Multiple System Atrophy

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Multiple system atrophy (MSA) is an adult-onset, progressive, neurodegenerative condition that has several different initial presentations. Ultimately affected patients develop parkinsonian features, autonomic dysfunction, cerebellar ataxia, and corticospinal deficits. Patients with MSA are often misdiagnosed as having Parkinson disease. This article discusses the epidemiology and pathophysiology of MSA, in addition to addressing clinical and diagnostic signs and symptoms, and the limited treatment options available to physicians.


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Key words: Multiple system atrophy • Parkinsonism • Cerebellar dysfunction • Ataxia • Dopaminergic therapy • Symptomatic treatment

In 1969, Graham and Oppenheimer suggested the term multiple system atrophy (MSA) to describe a single diagnostic entity that merged 3 different conditions into 1 unifying diagnosis. The history of the nosology of the diagnosis is relevant today because it displays the diversity of presentation and clinical challenges in making the diagnosis of MSA. Prior to the 1969 paper, MSA was considered to be 3 separate neurodegenerative entities: Shy-Drager syndrome (SDS), olivopontocerebellar atrophy (OPCA), and striatonigral degeneration (SND). SDS was a neurodegenerative condition presenting with parkinsonism and significant autonomic dysfunction. Olivopontocerebellar degeneration, first described by Dejerine and Thomas in 1900, was understood as a neurodegenerative disorder involving cerebellum, pons, and olivary structures, which presented as cerebellar dysfunction, dysautonomia, and mild parkinsonism. Finally, the discreet clinical entity of SND, described in 1960, was a parkinsonian condition that, unlike Parkinson disease (PD), had significant degeneration of the striatum, as well as degeneration of the cerebellum and pons. In essence, Graham and Oppenheimer recognized that the entities of SDS, OPCA, and SND were simply different presentations of the same clinico-pathologic...
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syndrome. It is described most succinctly in their own words:

What we wish to avoid is the multiplication of names for disease entities that in fact are merely the expressions of neuronal atrophy in a variety of overlapping combinations. We therefore propose the term multiple system atrophy to refer to the whole group.1

MSA is an adult-onset, progressive, neurodegenerative condition that has several different initial presentations. With progression, there is ultimately the development of parkinsonian features, autonomic dysfunction, cerebellar ataxia, and corticospinal deficits.5

Today, MSA is often considered in the Parkinson-Plus differential, and must be considered in adults presenting with parkinsonism. Other presentations include adult-onset cerebellar ataxia or adult-onset autonomic failure. As the name implies, multiple systems within the central nervous system are often simultaneously affected. There is progressive degeneration characterized pathologically by the presence of glial cytoplasmic inclusions (GCIs) in striatonigral or olivopontocerebellar structures.6 Although the motor dysfunction indicating involvement of extrapyramidal, pyramidal, and cerebellar systems is often the dominating feature, it is the autonomic dysfunction indicating degeneration within the intermediolateral cell columns and Onuf’s nucleus in combination with the motor dysfunction that is necessary to make the clinical diagnosis.5 Just as the early investigators of this condition struggled with formulating the entire picture of this diverse condition, the clinician today is often faced initially with the same diagnostic dilemma.

Epidemiology
MSA is a relatively rare neurodegenerative condition. The limited epidemiologic studies report prevalence in the range of 1.9 to 4.4 per 100,000 people, with a mean age of onset of 54 years.7,8 It is a rapidly progressive condition with a survival rate of 10 years after clinical onset in 39% of patients.10 In a prospective study, the mean survival time of 100 patients with MSA was 8.6 years and 7.3 years for men and women, respectively.11 Although MSA is rare in the general population, it is a common misdiagnosis for PD. Hughes and colleagues12 reported in an autopsy series of 100 patients diagnosed with [MSA] is a rapidly progressive condition with a survival rate of 10 years after clinical onset in 39% of patients.

Parkinsonism, characterized by bradykinesia, postural instability, rigidity, and tremor, can all be seen in MSA.

Clinical Characteristics
The key clinical features of MSA are dysautonomia with parkinsonism and/or cerebellar dysfunction.5 The initial diagnosis can be challenging when only a single dimension of the diagnosis is fully appreciated, such as mild parkinsonism or ataxia. However, over time, as the condition progresses, the full diagnosis becomes clear. In a review of pathologically confirmed patients with MSA, parkinsonism was the most common clinical feature, occurring in 87% of patients, followed by autonomic dysfunction in 74%. Cerebellar involvement occurred in 54%.13,14 There has also been increasing recognition of clinical signs and symptoms outside of these 3 characteristics that can provide supportive clues to the diagnosis.

The extrapyramidal features of MSA can be similar to PD, and often can lead to diagnostic confusion.15 Parkinsonism, characterized by bradykinesia, postural instability, rigidity, and tremor, can all be seen in PD, that 24% of those patients did not have PD. Of those 24 misdiagnosed patients, 5 had autopsy-confirmed MSA. MSA was the second most common misdiagnosis after progressive supranuclear palsy (PSP) (6/24 patients).

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The extrapyramidal features of MSA can be similar to PD, and often can lead to diagnostic confusion.15 Parkinsonism, characterized by bradykinesia, postural instability, rigidity, and tremor, can all be seen in PD, and it is uncommon to find a typical resting tremor in a patient with MSA.16 Hypomimia, micrographia, and a shuffling gait are common. There had been a longstanding belief that MSA was relatively unresponsive to levodopa. It has become clear that a significant number of patients with MSA have an initial response to levodopa, and some have a sustained response.17 The number of levodopa responders varies, but may be in the range of 30% to 70% of patients diagnosed with MSA. Patients with MSA may show a decline in motor function after discontinuing dopaminergic therapy. They can also develop levodopa-induced dyskinesia. Some patients with MSA may respond to dopaminergic therapy, and levodopa responsiveness may not help in diagnostically distinguishing MSA from PD.18 In addition to the parkinsonism, characteristic forms of dystonia have been described in MSA. Profound anterocollis of the neck, characterized by a sustained flexion, can be
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seen in up to 25% of patients with MSA. Anterocollis can occur early in the disease. It has been suggested that anterocollis can serve as a “red flag” diagnostic clue that distinguishes MSA from PD. Limb dystonia and other forms of craniofacial dystonia and dyskinesia have been described. Laryngeal dysfunction and possibly dystonia is also a recognized feature of MSA that can have life-threatening consequences. Vocal cord abductor paresis (VCAP) is characterized by loud nocturnal snoring and daytime inspiratory stridor. The mechanism of VCAP is unclear, but possible explanations include neuronal degeneration at the nucleus ambiguous and/or degeneration of the pyramidal and extrapyramidal systems resulting in dystonia of the laryngeal muscles. This dysfunction often leads to sleep-disordered breathing, and when severe, can lead to significant oxygen desaturation. Laryngeal dysfunction manifesting as dysarthria is also common in MSA, causing hypokinetic movements of the vocal cords. This results in a high-pitched, almost squeaky voice, and is another red flag that can help distinguish MSA from PD.

Autonomic nervous system dysfunction is a key criterion for the diagnosis of MSA, and it is a common, often subtle, presenting feature of the condition. In a clinical review and evaluation of 100 patients with MSA, Wenning and associates found that erectile dysfunction (ED) was by far the most common autonomic finding in men. In women, urinary incontinence predominated. Orthostatic hypotension (OH), defined by a reduction of systolic blood pressure of at least 30 mm Hg or of diastolic blood pressure by at least 15 mm Hg after 3 minutes of standing from a previous 3-minute interval in the recumbent position, is seen in a majority of patients. It is severe in only a minority of patients (15%). Symptoms include dizziness, syncope, and weakness. Pain in the neck, shoulders, and occipital region may also be a symptom of OH. This has been called the “coat hanger” sign. Craniofacial pain frequently occurs in the morning, in warm weather, or after exertion. The pain is thought to be secondary to hypoperfusion of craniofacial muscles due to the autonomic dysfunction. Similarly, the “cold hand” sign of MSA, describing the finding of cold, red, dusky hands with delayed capillary refill, has also been attributed to impaired neurovascular function. Constipation occurs in the majority of patients. It should be noted that although the autonomic symptoms of MSA are key to the diagnosis, they may be subtle. Moreover, the patient may not readily volunteer the symptoms of ED or bladder control, and direct questioning is often required. Recognition of these subtle signs of autonomic dysfunction is crucial to making an early diagnosis of MSA.

Although most patients will display a parkinsonian variant termed MSA-P, a minority of patients present with a cerebellar predominant syndrome termed MSA-C. A wide-based gait ataxia is the most common initial presenting feature of MSA-C. Ataxia is the most common cerebellar finding in all patients with MSA through their disease course, occurring in 49% of patients in a review of over 200 cases. Limb ataxia is also common, occurring in 47%. Oculomotor findings of nystagmus, impaired saccadic pursuit, and slowed saccades are seen in about one-quarter of all patients with MSA.

Diagnostic Criteria

In 2007, a second consensus conference funded by the National Institutes of Health and American Academy of Neurology was held to address and update the diagnostic criteria for MSA. The second consensus statement simplified the widely accepted previous diagnostic criteria established in the first consensus conference held in 1998. The criteria, listed in Table 1, reflect the importance of the presence of autonomic dysfunction to the diagnosis. Definite MSA is a neuropathological diagnosis based on characteristic features. It should be noted that the diagnosis of probable MSA is based on clinical findings alone.

Pathology and Pathophysiology

There is mounting evidence for the role of oligodendroglia degeneration in MSA. The presence of GCIs (also known as Papp-Lantos inclusions) are the hallmark pathologic feature of definite MSA. GCIs are protein aggregates that accumulate primarily in the cytoplasm of oligodendrocytes, but are also found in neurons and astrocytes. The dominant protein in these meshwork-like inclusions consists of filamentous α-synuclein; however, there is immunoreactivity for α-synuclein; therefore, there is an α-synucleinopathy, linking it to similar conditions such as PD and dementia with Lewy bodies (DLB). Ultrastructurally, GCIs are composed of filamentous proteins measuring between 15 and 30 nm. The interactions of these proteins toward the formation and

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Table 1  
Criteria for Diagnosis of MSA

<table>
<thead>
<tr>
<th>Probable MSA</th>
<th>Possible MSA</th>
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<tbody>
<tr>
<td>Autonomic dysfunction <strong>with</strong> parkinsonism or cerebellar dysfunction</td>
<td>Autonomic dysfunction that does not meet criteria for Probable MSA <strong>with</strong> parkinsonism or cerebellar dysfunction <strong>and</strong> 1 supporting feature (see below)</td>
</tr>
<tr>
<td>Features of autonomic dysfunction must fit strict criteria noted below</td>
<td>Criteria for parkinsonism and cerebellar dysfunction are unchanged</td>
</tr>
<tr>
<td>Autonomic dysfunction (must have 1 feature)</td>
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<tr>
<td>• Urinary incontinence with ED (in men)</td>
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<tr>
<td>• Presence of orthostatic hypotension characterized by a decrease in blood pressure by at least 30 mm Hg systolic or 15 mm Hg diastolic within 3 min of standing from supine position</td>
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<tr>
<td>Parkinsonism (not all need be present)</td>
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<tr>
<td>• Bradykinesia</td>
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<tr>
<td>• Rigidity</td>
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<td>• Tremor</td>
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<tr>
<td>• Postural instability</td>
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<tr>
<td>• Poor levodopa response</td>
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<tr>
<td>Cerebellar dysfunction (not all need be present)</td>
<td></td>
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<tr>
<td>• Wide based gait ataxia</td>
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<tr>
<td>• Cerebellar speech disorder</td>
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<tr>
<td>• Limb ataxia</td>
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<tr>
<td>• Oculomotor deficits indicating cerebellar dysfunction</td>
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<tr>
<td>Parkinsonism with either</td>
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<tr>
<td>• Poor response to levodopa</td>
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<tr>
<td>• Rapid progression</td>
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<tr>
<td>• Postural instability within 3 y of onset</td>
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<tr>
<td>Cerebellar dysfunction</td>
<td></td>
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<tr>
<td>• Diagnostic studies showing evidence of nigrostriatal or cerebellar dysfunction</td>
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<tr>
<td>Can include:</td>
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<tr>
<td>• MRI showing atrophy of putamen, middle cerebellar peduncle, pons, or cerebellum</td>
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<tr>
<td>• FDG-PET showing hypometabolism in putamen, brainstem, or cerebellum</td>
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<tr>
<td>• SPECT or PET showing presynaptic nigrostriatal dopaminergic deficit.</td>
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<tr>
<td>Supporting features (must have 1)</td>
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<tr>
<td>• Hyperreflexia and extensor babinski</td>
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<tr>
<td>• Stidor or dysphagia within 5 y of onset</td>
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<tr>
<td>Can include:</td>
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<tr>
<td>• Postural instability within 3 y of onset</td>
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ED, erectile dysfunction; FDG-PET, fluorodeoxyglucose-positron emission tomography; MRI, magnetic resonance imaging; MSA, multiple system atrophy; SPECT, single-photon emission computed tomography.

Data from Gilman S et al.5

1. RIND0247_08-13.qxd  8/13/10  1:34 PM  Page e48
Distinguishing MSA from PD and other atypical parkinsonian conditions is the most common diagnostic challenge facing the clinician.

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Distinguishing MSA from PD and other atypical parkinsonian conditions is the most common diagnostic challenge facing the clinician. There are key red flags that can help distinguish MSA from PD, as well as the other atypical parkinsonian conditions.

Table 2
Key Red Flags for Distinguishing MSA from PD (With > 90% Specificity)

<table>
<thead>
<tr>
<th>Rapid progression</th>
<th>Severe bulbar dysfunction characterized by dysphonia, dysphagia, or dysarthria</th>
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<tbody>
<tr>
<td>Early instability characterized by falls within the first 3 years</td>
<td>Abnormal postures characterized by anterocollis, Pisa syndrome, or camptocormia</td>
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<tr>
<td>Emotional incontinence</td>
<td>Jerky tremor</td>
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Adapted with permission from Köllensperger M et al.33


t proteinopathies. As proposed by Wenning and coworkers,29 MSA might be considered as a primary oligodendrogliopathy.

Differential Diagnosis

Diagnosing MSA can be difficult when only one feature is initially apparent. Although MSA can present as an isolated cerebellar syndrome or pure autonomic failure (PAF), the early clinical presentation of MSA will most frequently present with parkinsonism.14,25 The early diagnosis can be elusive, especially when patients present with an asymmetric parkinsonism with mild response to levodopa. Time is often the essential diagnostic tool in such a patient.

Distinguishing MSA from PD and other atypical parkinsonian conditions is the most common diagnostic challenge facing the clinician. There are key red flags that can help distinguish MSA from PD, as well as the other atypical parkinsonian conditions of PSP, corticobasal ganglionic degeneration (CBD), and DLB (Table 2). Unlike PD, and similar to the other atypical parkinsonian conditions, the parkinsonism of MSA shows a more rapid deterioration and weaker response to levodopa (however, as discussed, there is a subgroup of patients who do show initial and sometimes sustained response to levodopa). Initially, it should be noted the parkinsonism of MSA can appear similar to PD. Other red flags used to separate PD from MSA (Table 1) include the presence of early autonomic dysfunction along with the parkinsonism. This can be characterized by ED, OH, or genitourinary dysfunction. The presence of orofacial dystonia, dysphonia, dysarthria, or dysphagia is an additional clue. Disproportionate anterocollis and the presence of prolonged episodic trunk postures are also key red flags. Camptocormia, described as forward trunk flexion, as well as the Pisa syndrome, described as lateral trunk flexion, are highly specific for MSA when compared with PD. Pyramidal and cerebellar signs are also important clues that can be used to differentiate MSA from PD, as they are unusual in early PD.25 MSA can also present with an upper extremity tremor; however, unlike the classic pill rolling tremor of PD, the tremor commonly seen in MSA is almost myoclonic-like, and can sometimes be provoked by touch.33,34

Differentiating MSA from the other atypical parkinsonian conditions is important. The oculomotor examination can help. Patients with MSA can have hypometric saccades, nystagmus, and some limitation of upward gaze. However, the presence of slow saccades, limitation of downward gaze, and loss of vertical optokinetic nystagmus is more consistent with PSP. Difficulty in saccade initiation is also not seen in MSA, and is more suggestive of the diagnosis of CBD.35 Early falls are often seen in MSA; however, they frequently occur in the context of OH. The presence of early falls without orthostasis, especially within the first year of developing symptoms, is more suggestive of PSP. Moreover, falling backward is more a hallmark symptom of PSP. Examination of neck posture can be helpful in separating MSA from PSP. Patients with MSA are more likely to develop a profound anterocollis, whereas neck posture in PSP is often retrocollic with axial extension.36 The motor examination is most helpful in separating CBD from MSA. Whereas CBD can progress to involve all 4 limbs, it manifests initially as an asymmetric parkinsonism, typically with a rigid limb. Cortical sensory findings, limb apraxia, and alien limb are highly suggestive of CBD, and not seen in early MSA.37

Asymmetric limb dystonia that is unresponsive to levodopa is one of the most reliable indicators of CBD.38 The other common atypical parkinsonian condition, DLB, must be differentiated from MSA. Like MSA, DLB can present as a rapidly progressive symmetric parkinsonism. Moreover, OH and falls can be seen early in DLB. The cognitive examination is the most usual tool in distinguishing between each, as early dementia is required for a diagnosis of DLB, whereas early cognitive changes are unusual in MSA. Visuospatial deficits are common in DLB. Also, the presence of early visual hallucinations along with parkinsonism is highly suggestive of DLB.39

MSA can also present clinically with pure autonomic symptoms, and
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initially can be similar to PAF. The presence of postural OH is the cardinal feature of sympathetic failure and is a key symptom as well as a measurable trait of PAF and MSA. Nonetheless, there can be subtle differences in the character of the autonomic dysfunction. In a comparison between MSA and PAF, dizziness was common in both groups (80% in both samples). Syncope was more common in individuals with PAF. There is some suggestion that patients with PAF may have a more dramatic fall in blood pressure, resulting in the increased rate of syncope. Moreover, coat hanger neck pain, especially with exertion, and precordial chest pain were more common symptoms in PAF.

Although the cerebellar variant of MSA, termed MSA-C, is less common than the parkinsonian variant of MSA, it can present initially as a pure cerebellar syndrome in up to 5% of patients with MSA. Late-onset cerebellar syndromes must be considered in the differential in these cases, and frequently with the passage of time, the development of parkinsonism and/or autonomic failure will make the diagnosis more clear. The differential for progressive cerebellar dysfunction with parkinsonism is less comprehensive. The spinocerebellar ataxias (SCAs), particularly SCA 2 and 3, can have parkinsonism along with cerebellar dysfunction presenting later in life. A family history would be expected for the SCA diagnosis. Late-onset Friedreich’s ataxia, progressive multiple sclerosis, and cerebrovascular disease deserve consideration.

Diagnostic Studies

Given the diversity of presentations of MSA, many ancillary studies can be considered based on the clinical presentation. The diagnosis remains a clinical diagnosis, and diagnostic studies only aim to support the clinical suspicion. As put succinctly by Quinn, the utility of diagnostic studies depends on the question being asked. In most cases, patients will present with parkinsonism, and the examiner is faced with 2 questions: “Does the patient have PD? If not PD, then what atypical parkinsonian syndrome does he have?” Separate studies can assist in each of these questions. In patients presenting with a cerebellar syndrome, studies aimed at excluding genetic, structural, or metabolic syndromes are considered. Aside from imaging studies examining for structural abnormalities, diagnostic studies examining for autonomic dysfunction have the greatest utility, namely by demonstrating the degree of autonomic dysfunction. The autonomic failure in MSA often has less dramatic symptoms when compared with PAF, and ancillary studies can aid in quantifying autonomic involvement.

Neuroimaging can be helpful in improving the accuracy of diagnosis of MSA compared with PD. Conventional MRI findings that show strong specificity for MSA include putaminal atrophy as well as pontine and middle cerebellar peduncle hyperintensities, the so-called “hot cross bun sign” (Figures 1 and 2). Diffusion-weighted imaging (DWI) is able to differentiate MSA from PD showing increased putaminal apparent diffusion coefficient and trace (D) values. It should be noted that similar DWI findings can be seen in PSP. Functional imaging with positron emission tomography (PET) differentiates MSA from PD and PAF in patients with a well-established diagnosis. Common findings on fluorodeoxyglucose-PET (FDG-PET) include striatal, brainstem, and cerebellar hypometabolism. In patients presenting with initial cerebellar features, the presence of reduced density of striatal presynaptic monoaminergic terminals as measured by
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There are no current neuroprotective therapies for MSA, and treatment is primarily symptomatic.

Treatment
There are no current neuroprotective therapies for MSA, and treatment is primarily symptomatic. Moreover, there are no specific treatments for cerebellar symptoms of MSA, and treatments are largely aimed at parkinsonism and autonomic dysfunction. As with other parkinsonian conditions, physical, occupational, and speech therapy play a role in treatment and should be encouraged both for medical and psychological support.

The symptoms of bradykinesia, rigidity, and instability may respond to typical parkinsonian therapies. A significant proportion of patients
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with MSA have clear response to levodopa, ranging from 30% to 68%. Carbidopa/levodopa, 25 mg/100 mg, can be safely started at doses of 0.5 to 1 tablet 3 times a day, and escalated safely to at least 1000 mg/d if well tolerated to test for a dopaminergic response unless a sustained response is seen at lower doses. The dopamine agonists can also be considered, although the adverse effect of drug-induced hypotension must be considered as well. The use of bromocriptine, 10 to 80 mg/d, showed mild benefit.

Amphiphilic and amantidine have also been tested in small studies. In general, levodopa is the best tolerated and the drug of choice for the parkinsonian symptoms of MSA.

Botulinum toxin can also play role in treating several motor and nonmotor symptoms of MSA. Focal dystonia of the neck, face, or limbs is common. Treatment with botulinum toxin is a safe and effective treatment of neurogenic OH. Treatment begins with doses of 2.5 mg 3 times a day, increasing to 10 mg 3 times a day. Supine hypertension is a potential side effect common with midodrine. Fludrocortisone, used in doses of 0.1 to 0.3 mg/d, expands body fluid volume and improves α-adrenergic sensitivity and can be used as an alternative or in addition to midodrine.

Urinary symptoms of incontinence, hesitancy, and urgency in MSA are due to complex central and peripheral nervous system problems.

Other common conditions such as prostate hypertrophy and perineal laxity may contribute. Urinary frequency may be managed with anticholinergic agents such as oxybutynin, 5 to 10 mg, or tolterodine, 2 mg, at bedtime, or propantheline, 15 to 30 mg, at bedtime. Clean, intermittent self-catheterization can be an effective solution especially in patients with a large postvoid residual greater than 100 mL. Catheterization, however, may be limited due to the motor symptoms and ataxia, making it difficult to coordinate self-catheterization.

Parkinsonism Case Studies

Case 1
A 48-year-old man is referred for ataxia. He reports that over the past 2 years he has noticed deterioration in his gait. He occasionally bumps into walls when turning corners. He feels off-balance going up or down stairs. In his own words, he is “like a toddler” learning how to walk. There is no family history of ataxia. On further questioning, he admits to a 5-year history of ED. He has also been seeing a gastroenterologist for constipation. The result of his neurologic examination is notable for hypommetric saccades, mild finger-to-nose dysmetria, slight dysdiadochokinesia, and a wide-based, ataxic gait. Orthostatic blood pressure measurements demonstrated a > 30-point drop in systolic blood pressure.

Case 2
A 55-year-old woman had gradual onset of a jerky, irregular action tremor. She was seen by her local neurologist who noted bilateral bradykinesia and rigidity in addition to an irregular, unilateral tremor. A diagnosis of PD was made, and carbidopa/levodopa was prescribed. She initially experienced improvement, but quickly experienced complications with symptomatic OH that was attributed to her medication. She eventually sought further treatment at a movement disorders center, where further history was obtained. In addition to OH, she had other autonomic complaints, including urinary urgency and constipation. Her husband reported new snoring and “wild” behavior at night, which consisted of screaming and punching while asleep. Two years after her symptoms began, neurologic examination revealed facial hypomimia, moderate dystarthisia, a jerky, myoclonic postural and action tremor, postural instability, and moderately severe symmetric bradykinesia and rigidity. Orthostatic blood pressure measurements demonstrated a > 30 point drop in systolic blood pressure.
Also noted were cold, dusky-appearing hands.

Case 3
A 77-year-old woman is referred with a 5-year history of symmetric and slowly progressive parkinsonism, OH, and cognitive decline. She was originally diagnosed with PD 5 years ago and placed on carbidopa/levodopa, which she took for 3 months; however, there was no response. Her husband reports that her slowness and gait abnormality have not significantly worsened over the past 4 years. She developed OH that was documented recently with bedside orthostatic testing, and she complains of intermittent dizziness, which has improved since the discontinuation of several of her anti-hypertensive medications. She has had 2 falls in the past 3 years. Her husband noted that she developed cognitive problems 2 years after the development of her parkinsonism. She also developed frequent hallucinations approximately 2 to 3 years ago that have occurred even without dopaminergic therapy and continue today. Results of her examination were notable for diminished recent memory with a constructional apraxia. Her motor examination revealed no tremor, and mild symmetric rigidity. Her movements were symmetrically slow. There were no cerebellar findings. Gait was slow with 1 to 2 steps of retropulsion.

Diagnoses
Case 1 demonstrates a typical presentation of MSA-C. MSA is classified by the primary motor features at the onset of disease. The differential of sporadic, adult-onset ataxia is broad, and this case demonstrates the necessity of asking about autonomic symptoms. A careful history regarding the presence of autonomic involvement may prevent the clinician from ordering an expensive genetic work-up looking for hereditary ataxia, which accounts for 13% to 22% of apparently sporadic ataxias.40,65 As the disease progresses, some degree of parkinsonism may also become evident.

Case 2 demonstrates a typical presentation of MSA-P. At the first visit, it may not be immediately apparent that the diagnosis is MSA-P instead of PD. However, there may be subtle clues such as an atypical jerky or myoclonic-like tremor, the cold hands sign, or symmetric parkinsonism. It is not unusual to have an initially positive response to carbidopa/levodopa, though the response is not sustained. As time progresses, the rapid progression and appearance of early postural instability in addition to autonomic insufficiency helps separate MSA-P from PD.

Case 3 illustrates the hallmark features of an atypical parkinsonian syndrome. The presence of symmetric parkinsonism, poor response to levodopa, and rapid cognitive decline over a 5-year period make the diagnosis of PD unlikely. The development of OH suggests autonomic dysfunction and makes MSA a plausible diagnosis. However, early cognitive decline is unusual for MSA. Most importantly, the presence of early hallucinations, especially occurring in the absence of dopaminergic therapy, is not typical for MSA, and suggests the diagnosis of DLB. OH and dizziness are common in the atypical parkinsonian syndromes; moreover, medications can commonly exacerbate orthostasis as in this case.

Main Points
- Multiple system atrophy (MSA) is a sporadic adult neurodegenerative disorder characterized by autonomic instability with either parkinsonism (MSA-P) or cerebellar dysfunction (MSA-C).
- Although MSA typically begins with parkinsonism or cerebellar dysfunction, as the disease advances, patients develop parkinsonism, and cerebellar and pyramidal features.
- Early diagnosis may be difficult; however, a “red flag” approach and careful assessment of autonomic symptoms can improve diagnostic accuracy.
- MSA-P is often considered in the differential of Parkinson disease (PD), progressive supranuclear palsy, dementia with Lewy bodies (DLB), and corticobasal ganglionic degeneration. MSA-C is considered in the broad differential of adult-onset sporadic ataxia.
- MSA has characteristic microscopic findings of glial cytoplasmic inclusions and is considered an α-synucleinopathy, along with PD and DLB.
- Neuroimaging and other studies are not diagnostic but supportive.
- There are no current neuroprotective therapies, but symptomatic treatments are available.
- Most patients will not have a sustained response to levodopa; however, some will have a mild benefit to dopaminergic therapy.
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References