# Multiple System Atrophy

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## Synonyms of Multiple System Atrophy

- MSA
- progressive autonomic failure with multiple system atrophy
- Shy-Drager syndrome (SDS)
- sporadic olivopontocerebellar atrophy (sOPCA)
- striatonigral degeneration (SND

## Subdivisions of Multiple System Atrophy

- MSA-C (cerebellar phenotype)
- MSA-P (parkinsonian phenotype)

## General Discussion

Summary

Multiple system atrophy (MSA) is a rare sporadic progressive neurological disorder characterized by a varying combination of symptoms and signs. Onset is during adulthood (>30 years). Affected individuals may experience symptoms similar to those found in Parkinson's disease (parkinsonism); cerebellar signs such as progressive impairment of the ability to coordinate voluntary movements (cerebellar ataxia); and impaired functioning of the portion of the nervous system (autonomic nervous system) that regulates certain involuntary body functions (autonomic failure) such as heart rate, blood pressure, sweating, and bowel and bladder control. When parkinsonian symptoms predominate, the disorder may be referred to as MSA-P (parkinsonian phenotype); when the cerebellar symptoms predominate the disorder may be referred to as MSA-C (cerebellar phenotype). The exact cause of MSA is unknown.

Introduction

The term multiple system atrophy was first introduced in the medical literature in 1969. It encompasses three presentations of a single disease formerly thought to be separate disorders, specifically Shy-Drager syndrome (which emphasized autonomic dysfunction), striatonigral degeneration (which emphasized parkinsonian symptoms), and sporadic olivopontocerebellar atrophy (which emphasized cerebellar symptoms), although the cases of each of these that were originally described presented a combination of all three clinical features, and brain pathology was found in both the striatonigral and olivopontocerebellar structures. Additionally, there is a hereditary form of olivopontocerebellar atrophy that is not part of the multiple system atrophy spectrum.

## Signs & Symptoms

The range, severity, and distribution of symptoms vary greatly among affected individuals. For example, some may initially have only mild symptoms for several years; others may experience severe symptoms early in the course of the disease. Symptoms of MSA may vary depending upon which form of MSA predominates. The disorder can cause the progressive loss of motor skills and approximately 50% of individuals are wheelchair-bound within 5-6 years of the onset of motor symptoms. Eventually, affected individuals may become confined to bed and experience life-threatening complications.

Some affected individuals experience fatigue; a complaint of weakness, especially of the legs; blurred vision; and impaired bladder and bowel control including involuntary urination or defecation (urinary and rectal incontinence). Additional bladder disturbances may occur including the need to pass water at night, increased daytime frequency of urinating, an increased urgency to urinate, and incomplete bladder emptying. Erectile dysfunction is almost universal, and typically early, in affected males. Constipation may also be present. The skin may become extremely dry as a result of a decreased ability to sweat (anhidrosis). All cases of MSA will eventually develop some form of autonomic dysfunction (urogenital, cardiovascular, or both).

The symptoms mentioned above may be preceded or followed by neurological findings that are similar to those found in individuals with Parkinson's disease (parkinsonism). Approximately 90 percent of individuals with MSA will experience parkinsonism symptoms including slowness of voluntary movements (bradykinesia), muscle stiffness (rigidity) which may make it difficult to bend the arms and/or legs, and impaired balance (postural instability). Two thirds of patients have a tremor or jerky movements (myoclonus) of the hands or fingers, but rarely (<10%) the classical "pill-rolling" rest tremor characteristic of most cases of Parkinson's disease..

In approximately 20 percent of MSA cases, cerebellar signs may be the initial findings. These comprise progressive impairment of the ability to coordinate voluntary movements (cerebellar ataxia), progressive balance problems (disequilibrium), slurred speech (dysarthria), and jerkiness of following eye movements (nystagmus).

Additional neurological findings may include exaggerated reflexes (hyperreflexia); and increased muscle tone (spasticity), collectively called pyramidal signs, that can contribute to slowness and stiffness; and involuntary sustained muscle spasms (dystonia) of face, jaw, neck, trunk or limbs causing abnormal, sometimes painful, movements and postures, often involving neck flexion (antecollis) and flexion ("camptocormi") or curvature ("Pisa syndrome") of the spine.

When divided into the predominance of parkinsonism and cerebellar features, in most parts of the world MSA-P predominates, with 60-80% of cases in different series. However, for unknown reasons MSA-C predominates in Japan with a ratio to MSA-P of about 4:1. As regards initial symptoms, 20-40% of subjects develop autonomic symptoms before other neurological features are detected.

As MSA progresses, functions controlled by the autonomic nervous system become increasingly impaired. Individuals with MSA may develop vocal cord paralysis resulting in hoarseness and high-pitched, noisy respiration (stridor). In some cases, periodic episodes in which breathing is interrupted during sleep (apnea) may develop. (For more information on apnea, choose "sleep apnea" as your search term in the Rare Disease Database.) Irregular heart rhythms may also develop. Some individuals may develop painfully cold fingers and toes caused by constriction of small vessels in response to cold (Raynaud's phenomenon).

Additional sleep disorders such as REM sleep behavior disorder (RBD) occur in many individuals with MSA, but RBD is also common, but less so, in PD. Normally, people cannot move during REM sleep, but in RBD they can move and often act out their dreams potentially resulting in self-injury, or injuring their bed-partner.

In some cases, individuals with MSA experience a mild loss of cognitive ability although, unlike Parkinson's disease, frank dementia is uncommon. In addition, chewing, swallowing, and speaking may become more difficult as the disorder progresses. The symptoms associated with MSA are progressive so that affected individuals may ultimately become unable to walk unassisted, or require a wheelchair, lose the ability to speak or swallow, or develop severe respiratory complications. Continued neurological degeneration can potentially result in severe, life-threatening complications such as aspiration pneumonia or deep vein thrombosis and pulmonary embolism, secondary to immobility.

## Causes

The exact underlying cause of MSA is unknown. It appears to occur randomly for unknown reasons (sporadically). Researchers have suggested that multiple environmental or genetic factors are important, but more research is needed.

Pathology

MSA is characterized by progressive loss of nerve cells (neurons) in various structures of the brain. Gliosis is present and structures or "bodies" known as glial cytoplasmic inclusions (GCIs) develop which are always present in the MSA brain, and are unique to this disease. Gliosis is characterized by the proliferation of astrocytes in damaged areas of the central nervous system. Astrocytes are star-shaped cells that form the supportive tissue of the brain. The proliferation of astrocytes causes scarring in the affected areas of the brain.

GCIs are abnormal structures within the brain that contain clumps of proteins. These GCIs accumulate a specific protein known as alpha-synuclein. Although the exact function of alpha-synuclein is not fully understood, researchers believe that this protein is overexpressed in individuals with MSA and may have a toxic effect on the brain, so it is believed to play a central role in the development of MSA.

Researchers have been searching for variations in the alpha-synuclein (SNCA) gene that may lead to an increased risk of developing MSA. Accumulation of alpha-synuclein in the brain has also been seen in other neurological disorders such as Parkinson's disease and dementia with Lewy bodies. These disorders are sometimes collectively referred to as "synucleinopathies".

More research is necessary to determine the exact role that alpha-synuclein plays in the development of MSA and to fully understand the complex, underlying mechanisms that ultimately lead to the disorder.

Evolution of Terminology

The older names for MSA, specifically striatonigral degeneration and olivopontocerebellar atrophy, referred to the areas of the brain that were most affected.

Striatonigral degeneration refers to a disruption of communication between nerve cells within two structures of the brain involved with movement and balance known as the substantia nigra and the striatum.

Olivopontocerebellar atrophy refers to specific structures of the brain known as the olives, pons and cerebellum. The inferior olives are two small round structures in the medulla, the lowest part of the brainstem. The pons is part of the brainstem and contains important neuronal pathways between the cerebrum, spinal cord, and cerebellum, and serves as a relay point for messages between these structures. The cerebellum is a part of the brain that controls balance and posture as well as coordinating voluntary movement.

The term Shy-Drager syndrome was used to refer to cases of SND or OPCA in which autonomic failure was prominent, and there was associated neuronal loss in intermediolateral cell columns and Onuf's nucleus in the spinal cord.

The combination of parkinsonism with autonomic failure is present in a very high proportion of MSA cases. It is seen in a much lower proportion of Parkinson's disease (PD) patients but, because PD is 40 times commoner than MSA in total, PD is the more common cause of this combination.

## Affected Populations

MSA appears to affect males and females in equal numbers. The peak onset of MSA is between 55-60 years of age, with a range from 30 to over 90 years. The incidence of MSA in the United States is estimated at 0.6 cases per 100,000 people per year in the general population giving a current estimate of about 1,900 new cases per year in the USA. A prevalence study in London, UK, gave an age-adjusted figure of 4.4 living cases per 100,000 population at any one time, which would currently translate to about 14,000 living cases in the USA. There is about 1 living case of MSA in the population for every 40 cases of Parkinson's disease, but because survival in MSA is shorter than for PD, about 1 new MSA case presents every year for about every 20 who present with PD.

## Related Disorders

Symptoms of the following disorders can be similar to those of MSA. Comparisons may be useful for a differential diagnosis:

Parkinson's disease (PD) is a slowly progressive neurologic movement disorder characterized by involuntary, resting tremor, muscular stiffness or lack of flexibility (rigidity), slowness of movement (bradykinesia) and difficulty controlling voluntary movements. It also commonly causes autonomic symptoms and, in advanced, older, patients, dementia. Degenerative changes occur in areas deep within the brain (substantia nigra and other pigmented regions of the brain), resulting in decreasing levels of the neurotransmitter dopamine in the brain. Dopamine is a highly specialized brain chemical that sends a signal to other nerve cells, and participates in the regulation of body movements. Parkinson's disease usually begins in late adulthood. It is slowly progressive; however, it may not become incapacitating for many years. (For more information on this disorder, choose "Parkinson's disease" as your search term in the Rare Disease Database.)

Symptoms similar to those of PD (parkinsonian symptoms) may also develop secondary to hydrocephalus (a condition in which excessive cerebrospinal fluid accumulates the spaces in the brain [ventricles], increasing pressure in the brain. Parkinsonian symptoms may also occur as a result of head trauma, inflammation of the brain (encephalitis), strokes (infarcts), or tumors deep within the cerebral hemispheres (cerebrum) and base of the brain (i.e., basal ganglia), or exposure to certain drugs and toxins.

Progressive supranuclear palsy (PSP) is a rare degenerative neurological disorder characterized by postural instability and falls, often backwards, loss of control of voluntary eye movement (supranuclear gaze palsy, or SNGP), impaired voluntary muscle activity (akinesia), abnormal stiffness (rigidity), speech difficulties (dysarthria), and problems related to swallowing and eating (dysphagia). Affected individuals frequently experience personality changes and some degree of cognitive impairment. The exact cause of progressive supranuclear palsy is unknown. Unlike MSA, in which alpha-synuclein accumulates in the brain, a different protein called tau accumulates in PSP (and also CBD – see below), so they are known as "tauopathies". Prevalence is a bit higher than MSA, at about 6 per 100,000. Mean onset age is 60-65 years. (For more information on this disorder, choose "progressive supranuclear palsy" as your search term in the Rare Disease Database.)

Corticobasal degeneration (CBD) is an even rarer progressive neurological disorder characterized by cell loss and shrinkage (atrophy) in certain areas of the brain (cerebral cortex and substantia nigra). Affected individuals may have sufficient muscle power for manual tasks but often have difficulty directing their movements appropriately (apraxia). Initial symptoms typically appear in people during the seventh decade, and may include poor coordination, difficulty accomplishing goal-directed tasks (e.g., buttoning a shirt), and/or difficulty pantomiming actions. Symptoms usually begin on one side of the body (unilateral), but both sides are affected as the disease progresses. Cognitive impairment (e.g., memory loss) and/or visual-spatial impairments often develop. The exact cause of corticobasal degeneration is unknown. (For more information on this disorder, choose "corticobasal degeneration" as your search term in the Rare Disease Database.)

Hereditary olivopontocerebellar atrophy (OPCA) describes a rare group of disorders characterized by progressive balance problems (disequilibrium), progressive impairment of the ability to coordinate voluntary movements (cerebellar ataxia), and difficulty speaking or slurred speech (dysarthria). Additional symptoms may include generalized weakness, difficulty swallowing (dysphagia), and/or the progressive loss of intellectual abilities and mental deterioration (dementia). There are at least five distinct forms of hereditary OPCA. All forms of hereditary OPCA, except one, are inherited as autosomal dominant traits. (For more information on this disorder, choose "olivopontocerebellar atrophy" as your search term in the Rare Disease Database.)

Pure autonomic failure (PAF) is very rare, and characterized by orthostatic hypotension that has been present for 5 years or more without other evidence of a neurological condition. Orthostatic hypotension is a condition in which an excessive decrease in blood pressure occurs upon standing potentially resulting in dizziness or momentary loss of consciousness (syncope). Additional symptoms associated with autonomic failure include fatigue; blurred vision; impaired bladder and bowel control; and impotence. In some cases, the skin may become extremely dry as

a result of decreased ability to sweat. The exact cause of PAF is usually due to Lewy body pathology in the brainstem and autonomic ganglia.

## Diagnosis

The diagnosis of MSA may be suspected based upon a detailed patient history, identification of specific symptoms, and a thorough clinical evaluation that includes a comprehensive history of neurological and other symptoms. Various specialized laboratory tests may assist in diagnosis. Obtaining a diagnosis can be difficult because no specific test can make or confirm a diagnosis of MSA.

Clinical Testing and Workup

Specialized tests that can aid in the diagnosis of MSA include:

Magnetic resonance imaging (MRI), which may demonstrate changes in certain brain areas.

Positron emission tomography (PET), using fluorodeoxyglucose (FDG) to measure regional brain glucose metabolism, is being developed as a tool to differentiate between degenerative parkinsonian conditions.

Single photon emission computed tomography (SPECT) using a tracer for the dopamine transporter (DaT) in the brain can provide evidence of neuron loss in the substantia nigra, which is affected in all MSA subjects with parkinsonism, but will not differentiate between MSA, PD, PSP and CBD.

In some cases a 123I-metaiodobenzylguanidine (MIBG) SPECT scan of the heart can be helpful to distinguish between Lewy body diseases (PD, LBD and PAF), in which the scan is typically very abnormal, and MSA, where it is usually normal.

In individuals with symptoms of faintness it is important to take the blood pressure first lying (supine) and then after 2 and 3 minutes standing, and to record the drop in the upper (systolic) and lower (diastolic) figure. An otherwise unexplained systolic drop of more than 20 mm is abnormal, and one of over 30 mm more so.

If there is suspicion of orthostatic hypotension (OH, excessive BP drop on standing), but this simple testing does not show an excessive fall, it may be necessary to do a tilt table test. During this test, a patient lies down flat on a table. Straps are placed around the body to hold the patient in place. Then, the table is raised with the person’s head in the upward position. This simulates the action of a person standing from a sitting or lying down position. This test allows a physician to measure your heart rate and blood pressure in such situations.

Many people with MSA may originally be misdiagnosed with Parkinson’s disease. Specialized tests that measure the function of the autonomic nervous system may be performed, including pupillary and sweating responses, cardiovascular responses (e.g., orthostatic challenge and cold pressor test), and genitourinary and rectal responses (e.g., cremasteric, anal wink, and bulbocavernosus reflexes). A variety of tests may be conducted to assess the function of the autonomic nervous system including blood tests, sweat tests, tests to assess bladder and bowel function, and an electrocardiogram to assess the function of the heart.

Some individuals may be evaluated in a sleep laboratory to undergo a sleep study to assess the presence and extent of sleep abnormalities that are sometimes associated with MSA.

## Standard Therapies

### Treatment

There is no specific treatment for MSA. Treatment is aimed at controlling the symptoms of the disease. Drugs that are used to treat people with Parkinson's disease, most notably levodopa (given in tablets of Sinemet), may also be prescribed for individuals with MSA. However, the effectiveness of such medications varies greatly among affected individuals. In many cases, individuals do not respond or respond poorly to such therapy. Approximately 1/3 of affected individuals respond to levodopa therapy. However, in most cases, the effectiveness of this therapy decreases over time. In addition, these drugs must be used with caution because they may lower blood pressure.

In addition to levodopa, other drugs used to treat Parkinson's disease may be used to treat individuals with MSA. These include dopamine agonists such as ropinirole (Requip) and pramipexole (Mirapexin) and an antiviral drug known as amantadine (Symmetrel).

Low blood pressure upon standing (orthostatic hypotension) may be treated by dietary increases in salt consumption, using a head-up tilt of the bed at night, by ingestion of 500mls water before exertion, rising slowly, and avoiding heavy carbohydrate meals.

If non-drug methods fail to sufficiently control OH symptoms, the drug fludrocortisone (Florinef), a corticosteroid derivative, can be used. This drug must be used with caution and monitored carefully by a physician for possible side effects.

The drug midodrine hydrochloride (ProAmatine) has been approved by the Food and Drug Administration (FDA) for the treatment of low blood pressure sometimes associated with MSA.

Adrenergic drugs such as ephedrine may be used to treat low blood pressure. The drug L-threo-dihydroxyphenylserine (L-DOPS or L-threo-DOPS) can also be used to treat low blood pressure.

Urinary incontinence may be treated with drugs such as oxybutynin (Ditropan) or catheterization. The drug desmopressin may be used to treat the abnormally large production and passage of urine at night (nocturnal polyuria) but caution is advised in the elderly, and blood electrolytes need periodic monitoring. Constipation may improve along with increases in dietary fiber or the use of laxatives. Continuous positive pressure ventilation (CPAP) may be used to treat sleep apnea and anti-convulsant drugs such as clonazepam may be used to treat REM sleep behavior disorder or myoclonus. Dystonia may be treated by injections of botulinum toxin.

Drugs such as sildenafil (Viagra), tadalfil (Cialis) or vardenafil (Levitra) may be used to treat impotence. In some cases, these drugs may worsen low blood pressure and faintness.

A speech pathology evaluation and therapy may be helpful with swallowing or speech difficulties. Affected individuals may also benefit from physiotherapy, physical therapy, occupational therapy, and speech therapy.

In later stages of MSA, where there is a risk of aspiration due to swallowing difficulty, a feeding tube may be inserted directly into the stomach (gastrostomy tube). A tracheostomy may be required for life-threatening breathing complications, daytime stridor, or abnormal vocal cord mobility. A tracheostomy is a procedure during which a tube is placed through a surgical

opening in the throat to prevent breathing difficulties. In addition, affected individuals may be unable to walk unassisted or may require a wheelchair.

## Investigational Therapies

The European MSA Study Group is a consortium of scientific investigators from academic and research centers in Europe and Israel who are committed to clinical trial activity and other research studies aimed at improving the treatment of MSA. For more information, visit its website at, http://www.emsa-sg.org/

Contact for additional information about MSA:

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Information on current clinical trials is posted on the Internet at www.clinicaltrials.gov. All studies receiving U.S. government funding, and some supported by private industry, are posted on this government web site.

For information about clinical trials being conducted at the NIH Clinical Center in Bethesda, MD, contact the NIH Patient Recruitment Office:

Toll-free: (800) 411-1222

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