

Multiple System Atrophy

Multiple system atrophy (MSA) is a neurological disorder that has frequently been misdiagnosed as idiopathic Parkinson disease.¹ A proliferation of articles in recent literature has noted that MSA is a disease that primarily affects the functioning of the autonomic, basal ganglia, and cerebellar systems.¹⁻⁴

The History and Nomenclature of MSA

The recognition of MSA as a unique entity has emerged gradually during the last century. Quinn,¹ in describing several cases occurring in the late 1800s and early 1900s, may have provided the first descriptions of MSA. In 1925, Bradbury and Eggleston⁵ wrote the first clear case report of 3 patients with postural hypotension. Today, we know that postural hypotension is a characteristic sign of MSA. In 1960, Shy and Drager⁶ distinguished a separate syndrome from idiopathic Parkinson disease (IPD). They correlated postural hypotension and the neurological signs of parkinsonism and/or cerebellar dysfunction. This observation was a first red flag for the potential diagnosis of MSA. Graham and Oppenheimer,⁷ in 1969, described a patient with orthostatic hypotension, impotence, incontinence, and cerebellar ataxia. They advocated the use of a general term for the increasing reports of autonomic dysfunction that appeared with neurological signs. They proposed the use of the term “multiple system atrophy” to avoid any of the many terms then being used to describe various forms of neuronal atrophy, many of which have overlapping characteristics. In 1972, Bannister and Oppenheimer⁸ presented postmortem evidence from 4 patients with MSA and identified the autonomic pathology as more efferent than afferent, more central than peripheral, and more preganglionic than postganglionic. More importantly, they demonstrated that the Lewy bodies, which are eosinophilic cytoplasmic inclusions, are found in the basal ganglia of patients with IPD but are often absent in patients with MSA.

Key Words: *Multiple system atrophy, Olivopontocerebellar atrophy, Orthostatic hypotension, Parkinson disease, Shy-Drager syndrome, Striatonigral degeneration.*

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The term "multiple system atrophy" has been used interchangeably with Shy-Drager syndrome, striatonigral degeneration, and olivopontocerebellar atrophy.² In 1995, a consensus statement was approved by the American Autonomic Society and the American Academy of Neurology to clarify the definitions of MSA, pure autonomic failure (PAF), and orthostatic hypotension.⁹ *Multiple system atrophy* is now defined as "a sporadic, progressive, adult-onset disorder characterized by autonomic dysfunction, parkinsonism, and ataxia in any combination."⁹(p125) Autonomic dysfunction commonly appears as postural hypotension, bowel and bladder incontinence, and impotence.¹⁰ Characteristics of parkinsonism include bilateral involvement, bradykinesia, impaired writing, slurred speech, and rigidity.¹⁰ The cerebellar component of MSA should not be confused with inherited cerebellar disorders. Inherited disorders usually present at an earlier age and have a different cytological picture and a longer rate of survival.² Cerebellar features that are characteristic of MSA have their initial manifestations in the trunk and lower extremities, leading to disturbances in gait.¹⁰ In MSA, patients often have symptoms that are characteristic of autonomic dysfunction, parkinsonism, or cerebellar dysfunction. As the disease progresses, additional symptoms emerge (Fig. 1).

Some patients may initially have autonomic features and may be diagnosed with PAF. Pure autonomic failure is a primary form of orthostatic hypotension in that the etiology is unknown.¹¹ Most patients develop additional autonomic symptoms, but these symptoms are constrained to the autonomic nervous system.⁹ The damage is primarily in the peripheral, postganglionic portion of the sympathetic nervous system, and the parasympathetic system is less involved.¹² Patients who are initially misdiagnosed with PAF may later be correctly diagnosed with MSA as the neurological symptoms of parkinsonism and/or cerebellar ataxia appear.⁹ The autonomic damage in MSA differs from that of PAF. Multiple system atrophy is a central disorder of the autonomic nervous

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system affecting the preganglionic sympathetic system as well as the parasympathetic system.¹²

Incidence

The prevalence of MSA has been estimated to be as high as 20 per 100,000 people.¹³ Most patients with MSA are initially diagnosed with IPD, and approximately one third of them die with this misdiagnosis.² The mean age at onset has been reported as between 52.5 and 55 years,^{3,14} with death usually occurring between 7.3 and 9.3 years later.^{3,15} Multiple system atrophy is found more often in men than in women (1.9:1).³ The more frequent reporting of urinary incontinence in men as compared with women may explain this finding. In addition, men report impotence, which may be another diagnostic clue.¹ Wenning et al³ completed an analysis of 100 patients with MSA. They used the Hoehn and Yahr grades to measure disability and found that patients with MSA become disabled at a faster rate than patients with IPD. Within 5 years of onset of symptoms normally associated with parkinsonism, 50% of the patients with MSA were in Hoehn and Yahr stages IV or V.³

Neuropathology

The pathology underlying MSA has been identified as cell loss and gliosis throughout much of the central nervous system.¹ The caudate nucleus and putamen, the globus pallidus, and the substantia nigra are substantially involved.¹ The pontine nuclei and the Purkinje cells of the cerebellum are also involved, and the locus ceruleus and vestibular nuclei are secondarily involved.¹ The inferior olives are also affected, and the dorsal motor nucleus of the vagus and pyramidal tracts are secondarily involved.¹ Primary damage in the spinal cord includes damage to the autonomic structures of the intermediolateral cell column and the preganglionic neuron cell

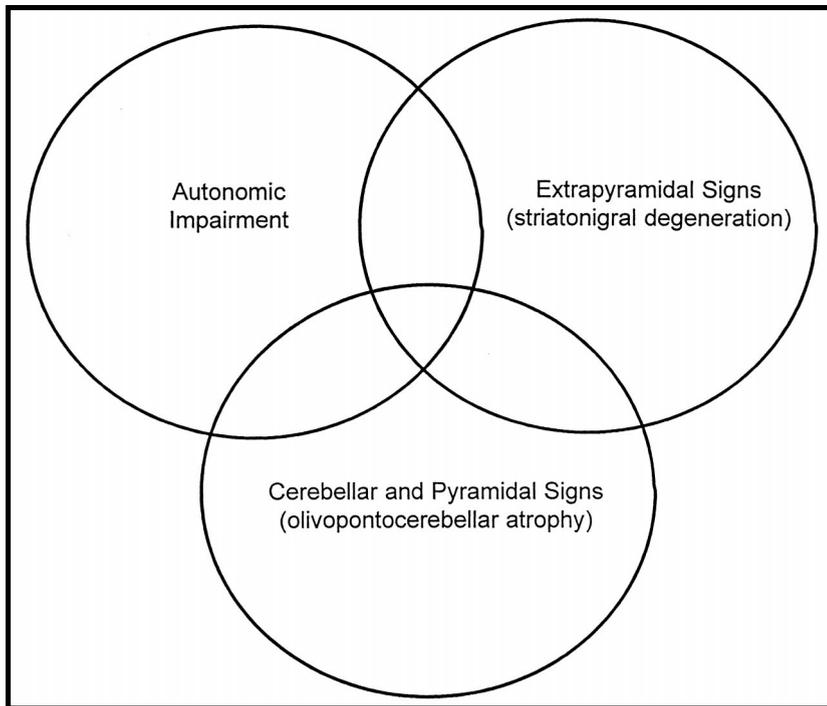


Figure 1. A schematic representation of multiple system atrophy. Patients may initially have symptoms in only one category. As the disease progresses, symptoms usually emerge in additional categories.

bodies of the parasympathetic nervous system at spinal cord levels S2 through S4.¹ Secondary damage in the spinal cord includes damage to the pyramidal tracts and anterior horn cells.¹

Based on postmortem examination of the brains of 20 patients with MSA, Wenning et al¹⁶ found that all patients had cell loss and gliosis of the striatonigral system and that 17 patients had olivopontocerebellar atrophy. Eleven of these 17 patients had no signs of cerebellar dysfunction in life. The researchers concluded that the relationship between cell loss in the olivopontocerebellar system and the presence or absence of cerebellar signs was unclear.

Cytoplasmic inclusions are pathological features found at the subcellular level in both IPD and MSA. In IPD, the inclusions are Lewy bodies, and they are found primarily in the substantia nigra.¹⁷ In MSA, argyrophilic cellular inclusions can be found in oligodendrocytes throughout the damaged structures of the central nervous system,⁴ whereas Lewy bodies are more often absent.¹ Postmortem studies^{18,19} have shown degeneration of the striatal and nigral efferent pathways. The loss of postsynaptic

dopamine receptors in these pathways may account for the poor or absent response to levodopa treatment.¹⁸ Studies of the spinal cords of patients who had MSA have revealed a loss of the intermediolateral column cells,^{20,21} which are the preganglionic component of the sympathetic nervous system. The smaller-diameter fibers of the autonomic nervous system appear to be affected first, followed by the gamma fibers and finally the alpha fibers.²¹ The losses are initially caudal and ascend as the disease progresses.²¹

Imaging techniques have been used in an attempt to elucidate the disease process of MSA. Schulz et al²² used magnetic resonance imaging (MRI) and single-photon emission computed tomography to examine patients with the cerebellar and parkinsonian forms of MSA. Sixty-three percent of the patients in this study had loss of striatal dopamine receptors, which was equally distributed

among the 2 forms.²² In addition, there was atrophy of the cerebellum and the brain stem, which was more prominent in the patients with the cerebellar type of MSA.²² These neuroanatomical changes are typical of the neuropathology of olivopontocerebellar atrophy but can also be found in other types of cerebellar pathology.²² The researchers used a quantitative approach to document signal intensity measured on the MRI images of patients with MSA.²² The images on the radiographic film were independently rated on the degree of cortical atrophy and the signal intensities of the putamen.²² Analysis showed a decrease of the signal intensity extending through part of the body of the putamen (median putamenal hypointensity equal to 2 on a scale ranging from 0 to 3) compared with controls.²² In addition, these putamenal hypointensities were more severe in patients with the predominantly parkinsonian type of MSA.²² The researchers also found that the signal intensity measured within the pons and middle cerebellar peduncles was higher than for controls, and these hyperintensities were more pronounced for patients with the cerebellar types of MSA.²²

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Wakai et al,²³ using MRI, found no relationship between the decrease in size of the pars compacta of the substantia nigra and the hypointensity of the putamen of patients with MSA. This finding did not match the clinical observations of the severity of parkinsonism²³ and led to 2 main conclusions. First, there is no relationship between degeneration of the pars compacta and the putamen, and second, the degeneration of the putamen could be used as a biological marker for the parkinsonian form of MSA.²³ The loss of dopamine receptors in the striatum may be a separate phenomenon rather than a consequence of degeneration of the nigral projections.²³

Otsuka et al²⁴ used positron emission tomography (PET) to compare patients with MSA, patients with IPD, and a control group. Markers were used to visualize the uptake of dopamine (DA-PET) and the uptake of glucose (glucose-PET). The results of the DA-PET studies revealed that patients with MSA had a decreased uptake in the putamen and caudate and that patients with IPD had a decreased uptake in the putamen and a much smaller decrease of uptake in the caudate.²⁴ The researchers were able to use these ratios to formulate a caudate-putamen index that could potentially be used to discriminate between diagnoses of MSA and IPD.²⁴ The glucose-PET studies showed no difference between the patients with IPD and the control subjects.²⁴ The patients with MSA had a decreased uptake of the glucose marker in the frontal and temporal cortices, the caudate and putamen, and the cerebellum and brain stem.²⁴

The normal response to maintaining appropriate blood pressure with postural changes is dependent on an intact baroreflex arc. Damage to the autonomic nervous system interrupts this reflex arc in patients with MSA.²⁵ Patients with MSA do not demonstrate the normal rise in plasma norepinephrine levels when coming to a standing position.²⁵ The loss of this mechanism results in vasodilation rather than vasoconstriction of the large vascular beds of the skeletal muscle and splanchnic regions.²⁵ The lack of vasoconstriction results in the decreased blood pressure.²⁵

Symptoms of MSA

Orthostatic hypotension is a characteristic hallmark of MSA. Orthostatic hypotension has been defined as a drop in systolic blood pressure of at least 20 mm Hg or a drop in diastolic blood pressure of at least 10 mm Hg within 3 minutes of coming to a standing position.⁹ An alternative position for assessing orthostatic hypotension is to place the patient on a tilt table at an angle of 60 degrees or greater in the head-up position.⁹ Orthostatic hypotension can be enhanced by many different factors. It is usually worse in the morning due to nocturnal polyuria, which reduces overall fluid volume.¹⁰ Pro-

longed supine positioning as well as quick changes in position contribute to orthostatic hypotension.²⁵ Warm environmental temperatures may lower blood pressure.¹⁰ Ingestion of food has been found to increase orthostatic hypotension in patients with MSA through impairment of the sympathetic response to splanchnic region vasodilation.²⁶ Similar findings have been demonstrated with ingestion of small amounts of alcohol.²⁷

A complex relationship among exercise, blood pressure, and orthostatic hypotension has been demonstrated in patients with MSA. Smith et al²⁸ had patients with MSA complete supine exercise by pedaling a cycle ergometer. The patients' cardiac output was similar to that of a control group, but their blood pressure was lowered and remained low 10 minutes after exercise. The low blood pressure appeared to be a result of vasodilation within skeletal muscle without a compensatory vasoconstriction in other large vascular beds. In another study,²⁹ blood pressure response to exercise was compared between patients with the predominantly striatonigral form of MSA and patients with a predominantly olivopontocerebellar form of MSA. A fall in blood pressure was seen with the patients with the olivopontocerebellar form of MSA during supine exercise, whereas patients with the striatonigral form of MSA showed no fall in blood pressure with supine exercise or in a supine position following exercise. Both groups, however, demonstrated a fall in blood pressure when coming to a standing position following the supine exercise. The investigators theorized that patients with the olivopontocerebellar form had more difficulty with blood pressure regulation due to greater damage to the cardiovascular control structures of the brain stem.²⁹

Genitourinary dysfunctions are common symptoms of MSA. Urinary bladder dysfunction may include frequency, urgency, incontinence, and retention.¹⁰ Men may experience erectile difficulties early in the course of the disease.¹⁰

Patients with MSA frequently have motor symptoms that initially mirror those of IPD. Signs that should raise suspicion for a diagnosis of MSA over IPD include a symmetrical onset of movement disorders, lack of tremor at onset, lack of response or poor response to levodopa, and a rapid progression of symptoms.¹³ In addition, there may be signs of early instability and falling.¹ Rivest et al³⁰ reviewed the case report literature to determine the prevalence of dystonia in patients with MSA. Although there appear to be some reported incidents of dystonic posturing, the literature was inconclusive as to the evidence of their occurrence.³⁰ Antecollis has been observed in some patients with MSA.³⁰ It is unclear whether this antecollis is true dystonia or an

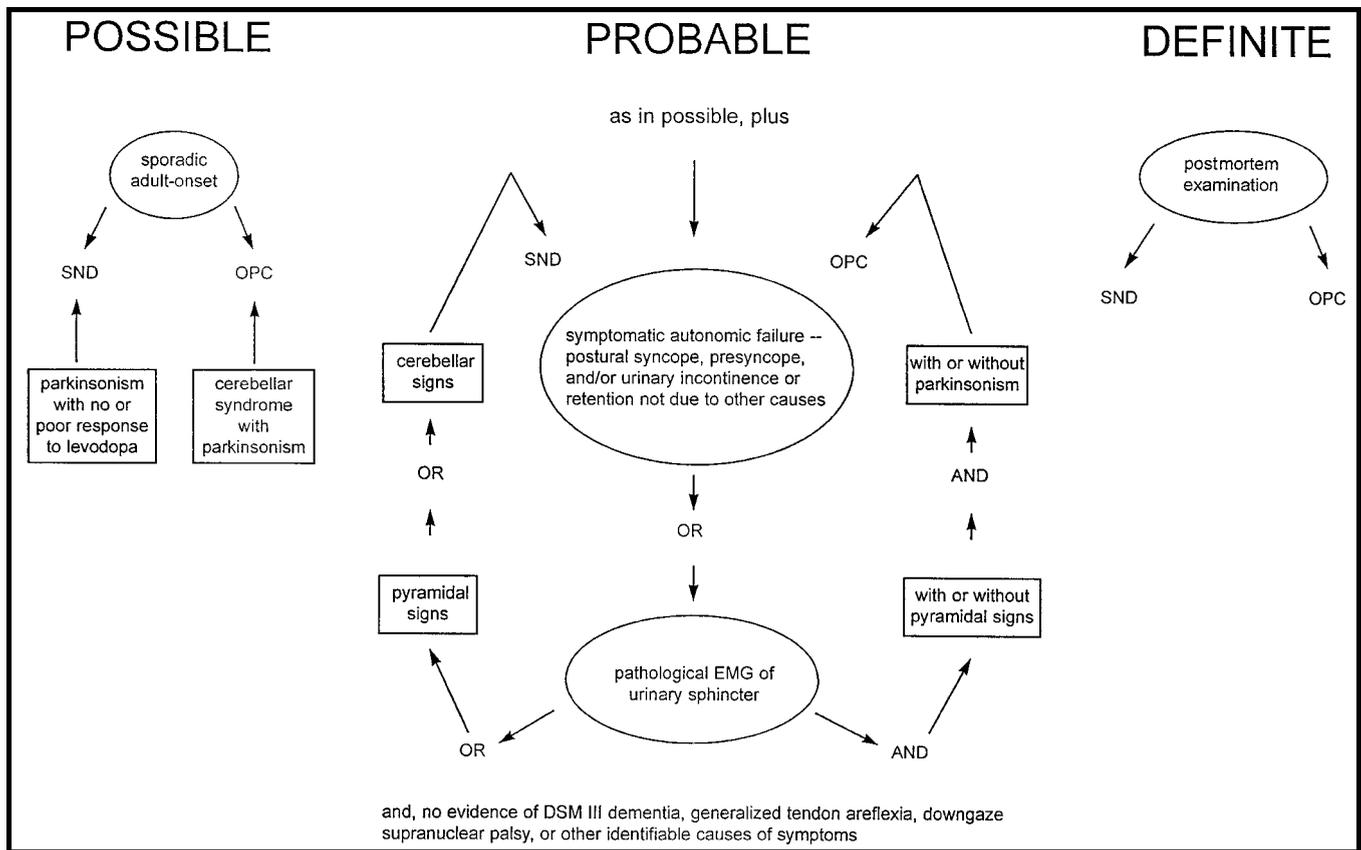


Figure 2. Diagnostic criteria for multiple system atrophy. SND=predominantly striatonigral degeneration type; OPC=predominantly olivopontocerebellar type; EMG=electromyography; DSM III=*Diagnostic and Statistical Manual of Mental Disorders*, 3rd edition. Redrawn from Quinn and Wenning's criteria.⁴

imbalance of muscular forces resulting in a sustained posture.³⁰

Patients with the olivopontocerebellar presentation of MSA have an atypical form of ataxia.³¹ Their gait is narrow based and unsteady.³¹ Wenning et al³¹ theorized that patients with the olivopontocerebellar type of MSA also have an impairment of postural reflexes leading to their narrow base of support and early history of frequent falls.

Dysphagia and dysarthria are symptoms that occur later in the disease.¹⁰ Sudden death may occur due to abnormal patterns of respiration during sleep.³² Stridor during sleep results from unilateral or bilateral vocal cord adduction due to paresis of cord abductors.³² Damage to the respiratory control centers of the brain stem may lead to a lethal desaturation of oxygen during sleep.³²

Tison et al³³ followed 100 patients with MSA over a 1-year period and found that 47% of the patients had complaints of pain that seemed to be associated with disease progression. The majority of these patients reported a rheumatic type of pain that affected the extremities more often than the neck and spine.³³ The next most

common type of pain was associated with sensory symptoms such as cold or burning sensations, paresthesia, or numbness.³³ Dystonic pain was also reported, although this pain may have been related to levodopa therapy in some cases.³³

Patients with MSA often demonstrate difficulty with thermoregulation.³⁴ The presence of cold hands, with a poor circulatory return after removal of pressure, may be another factor that points to a diagnosis of MSA.³⁴ Klein et al³⁴ found the mean (\pm SD) baseline temperature to be $29.5^{\circ} \pm 3.9^{\circ}\text{C}$ for patients with MSA, $32.6^{\circ} \pm 0.9^{\circ}\text{C}$ for patients with IPD, and $32.2^{\circ} \pm 1.1^{\circ}\text{C}$ for a control group. The baseline temperature for the patients with MSA was statistically significantly lower than that of the patients with IPD or the control group.³⁴ When the hands were cooled by placing them between cold packs for 5 minutes, the patients with MSA showed the greatest reduction in skin temperature (to a mean of 59.5% of initial baseline temperature) than either the patients with IPD (mean of 77.4% of initial baseline temperature) or the control group (mean of 71.6% of initial baseline temperature).³⁴ The mean skin temperatures of the patients with IPD and the control group had returned to their initial baseline measurements 10 minutes after removing

the cold packs.³⁴ In contrast, the mean skin temperature of the patients with MSA was at 87.4% of their initial baseline measurement 10 minutes after removal of the cold packs.³⁴

Although intellectual function and mental state have been reported as intact in patients with MSA,^{1,10} extensive neuropsychological testing has uncovered some problems with cognition. Meco et al³⁸ compared patients with the striatonigral degeneration form of MSA and patients who had IPD. The 2 groups performed similarly on memory, speech, and conceptual thinking tasks but differed on tasks of executive functioning.³⁵ The patients with MSA had great difficulty switching attention from one stimulus to another.³⁵ The authors theorized that patients with MSA may show a greater attentional deficit than patients with IPD due to the loss of input to the frontal lobe by the damaged striatal region.³⁵

The many potential forms of MSA have led to difficulty in diagnosis. Quinn and Wenning⁴ have proposed diagnostic criteria that are continually being updated to classify patients as possibly having MSA, probably having MSA, or definitely having MSA (Fig. 2).

Treatment Strategies

Due to the diverse presentation of symptoms, potential regimens of pharmacological intervention are numerous. An extensive review is beyond the scope of this article, and the reader is encouraged to examine each patient's pharmacological intervention on a case-by-case basis. The pharmacological control of parkinsonism and orthostatic hypotension will briefly be mentioned here, as they are common problems across this population.

Patients with parkinsonism are often started on levodopa. Early in the course of the disease, some patients show clinical improvement on levodopa.³⁶ Unfortunately, the beneficial effects are seldom sustained.³⁶ This poor response may correlate with the decreasing numbers of dopaminergic receptors during the course of the disease and was illustrated in the study by Wenning et al,¹⁵ who followed 33 patients with MSA who were given levodopa. The initial clinical response was excellent in 13% of the patients, good in 25%, and poor in 62%.¹⁵ The last recorded response was good in 7% of the patients and poor in 93%.¹⁵

The majority of current treatment strategies for MSA focus on the control of orthostatic hypotension. Robertson and Davis³⁷ advocated measuring progress through functional goals rather than achieving a target blood pressure. Medication can be used to control orthostatic hypotension by increasing the total plasma volume or through vasoconstriction.³⁸ Nonpharmacological interventions include increasing the consumption of caffeine,

salt, and fluids while decreasing alcohol intake and eating smaller, more frequent meals throughout the day.³⁸ Mechanical interventions include elevating the head of the bed up to 20.3 cm (8 in) for sleeping³⁷ and use of elastic garments.³⁸ Further patient education should include advising the patient to refrain from quick postural changes, especially on awakening³⁸; scheduling activities for later in the day³⁷; and avoiding motionless standing activities.³⁷ Warm environmental temperatures and activities that invoke the Valsalva maneuver should also be avoided.³⁷ Concerns about orthostatic hypotension should not preclude patients from the long-term benefits of a reasonable exercise regimen. Robertson and Davis³⁷ suggested that swimming may be an ideal exercise, as the hydrostatic pressure of the water counteracts the hypotension.

As MSA progresses, patients and families are faced with the difficult decisions of undergoing possible tracheotomy secondary to respiratory stridor and gastrostomy due to dysphagia.¹

Physical therapists need to be aware of clinical distinctions between IPD and MSA. A patient with parkinsonism who has difficulty with postural hypotension and/or a poor response to levodopa treatment should be referred back to the physician with a suspicion of MSA.

Quinn¹ has clearly described the need for the services of physical therapists, occupational therapists, speech-language pathologists, and social workers in the treatment of patients with MSA. The expertise of these professionals in the numerous practical difficulties encountered by patients with MSA may positively affect the patients' status.¹ In particular, physical therapists can be instrumental in monitoring and making adjustments for blood pressure within the context of activities of daily living and exercise programs. Additionally, they can guide motor control activities for patients with parkinsonism and ataxia, provide modalities for pain relief, and facilitate education of the patient and family.

Summary

Multiple system atrophy is a neurological disorder that has gone unrecognized for too long due to its involvement across multiple regions of the central nervous system. This disorder is finally being unveiled through increased reporting in the scientific literature. Further research will enhance our understanding of this disease and lead to more effective treatment regimens as well as an improved quality of life for patients with MSA.

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