left with brief pauses before changing direction.

Patients with PSP often have an unusual facial expression, labeled dystonia, with deep nasolabial folds and furrowed brow, giving them an angry or puzzled expression. Patients may have hypophonia, often have growling speech, and frequently become aphonic. Patients with PSP develop dysphagia early in the course of the disease, and aspiration pneumonia is common. They often have a broad-based, slightly ataxic gait and often walk with their arms abducted and elbows flexed (a "gunslinger" gait). Gait freezing is common, and freezing of speech and manual movements may also occur.

Patients with Richardson syndrome (and other PSP subtypes) have a large variety of visual symptoms and signs. Patients with PSP often have limited downgaze and report difficulty reading, seeing the food on their plates, and looking at their feet while walking. They report diplopia, blurred vision, or more vague visual disturbances. They often have a severe reduction in blink rate and lid retraction, giving them a staring appearance. They have loss of vertical optokinetic nystagmus, and they may also develop blepharospasm. Occasionally, patients with PSP are unable to open their eyes, even without activation of the orbicularis oculi, which is referred to as apraxia of eyelid opening; even less commonly, patients are unable to close their eyes on command, referred to as apraxia of eyelid closing. It is now known that the apraxia of eyelid opening is not a true apraxia but a result of prolonged levator palpebrae inhibition following normal antagonist inhibition after a blink.[13]

The dementia of Richardson syndrome usually involves bradyphrenia (ie, difficulty with attention and difficulty shifting tasks) and is considered a subcortical dementia, but the dementia of other PSP subtypes may differ, and mixed features of dementia are not uncommon. Bradyphrenia is when patients can answer questions and reason appropriately but take longer to do these tasks than would be reasonably expected. Patients usually have frontal release signs, such as glabellar, snout, and grasp reflexes. Depression is common, but apathy without depression is also common. Disinhibition leads to frequent falls in those with poor balance. Emotional incontinence can lead to emotionless crying or laughing (pseudobulbar palsy). A patient with Richardson syndrome is described in **CASE 2-1**.

Some patients with the pathology of PSP present with what looks like levodopa-responsive, asymmetric PD with resting tremor. These patients go on to lose levodopa responsiveness and develop imbalance, eye movement abnormalities, and the other signs and symptoms of classic PSP, which is referred to as PSP with

KEY POINTS

- **Patients with parkinsonian features who do not improve with levodopa usually do not have idiopathic Parkinson disease and often have either progressive supranuclear palsy, multiple system atrophy, or corticobasal degeneration.**
- **Progressive supranuclear palsy is a likely diagnosis in patients with parkinsonian features and early development of a supranuclear gaze palsy.**
- **Some patients with progressive supranuclear palsy do not develop a supranuclear gaze palsy until later in the course of the disease. Early features that suggest progressive supranuclear palsy are an angry or puzzled look, growling speech, early development of dysphagia, and a broad-based gait with abducted arms.**

predominant parkinsonism (PSP-P). Some patients' symptoms begin with gait freezing, micrographia, and imbalance, which is referred to as pure akinesia or PSP with progressive gait freezing (PSP-PGF). Some patients present with nonfluent primary progressive aphasia or progressive apraxia of speech, referred to as PSP with predominant speech/language disorder (PSP-SL). Other patients have PSP with predominant corticobasal syndrome (PSP-CBS).

As the number of autopsies on patients with PSP grows, less common initial symptoms of PSP pathology have resulted in more categories, such as PSP with predominant ocular motor dysfunction (PSP-OM), which begins with oculomotor signs/symptoms; PSP with predominant postural instability (PSP-PI); PSP with predominant frontal presentation (PSP-F), which begins with a frontal syndrome

CASE 2-1

A 68-year-old woman presented for a neurologic consultation because of a 2-year history of progressive neurologic symptoms. She had begun losing her balance and falling since age 66. Shortly after that, her speech had become difficult to understand, and she coughed when swallowing liquids. She did not have diplopia but described blurred vision, especially when she looked down to read or to see the food on her plate. Her family noticed that she was impulsive and sometimes would begin laughing at odd times. She was forgetful and seemed confused at times. Her balance continued to worsen, and she fell sideways if she used a walker, so she began to use a wheelchair. She needed help to dress and feed herself, but it was not clear if this was because of lack of dexterity or confusion. She developed apraxia of eyelid opening, which did not improve with botulinum toxin injections in a low dose. She had a history of diabetes mellitus, hyperlipidemia, and hypertension.

On examination she had glabellar, snout, and bilateral grasp reflexes. She had a furrowed brow but no other facial dystonia. She had apraxia of eyelid opening and a markedly reduced blink rate when her eyes were forced open. She had continuous square-wave jerks. She had no downgaze and reduced upgaze but full range with doll's eyes maneuver and had no saccades in any direction. She had a mildly soft voice with a growling quality. She had no resting tremor. She had mild rigidity of the neck in the anterior-posterior direction but no limb rigidity. Her rapid alternating movements were slow and clumsy in all limbs. She needed assistance to rise from a chair. She fell spontaneously in all directions. When supported, she had a slow, broad-based gait with marked reduction in stride. She turned en bloc and had start-and-turn freezing of gait.

COMMENT

This case shows a typical presentation and examination for the classic presentation of progressive supranuclear palsy (PSP) (PSP–Richardson syndrome). The supranuclear gaze palsy developed fairly early, making the diagnosis easier, but some patients with PSP may not develop eye movement abnormalities until late in the course. The early loss of postural stability, growling voice, furrowed brow, and apraxia of eyelid opening were important clues to the correct diagnosis.

including behavioral changes such as irritability and other personality changes, lack of insight, inappropriate behavior, impulsivity, and stereotyped behaviors; PSP with cerebellar ataxia (PSP-C), which begins with ataxia; and PSP with primary lateral sclerosis (PSP-PLS), which starts with a generalized spasticity syndrome similar to primary lateral sclerosis.[12] In some patients with PSP pathology, symptoms may start with just dementia, although no abbreviation for the terminology currently exists,

To complicate matters even more, a variety of other pathologies may present clinically as PSP (sometimes called PSP syndrome). These include the pathologies of Whipple disease, Niemann-Pick disease type C, Gaucher disease, prion disease, Alzheimer disease, and others.[12]

The course of PSP depends on the initial symptoms but the course can vary even with the same initial symptoms. Duration of disease ranges from 2 years to 28 years (mean of 8.7 years) depending on the subtype.[14] The life-threatening symptoms of all forms of PSP are loss of balance leading to falls, aspiration, and infection due to pressure ulcers.

Pathology

The pathology of PSP consists of widespread atrophy and neuronal loss with marked atrophy of the midbrain, subthalamic nucleus, dentate nucleus, and superior cerebellar peduncle but also of the frontal cortex and other basal ganglia structures.[15] Accumulation occurs of mainly 4-repeat tau in neurofibrillary tangles in neurons in widespread areas including the subthalamic nucleus, globus pallidus, substantia nigra, locus coeruleus, periaqueductal gray matter, superior colliculi, inferior olive, red nucleus, oculomotor nuclei, and the prefrontal and precentral cortex. Tau also accumulates in astrocytes (called tufted astrocytes), distinct from the astrocytic plaques in CBD, and accumulations in oligodendroglia (called coiled bodies) and threadlike processes in the white matter. For a detailed description of the pathology of the subtypes of PSP, see the study by Dickson and colleages.[15]

Treatment

Treatment options for the symptoms of PSP are similar to the options in the other disorders discussed in the section below on the treatment of symptoms in PSP, MSA, and CBD. Attempts to treat the disease itself have not had success as of 2019.[14] The most recent attempts to arrest or at least modify the course of PD and the syndromes discussed here depend on the hypothesis that diseases involving misfolded tau or α-synuclein depend on the prionlike properties of misfolded tau or α-synuclein.[14,16] Clinical trials are underway of agents that might potentially reduce the spread of misfolded tau in PSP.[14]

CORTICOBASAL DEGENERATION

The classic presentation of CBD combines markedly asymmetric rigidity and bradykinesia with focal or hemidystonia and cortical deficits. Most patients develop symptoms in their fifties to seventies.

Clinical Symptoms and Signs

As with the other syndromes discussed in this article, the parkinsonism is usually without tremor, does not respond to dopamine replacement therapy, and loss of balance usually occurs early in the course. The dystonia, which may be painful, develops gradually but often becomes severe and fixed, leading to contractures.

KEY POINTS

- A minority of patients with the pathology of progressive supranuclear palsy may have signs and symptoms suggesting a variety of conditions, including corticobasal degeneration and, rarely, idiopathic Parkinson disease, primary progressive aphasia, cerebellar ataxia, frontotemporal dementia, and primary lateral sclerosis.
- Other pathologies may produce signs and symptoms suggestive of progressive supranuclear palsy, including Alzheimer disease, some frontotemporal dementias, Whipple disease, Niemann-Pick disease type C, and Gaucher disease.
- The pathology of progressive supranuclear palsy is characterized by deposits of 4-repeat tau in astrocytes and oligodendroglia in multiple regions of the basal ganglia and cortex of the brain.
- Preliminary studies of agents that interfere with the formation or spread of misfolded tau are being conducted with the hope of stopping or slowing the progression of progressive supranuclear palsy.

The patient's dystonia may make it difficult to assess apraxia. Speech is hesitant and dysarthric, and aphasia and apraxia of speech occur. Other cortical signs may include apraxia (difficulty performing motor activities despite normal understanding and normal sensory/motor systems); cortical sensory loss (eg, two-point discrimination, agraphesthesia [difficulty recognizing letters/numbers written on the skin with eyes closed] and astereognosis [difficulty recognizing objects by touch alone]); cortical myoclonus (spontaneous or reflex, or both), which can be diagnosed accurately only with electrophysiology but usually consists of multifocal, very rapid shocklike jerks; alien limb phenomenon

CASE 2-2

A 78-year-old woman presented for evaluation of a 2-year history of neurologic symptoms. Her initial symptoms were slowness, difficulty walking, and imbalance causing falls in all directions. One year after onset, she began to rub the fingers of her right hand on her leg. She lost dexterity in that hand, developed dystonic posturing, and switched to using her left hand. She then developed jerks of her right arm that were present at rest and increased when she tried to use her arm. When she lifted the right arm while sitting, her right leg would rise off the ground. She noticed that she had difficulty performing tasks with her left hand, although that hand was not particularly slow or stiff. The hand would sometimes move out of her control. Her voice became soft and hoarse, and she had difficulty finding the words she wanted and spoke in short phrases. She developed mild to moderate forgetfulness. She had been diagnosed with parkinsonism and given carbidopa/levodopa without benefit.

On examination she had no frontal release signs. Extraocular movements were intact without nystagmus or square-wave jerks. She had mild hypomimia and hypophonia. She had no resting tremor but had a coarse, jerky action greater than postural tremor of the left upper extremity that suggested myoclonus as well as tremor. She had mild slowing and rigidity of the left upper extremity. Her right upper extremity could not be tested because of severe dystonic posturing that increased when she tried to use the hand. She had slowing of the right more than the left lower extremity. She could not imitate picking up a key with her left hand and could not identify a penny or paper clip placed in either hand. She could not recognize letters written on her left hand with her eyes closed. She needed assistance to rise from a chair. Her dystonic posturing of the right upper extremity worsened with walking, she had a slow gait with decreased stride, and she had very poor postural reflexes.

COMMENT

The asymmetric dystonia suggests corticobasal degeneration (CBD), although it may occur in progressive supranuclear palsy as well. The presence of myoclonus in one limb and apraxia, astereognosis, and agraphesthesia make the diagnosis of CBD more likely. Most patients with CBD have dystonia, myoclonus, and cortical deficits all on the same side, but occasionally they may have dystonia on one side and the other findings on the opposite side as in this patient.

(involuntary movements of a limb together with the patient's feeling that the limb does not belong to him or her); aphasia; apraxia of speech; and even hemiparesis. Dementia is common in patients with CBD.

Although some patients with CBD do make movements with a limb that seems foreign to them, they often have an overflow phenomenon in which movement in one limb triggers an involuntary movement in another, usually ipsilateral, limb. Resting tremor is very rare, but action tremor, often combined with myoclonus, is common. Supranuclear gaze palsies can occur late in the disease. CASE 2-2 describes a patient with classic CBD.

Pathology

The pathology of CBD consists of asymmetric cortical atrophy usually in the frontoparietal region with relative sparing of the occipital lobes. Swollen vacuolated neurons are found in the atrophic cortical areas and to a lesser degree in the affected subcortical regions. These ballooned neurons contain phosphorylated neurofilaments and sometimes tau and ubiquitin. As with PSP, widespread neuronal loss and gliosis is seen, not just in the affected cortex but also in the globus pallidus, putamen, red nucleus, thalamus, subthalamic nucleus, substantia nigra, locus coeruleus, and, to a lesser degree, in the dentate nucleus. Remaining neurons in affected areas contain inclusions: globose tangles called corticobasal bodies and tau fibrils around nuclei of oligodendroglia called coiled bodies. Unlike the tufted astrocytes in PSP, the typical glial findings are tau-containing processes surrounding astrocytes called astrocytic plaques. As in PSP, 4-repeat tau predominates, but the insoluble tau fragments in CBD have a different ultrastructure from the insoluble fragments of tau in PSP.[17]

As with PSP, the pathology of CBD may also present as multiple other syndromes: a classic PSP syndrome, primary nonfluent aphasia, a frontal dementia with executive dysfunction and behavioral change, pure Alzheimerlike dementia or, rarely, idiopathic PD.[10,17] Also, as in PSP, a variety of other pathologies can mimic the clinical features of CBD, known as corticobasal syndrome (CBS). These include the pathologies of PSP, Alzheimer disease, Pick disease, frontotemporal lobar degeneration with ubiquitin– and TDP-43–positive inclusions, dementia with Lewy bodies, frontotemporal lobar degeneration with fused-in-sarcoma–positive inclusions, and Creutzfeldt-Jakob disease.[18] Consensus criteria have been proposed for the clinical diagnosis of CBD, but the criteria have proven neither sensitive nor specific (sensitivity was 68.4%, specificity was described as low but percentage was not given).[10,19] VIDEO 2-1 (*links.lww.com/CONT/A56*) and VIDEO 2-2 (*links.lww.com/CONT/A204*) contain examples of patients with CBS and CBD, respectively.[20,21]

Treatment

As with PSP, the current attempts at treating CBD itself as opposed to treating the symptoms are focused on detoxifying misfolded tau.[22]

MULTIPLE SYSTEM ATROPHY

PSP and CBD have overlapping symptoms with PD despite having a pathology that includes misfolded tau and not–misfolded α-synuclein. MSA also shares symptoms with PD, and its pathology includes misfolded α-synuclein, not–misfolded tau, but MSA also can have a variety of complex presentations.

KEY POINTS

- The clinical hallmarks of classic corticobasal degeneration are parkinsonism combined with unilateral dystonia, myoclonus, and cortical deficits such as apraxia, cortical sensory loss, and alien limb phenomenon.
- As in progressive supranuclear palsy, the pathology of corticobasal degeneration also involves widespread deposition of 4-repeat tau but also includes asymmetric cortical atrophy and neuronal, oligodendroglial, and astrocytic deposits distinct from the deposits in progressive supranuclear palsy.
- As with progressive supranuclear palsy, multiple pathologies may mimic the signs and symptoms of corticobasal degeneration, including progressive supranuclear palsy, Alzheimer disease, Pick disease, and Creutzfeldt-Jakob disease. When this happens, it is known as corticobasal syndrome. Similarly, the pathology of corticobasal degeneration may present as progressive supranuclear palsy, primary nonfluent aphasia, Alzheimer disease, and other conditions.

Clinical Symptoms and Signs

When middle-aged patients have sporadic disease with parkinsonism (usually including bradykinesia and rigidity), autonomic insufficiency (usually including urinary incontinence or retention, orthostatic hypotension sometimes alternating with hypertension, anhidrosis, and impotence in men), and cerebellar abnormalities (including ataxia, dysmetria, and nystagmus), MSA is the most likely diagnosis. However,

CASE 2-3

A 58-year-old right-handed man presented for a movement disorders consultation for a 3-year history of progressive neurologic symptoms that began with impotence, urinary incontinence followed by urinary retention, and loss of balance leading to multiple falls. He then developed curling of toes on his right foot, right greater than left rigidity, and generalized slowing. He had no resting or action tremor. He had been diagnosed with Parkinson disease but developed severe orthostasis when given carbidopa/levodopa. Attempts to control his orthostasis with fludrocortisone and then midodrine led to episodes of hypertension. About 3 years after the onset, he developed laryngeal stridor that persisted during sleep and was treated with a tracheostomy. He went on to develop constipation and dysphagia.

On examination, his extraocular movements were intact with occasional square-wave jerks and bilateral sustained end-gaze nystagmus. He had moderate hypomimia and mild hypophonia with tachyphemia (as he spoke, his voice got softer and his speech became faster to the point where his words overlapped each other). He had occasional inspiratory stridor. He had no resting tremor and mild left greater than right intention tremor. He had occasional myoclonic jerks of both lower extremities and mild rigidity of his neck and extremities, left greater than right and upper extremities greater than lower extremities. He used his arms to rise slowly from a chair, had a mild left kyphoscoliosis, and had start-and-turn freezing of gait. When he was not freezing, he had a broad-based gait and reduced stride and pace. His arm swing was reduced on the left greater than right side, and he scuffed both heels. His pull test was markedly positive, and he tended to fall not only backward but to the right and left.

His dexterity and gait did not improve with levodopa, but his daytime stridor did disappear.

COMMENT

This patient has multiple system atrophy with predominant parkinsonism (MSA-P), although his initial symptoms were autonomic dysfunction. His orthostasis was severe, but this can be seen in dementia with Lewy bodies as well. The stridor was a major clue that the diagnosis was MSA. In addition, he also had some signs of cerebellar dysfunction: sustained nystagmus, broad-based gait, and falling to the side as well as forward and backward. Stridor in patients with MSA may respond to levodopa even when other motor manifestations do not.

patients diagnosed with MSA (either clinically or pathologically) often initially have symptoms in just one of these categories, although they eventually develop additional symptoms. Patients starting with bradykinesia and rigidity (called MSA with predominant parkinsonism [MSA-P]) usually do not have resting tremor and do not improve with levodopa. However, a significant minority of patients may have resting tremor and respond well to levodopa, at least for some time. Most symptoms are bilateral and symmetric but some may resemble idiopathic asymmetric PD. Patients starting with ataxia and other cerebellar features (eg, scanning speech, hypometric saccades, square-wave jerks) would be consistent with MSA with predominant cerebellar ataxia (MSA-C). There is not currently a category of MSA with predominant autonomic symptoms (MSA-A) even for patients that begin with autonomic symptoms. Nonetheless, there are patients with pure autonomic failure that eventually develop an MSA syndrome and have the pathology of MSA.

Any of these subtypes may also develop some other characteristic (although not pathognomonic) features. Axial dystonia (including anterocollis) is common.[23] A variety of gastric motility problems may evolve. Laryngeal stridor, which often occurs at night but sometimes during the day as well, can be life-threatening. Stridor is the choking sound made when the vocal cords involuntarily adduct during breathing. In patients with MSA, this happens during inspiration.

Since MSA is a synucleinopathy, sleep disturbances such as rapid eye movement (REM) sleep behavior disorder are common. Other sleep symptoms such as dysrhythmic breathing and central apnea can also occur.

Cases of pathologic MSA that combined amyotrophy mimicking amyotrophic lateral sclerosis (ALS) with parkinsonism have been reported.[24] Dementia in MSA was usually reported to be mild, but recently, cases with the pathology of MSA were reported to have a frontotemporal-type dementia called frontotemporal lobar degeneration–synuclein. Patients with this variant can have CBS, progressive nonfluent aphasia, or behavioral-variant frontotemporal dementia.[25]

Most forms of the disease progress rapidly, and more than 40% of people diagnosed with probable MSA were severely disabled or used a wheelchair by 5 years after onset, although patients with cerebellar deficit predominance seem to progress more slowly.[11] As with the other disorders discussed in this article, patients can die of pulmonary, urinary tract, and pressure ulcer infections and complications of falls. Unlike PSP and CBD, patients with MSA are also at risk for anoxic damage from stridor and cardiopulmonary arrest due to autonomic dysfunction. Consensus criteria for the clinical diagnosis of MSA were proposed in 2008.[26] **VIDEO 2-3** (*links.lww.com/CONT/A283*) includes an example of a patient with MSA, and **CASE 2-3** describes a typical patient with MSA-P.

KEY POINT

- **Middle-aged patients presenting with parkinsonism, autonomic insufficiency, and ataxia usually have multiple system atrophy. However, many patients with multiple system atrophy may initially only have symptoms in one or two of these categories, making the correct diagnosis more difficult. The development of laryngeal stridor is a strong clue that the diagnosis is multiple system atrophy.**

Pathology

Classically, the pathology of MSA consists of widespread neuronal loss and atrophy including striatonigral, cerebellar, autonomic, and corticospinal pathways. These can involve the substantia nigra, globus pallidus, parts of the cerebellum, middle cerebellar peduncle, inferior olives, intermediolateral cell columns, corticospinal tracts, anterior horn cells, and other structures. Unlike in PSP, the subthalamic nucleus, dentate nucleus, and superior cerebellar peduncle are relatively uninvolved.

TABLE 2-1 **Distinguishing Diagnostic Features of Progressive Supranuclear Palsy, Corticobasal Degeneration, and Multiple System Atrophy**

Feature	Progressive Supranuclear Palsy	Corticobasal Degeneration	Multiple System Atrophy
Improvement with levodopa	Very small subgroup, usually modest and short lived	Rare	Small subgroup (multiple system atrophy with predominant parkinsonism), usually modest
Early imbalance leading to falls	Common	Common	Common
Resting tremor	Very uncommon (may occur in progressive supranuclear palsy with predominant parkinsonism or progressive supranuclear palsy-Richardson syndrome)	Probably very uncommon (hard to separate from myoclonus)	Very uncommon but possible
Early dysphagia/ aspiration	Common	Common, somewhat later than progressive supranuclear palsy	Common, somewhat later than progressive supranuclear palsy
Supranuclear gaze palsy	Common; early in many but not all patients	Occurs in small subgroup	Very uncommon but possible
Axial rigidity	Marked axial rigidity, especially in progressive supranuclear palsy-Richardson syndrome	Common, often not dramatic	Common, often not dramatic
Facial dystonia	Very common	Uncommon	In a subgroup as a side effect of levodopa
Growling voice	Common	Uncommon	Unlike typical progressive supranuclear palsy growl, MSA with predominant cerebellar ataxia may have loud, unmodulated speech
Cortical deficits (eg, apraxia, agnosia, astereognosis)	Very small subgroup (progressive supranuclear palsy-corticobasal syndrome)	Very common	Very uncommon
Focal cortical myoclonus	Small subgroup (progressive supranuclear palsy-corticobasal degeneration)	Common	Small subgroup
Ataxia/cerebellar deficits	Gait ataxia is common, limb ataxia rarely reported	Rare	Cerebellar signs sometime during the course are common
Autonomic failure orthostasis	Some features common (eg, impotence, constipation, urinary urgency), but orthostasis uncommon	Same as progressive supranuclear palsy	Multiple failures common (eg, urinary retention, sweating)
Inspiratory stridor	Very rare	Very rare	Small but significant minority

The characteristic microscopic finding is the glial cytoplasmic inclusion consisting mainly of α-synuclein. These inclusions occur throughout the brain, but mostly in the basal ganglia. There are also neuronal nuclear and cytoplasmic inclusions and dystrophic neurites in striatonigral and cerebellar structures but also in some cortical structures. The neuronal cytoplasmic inclusions take various forms including Picklike bodies, ring-shaped, and neurofibrillary tangle–like inclusions. The predominant symptoms in MSA roughly correlate with the regions most affected pathologically. In a small minority of patients with MSA, synuclein pathology results in the presence of Lewy bodies.[25]

As with PSP and CBD, other pathologies can produce signs and symptoms that can be confused with MSA; spinocerebellar ataxias (especially types 1, 2, 3, 6, and 7), fragile X tremor-ataxia syndrome, and inflammatory diseases such as paraneoplastic conditions can rarely be misdiagnosed as MSA.[26]

Treatment

Attempts to treat MSA rather than just the symptoms of MSA have so far been unsuccessful.[25] As with PD, new attempts at treating MSA have focused on detoxifying misfolded α-synuclein, which remains a promising approach.[25]

TABLE 2-1 summarizes the distinguishing clinical features of PSP, MSA, and CBD. **TABLE 2-2** summarizes the pathologic features of these diseases.

EPIDEMIOLOGY AND GENETICS OF PSP, CBD, and MSA

The reported prevalence of each syndrome is probably underestimated in clinical studies and overestimated in pathologic studies since unusual cases are more likely to come to autopsy. Among the three disorders discussed here, PSP is most commonly reported in clinical studies. A recent study reported estimates of the prevalence of clinically defined PSP as about 1.4/100,000 to 6.4/100,000 and the prevalence of clinically defined MSA as about 1.9/100,000 to 4.4/100,000 in people older than 50 years of age.[27] The prevalence of CBS based on clinical criteria was about 2/100,000 in a population initially defined by all physicians, including primary care doctors, and then refined.[28]

Citing a large community-based autopsy study of 233 cases, a recent report estimated the prevalence of PSP as 15.8% of the prevalence of PD, the prevalence of MSA as 4.7% of the prevalence of PD, and the prevalence of CBD as 2.1% of the prevalence of PD.[29] That study followed all 1920 people living in two districts of Vienna for up to 13 years, of which 233 had autopsies after dying in one target hospital. The study does not report how many people died in other hospitals, perhaps producing bias. Also, it is extremely likely that people with non-PD diagnoses died more often during that period than people with PD, which would increase their relative prevalence. However, the relative prevalence of PSP versus MSA versus CBD should be more accurate.

In the past, PSP, CBD, MSA, and their syndromes were thought to be sporadic, but recently a small number of rare genetic conditions have been identified that may be clinically diagnosed as PSP, MSA or CBD, including mutations in the genes *MAPT* and *PGRN* (for tau and progranulin) as well as mutations in *C9orf72* (commonly causing familial ALS and frontotemporal dementia), *TARDBP*, *CHMP2B*, and other rare genetic disorders.[30] Multiple genetic susceptibility variants have been proposed for PSP and CBD (in the microtubule-associated protein tau or *MAPT* gene and other genes that can

KEY POINTS

- Unlike progressive supranuclear palsy and corticobasal degeneration, multiple system atrophy is a synucleinopathy, not a tauopathy. This may have implications for future treatments.
- Like progressive supranuclear palsy and corticobasal degeneration, there are widespread pathologic abnormalities in multiple system atrophy, but the characteristic inclusions contain α-synuclein, not tau. The first identified abnormality was a glial cytoplasmic inclusion containing α-synuclein, but neuronal inclusions have also been identified. Rarely, Lewy bodies are found in multiple system atrophy.
- There has been an intensive search for genetic risk factors for these conditions. Some candidate genes have been identified, but this has not currently led to any therapeutic innovations. Some genes have been identified that occasionally produce one of these syndromes, but those, so far, have been responsible for only a small percentage of known cases.

affect the tau protein) and for MSA (in the gene *COQ2*) but the significance of these findings is not clear.[31]

DISTIGUISHING THESE DISORDERS FROM PARKINSON DISEASE AND FROM EACH OTHER

The clinical diagnosis of PSP is primarily based on the history, signs, and symptoms, as mentioned above. There are auxiliary tests that may occasionally be helpful, but none are definitive except for autopsy. Midbrain atrophy in PSP may give a characteristic sign on brain MRI (sometimes called the hummingbird sign on sagittal MRI or morning glory sign on axial MRI) (FIGURE 2-1[32]), and these may be specific but are not sensitive.[33] Supranuclear vertical ophthalmoparesis early in the course of disease suggests PSP–Richardson syndrome, but this can also develop in CBD, usually later in the course. The ophthalmoparesis is usually horizontal in MSA. Demonstration of a dopamine deficiency state by fludeoxyglucose positron emission tomography (FDG-PET) or dopamine transporter imaging is sensitive for many forms of

TABLE 2-2 **Pathology of Progressive Supranuclear Palsy, Corticobasal Degeneration, and Multiple System Atrophy**

Disease	Involved Structures	Characteristic Pathology
Progressive supranuclear palsy	Widespread neuronal loss and atrophy of the midbrain, substantia nigra, subthalamic nucleus, globus pallidus, dentate nucleus, superior cerebellar peduncle, and multiple areas of the frontal cortex; the particular frontal areas involved depend on the subtype of progressive supranuclear palsy	Neurofibrillary tangles in neurons in the involved areas consisting of mainly abnormally phosphorylated 4-repeat tau; tau inclusions in astrocytes consisting of fibrils in a tuft configuration (tufted astrocytes); tau inclusions in oligodendroglia that form perinuclear fibers (coiled bodies); tau-containing threadlike structures in the white matter (neuropil threads)
Corticobasal degeneration	Widespread neuronal loss and atrophy asymmetrically in the cortex, usually maximal in the frontoparietal areas and much less involvement of the occipital lobes; widespread neuronal loss and gliosis in the globus pallidus, putamen, red nucleus, thalamus, subthalamic nucleus, substantia nigra, locus coeruleus, and dentate nucleus	Swollen, vacuolated neurons containing phosphorylated neurofilaments and sometimes 4-repeat tau are found in affected areas, more commonly in cortical areas, which are common in corticobasal degeneration but are not specific for that disease; the 4-repeat tau has a different structure from the 4-repeat tau typical of progressive supranuclear palsy; tau inclusions in astrocytes (astrocytic plaques) are more diffuse than the tufted astrocytes of progressive supranuclear palsy; tau-containing threads (neuropil threads) in gray and white matter of the cortex in corticobasal degeneration
Multiple system atrophy	Widespread neuronal loss and atrophy in the substantia nigra, globus pallidus, putamen, thalamus, parts of the cerebellum, middle cerebellar peduncle, inferior olives, red nucleus, intermediolateral cell columns, corticospinal tracts, anterior horn cells, and other structures; subthalamic nucleus, dentate nucleus, and superior cerebellar peduncle are relatively uninvolved	Abnormal inclusions in multiple system atrophy contain abnormal α-synuclein, not tau; the characteristic inclusion is the glial cytoplasmic inclusion; there are less frequent glial nuclear inclusions containing α-synuclein and α-synuclein-containing neuronal cytoplasmic inclusions (similar in structure to the glial cytoplasmic inclusions) and neuronal nuclear inclusions (consisting of networks of fibrils) as well as dystrophic neurites in involved structures

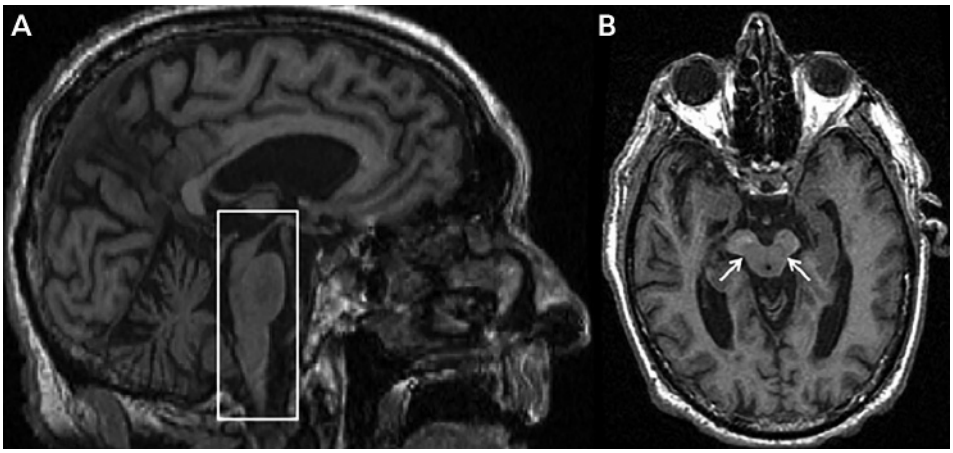

FIGURE 2-1

Hummingbird sign and morning glory sign. T1-weighted images of the brain in a patient with clinically diagnosed progressive supranuclear palsy. *A*, Hummingbird sign is shown (*box*). B, *Arrows* indicate morning glory sign.

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PSP but does not distinguish PSP from PD, CBD, or MSA and may not be sensitive for all subtypes.[14]

The most important clinical clues to the diagnosis of CBD/CBS are focal cortical deficits such as myoclonus, apraxia, and aphasia. However, these can occur in a minority of patients with PSP and other conditions.

It is currently very difficult to identify MSA in patients whose MSA begins with isolated cerebellar signs or autonomic failure. Fluorodopa PET can accurately identify patients with unsuspected dopaminergic deficiency, but the test is currently not easily available. Brain MRI in patients with MSA may show hyperintensity in the dorsolateral margin of the putamen (putaminal slit sign) (FIGURE 2-2[34]) and cruciform increased signal in the pons (hot cross bun sign) (FIGURE 2-3), but the sensitivity of these tests, while unknown, is probably low.[26,35] If orthostasis is an early feature in a patient with parkinsonism, the diagnosis may be either MSA or diffuse Lewy body disease. In MSA, the central preganglionic sympathetic neurons are mostly affected (plasma epinephrine is normal when the patient is supine but fails to rise when the patient stands), and this may differentiate it from diffuse Lewy body disease, where the autonomic impairment affects mostly peripheral postganglionic neurons.

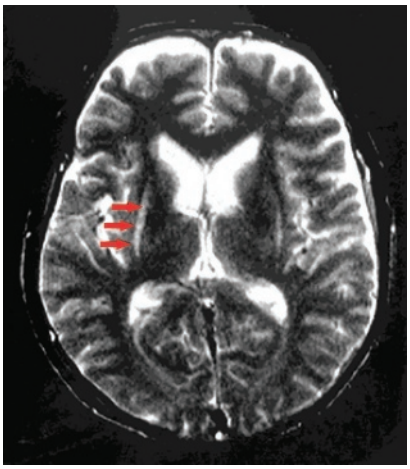

FIGURE 2-2

Putaminal slit sign. Axial T2-weighted MRI of a patient with autopsy-confirmed multiple system atrophy with predominant parkinsonism showing slitlike hyperintensity in the dorsolateral putamen (*arrows*).

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Moderate to marked cognitive impairment is common is PSP and CBD but uncommon

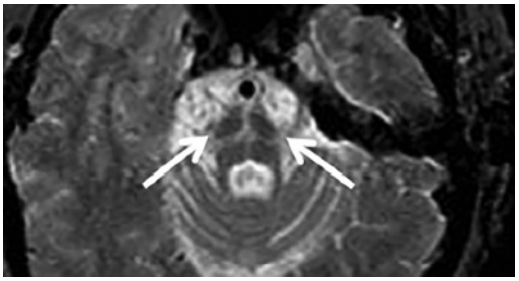

FIGURE 2-3
Hot cross bun sign. Proton density MRI sequence of a patient with clinically defined multiple system atrophy showing the hot cross bun sign in the pons (*arrows*).
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in MSA. Visual hallucinations and levodopa-induced dyskinesias are more likely to be present in PD than in PSP-P or the other syndromes. Frontotemporal lobar degeneration–parkinsonism can mimic any of these conditions, especially if the dementia lags behind the motor symptoms.

The use of biomarkers for PSP, CBD, and MSA is being studied. The hope is that treatment strategies for these diseases are more likely to be successful if used early in the course and that specific biomarkers would allow identification of the disease before symptoms develop or when symptoms are very mild. However, currently tested biomarkers lack sufficient specificity and sensitivity for clinical use.[14,22]

TREATMENT OF SYMPTOMS IN PSP, MSA, and CBD

Since none of these diseases are curable, treatment is directed to specific symptoms, many of which can occur in any of the conditions. Medications are usually ineffective for parkinsonian symptoms in these conditions, but occasionally provide benefit, at least temporarily, especially in PSP-P and MSA.

Treating patients with MSA with dopaminergic agents often worsens orthostasis, which may be difficult to manage since blood pressure support agents such as supplemental salt, fludrocortisone, midodrine, desmopressin, and other agents may produce hypertension. Botulinum toxin injections can treat apraxia of eyelid opening, blepharospasm, painful dystonia or rigidity, and sialorrhea. Botulinum toxin type B is more potent at reducing sialorrhea but is more painful to inject than botulinum toxin type A. However, patients with these syndromes are at higher risk for developing dysphagia, and it is prudent to start with lower doses than are used for PD. A pseudobulbar state can be treated with tricyclic antidepressants or dextromethorphan/quinidine.

Depression can be treated as it is for PD (it is not known if some antidepressants are better than others for these syndromes). Patients with all forms of parkinsonism do not tolerate dopamine receptor–blocking agents that are sometimes used as adjunctive antidepressive medications. Desmopressin at bedtime may help avoid nocturnal incontinence (and also help orthostasis). Constipation is managed similarly to idiopathic PD but may be less responsive to treatment. Mild constipation may be successfully managed with high-fiber diets or laxatives such as bisacodyl or senna. Liquifying stool with agents such as polyethylene glycol or lactulose may help more severe cases. Newer laxatives such as lubiprostone or linaclotide have also been used in PD. Feeding tubes can be used for patients with dysphagia who are at risk of aspiration, but not all patients and families choose this option.

CONCLUSION

PSP, CBD, and MSA were first identified by pathology that involved the substantia nigra but, unlike PD, also involve other cortical and subcortical

structures. Once levodopa was introduced for the treatment of PD, these diseases could be suspected when people with dopamine deficiency symptoms (soft voice, facial masking, rigidity, bradykinesia, postural change, generalized slowing, including gait) did not improve with levodopa, had relatively early development of dysphagia and imbalance compared to patients with PD, and had other neurologic signs not seen in patients with PD. Initially, it appeared that the three conditions were easily separated. In addition to parkinsonian features, people with PSP develop multiple visual abnormalities including a supranuclear gaze palsy, have early dysphagia leading to aspiration pneumonia, have a growling voice, tend to have marked axial rigidity, and start falling in the first few years of disease. People with CBD have marked limb dystonia (often unilateral and painful), cortical signs such as multifocal myoclonus, apraxia, agnosia, agraphesthesia, and falls in the first years of disease. People with MSA have some combination of autonomic failure (eg, orthostasis, urinary frequency/urgency or urinary retention, constipation, impotence in men) and cerebellar deficits (eg, gait and limb ataxia, scanning speech). Inspiratory stridor, although uncommon in MSA, is not seen in the other conditions.

As more autopsies were conducted, it became clear that the signs and symptoms of PSP and CBD could be identical in some patients. In addition, some other disease pathologies could look like PSP or CBD, and PSP or CBD pathology could look like other diseases as well. Although some signs and symptoms are characteristic of each of these diseases, it has been difficult to devise clinical guidelines for these conditions that are both highly sensitive and highly specific.

Most recently, there has been a hypothesis that misfolded tau (in PSP and CBD) and misfolded α-synuclein (in MSA) may act like prions and drive the progression of these conditions. Studies are now underway to slow or stop the spread of these proteins inside the brain.

KEY POINTS

- **The typical features of progressive supranuclear palsy (supranuclear gaze palsy), corticobasal degeneration (cortical myoclonus and other focal cortical deficits), and multiple system atrophy (autonomic failure and ataxia) suggest the correct diagnosis but do not achieve both sensitivity and specificity.**
- **Some symptoms of progressive supranuclear palsy, corticobasal degeneration, and multiple system atrophy can be treated, such as constipation; blepharospasm and other dystonias (with botulinum toxin injections); orthostasis; depression; pain; pseudobulbar affect; and other symptoms.**

VIDEO LEGENDS

VIDEO 2-1
Corticobasal syndrome. Video shows a 75-year-old woman clinically diagnosed with corticobasal syndrome. 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

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VIDEO 2-2
Corticobasal degeneration. Video shows an 80-year-old man demonstrating progressive asymmetric limb dysfunction, rigidity, bradykinesia, dystonia, apraxia, and cortical sensory deficits consistent with probable corticobasal degeneration.
links.lww.com/CONT/A204

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VIDEO 2-3
Multiple system atrophy. Video shows a man with signs of a mild cerebellar syndrome. On initial presentation (*not shown*), he had a hint of facial masking, decreased arm swing, and some dystonic posturing with his right arm when walking. He developed bowel and bladder dysfunction, erectile dysfunction, temperature dysregulation, and a cerebellar syndrome (primarily scanning speech and ataxia). Video shows mild flattening of the left nasolabial fold, depression of the left corner of the mouth and, at times, a widened left palpebral fissure. Video also shows his mildly broad-based stance and gait and his difficulty standing with feet together and eyes closed. When walking, occasionally either foot will be placed either laterally or medially, especially when walking quickly. His right arm tends to be flexed, and his stride and arm swing are reduced on the right (most obviously when walking quickly). When pulled backward, he moves his feet quickly to recover, which may throw him off balance. The patient later developed clear signs of parkinsonism (not shown) that were not responsive to levodopa, and he did not develop orthostasis until late in the disease course.
links.lww.com/CONT/A283

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