



DEPARTMENT OF
NEUROLOGY

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Multiple System Atrophy

Multiple system atrophy (MSA) refers to a group of progressive neurodegenerative disorders that affect the autonomic nervous system (the part of the nervous system that controls involuntary functions such as blood pressure and heart rate) and movement. MSA has had several names in the past including striatonigral degeneration, olivopontocerebellar atrophy and Shy-Drager syndrome. The latter was named after the two physicians who first described it in 1960; Dr. Milton Shy at the National Institutes of Health and Dr. Glenn Drager at the Baylor College of Medicine.

MSA is considered a rare disease affecting potentially 15,000 to 50,000 people in the United States. Symptoms tend to rapidly progress over 5-10 years with loss of function and increasing disability.

Currently, MSA is divided into two categories: MSA-P, which refers to MSA with predominant parkinsonism (stiffness, slowness and walking problems) and MSA-C, which refers to MSA with predominant cerebellar ataxia (problems with coordination). When MSA was known as Shy-Drager syndrome, it was defined by the presence of dysautonomia (dysfunction of the autonomic nervous system), but this is now considered an important part of both MSA-P and MSA-C, so a separate category is not needed. Usually, over time, people with MSA will develop both parkinsonism and cerebellar features, though the diagnosis of MSA is typically followed with the letter P or C to denote which features are most prominent.

Symptoms and Signs of Dysautonomia

Dysautonomia refers to a disturbance of the autonomic nervous system, the nerve pathways which regulate unconscious bodily functions including heart rate, blood pressure, digestion, salivation, perspiration, micturition (release of urine), and some sexual functions. Patients with dysautonomia experience symptoms of fainting or dizziness when changing to an upright position (such as lying to sitting or sitting to standing). The lightheadedness results from a decrease in blood pressure upon rising which decreases the amount of blood working against gravity to reach the brain. When a patient collapses to the floor, the amount of blood reaching the brain increases as the blood pressure rises and the patient regains consciousness. Other typical symptoms of autonomic nervous system dysfunction are constipation, impotence in males, and loss of bladder or bowel control leading to incontinence or constipation. Some patients experience abnormal sweating and develop reddish-blue discoloration of the skin known as the “cold hand” or “cold

foot” sign. MSA patients also frequently snore, have longer than normal pauses in breathing during sleep (sleep apnea), and exhibit combative behavior while asleep, known as REM Sleep Behavioral Disorder (RBD).

Symptoms and Signs of Parkinsonism (MSA-P)

The parkinsonian features of MSA typically include a slowed and shuffling gait, difficulty with balance, stiffness (rigidity) of muscles, particularly those of the neck, and slurred and low-volume speech. Neck and trunk muscle rigidity or weakness may result in abnormal postures such as forward bending of the neck (anterocollis) or a body tilt when sitting (Pisa sign). Tremor, if present, is usually mild. Patients also may develop hoarseness, difficulty breathing due to vocal cord weakness, and frequent involuntary sighing.

Initial symptoms of MSA overlap with those of Parkinson's disease, and many patients with MSA are first diagnosed with classic Parkinson's disease. Some patients initially respond to the same medications used for Parkinson's disease but unfortunately, the benefit is usually transient. The course of MSA-P varies markedly from one individual to another. While some patients live for up to 20 years after the onset of symptoms, most patients reach severe disability, requiring assistance with walking and other activities of daily living within 5-8 years. It usually progresses much more rapidly than classic Parkinson's disease.

Symptoms and Signs of Cerebellar Dysfunction (MSA-C)

MSA-C is characterized by poor coordination and progressive loss of balance (ataxia). In addition, patients with MSA-C may have tremor with action, which is different from the resting tremor seen in typical Parkinson's disease. This tremor is present during activities, such as reaching for objects or eating, and can be elicited on examination by the finger-to-nose maneuver. Other features include slurring of speech, difficulty with swallowing, and progressive weakness. The first symptom is usually mild incoordination in the hands and legs, which eventually progresses to loss of balance requiring a walker or a wheelchair.

Diagnosis

There is no diagnostic test for MSA, but a neurologist usually suspects the diagnosis based on a patient's physical examination and clinical course. Early in the disease, it can be challenging to differentiate MSA-P from Parkinson's disease. MSA-C may be confused with several inherited or acquired forms of cerebellar ataxia if a careful history is not elicited.

A probable diagnosis is made when patients exhibit autonomic failure with either parkinsonism or cerebellar ataxia. A definite diagnosis can only be made upon autopsy where characteristic patterns of degeneration may be seen but the diagnosis of MSA cannot be confirmed unless typical alpha-synuclein protein

collections known as “glial intracytoplasmic inclusions” are present. In North America, the parkinsonian subtype seems to predominate whereas in Japan, the cerebellar pattern is more common.

In MSA-P, brain MRI scans, may demonstrate abnormal signal in the putamen (a cluster of cells deep in the brain involved in regulating movement). In cases of MSA-C, brain MRI shows atrophy (or shrinkage) of the cerebellum and brainstem. It may also show the "hot cross bun sign" which suggests degeneration of nerve fibers in a part of the brain stem called the pons. Brain scans, however, cannot always distinguish MSA from other neurodegenerative diseases. Additionally, as MSA is a rare disease, these characteristic changes are sometimes not recognized by radiologists. Therefore, the scans should be examined by a neurologist experienced in the diagnosis of MSA.

Diagnosis of MSA may also be aided by testing the autonomic nervous system. One method of testing this is by measuring blood pressure and heart rate with the patient lying down compared with standing up. A decrease in blood pressure while standing (orthostatic hypotension) is suggestive of autonomic dysfunction. A sleep study (polysomnogram) can find sleep apnea.

Cause

Despite intensive research, the cause of MSA is still unknown. There is little evidence that MSA is a genetic disorder, as most patients with MSA have no family history of a neurological disease. The pathological findings of MSA are distinct from Parkinson's disease; however, studies suggest that there may be an overlap between these two disorders. Like those with Parkinson's disease, patients with MSA accumulate the protein, alpha-synuclein, within specific brain cells. Why this protein is mishandled and how that results in nerve cell damage remains an area of intense interest among neuropathologists and other neuroscientists. Abnormalities with the SNCA (alpha synuclein gene) have been found to increase the risk of developing MSA. MSA-C has also been reported to be rarely caused by the gene for another disorder of coordination called spinocerebellar ataxia (SCA3).

Treatment

In the early stages of MSA, levodopa and drugs that act directly on dopamine receptors (dopamine agonists) may lessen parkinsonian symptoms, such as slowness of movement. On average, however, these drugs are less effective in patients with MSA compared to those with Parkinson's disease. Also, as in Parkinson's disease, many patients with MSA develop involuntary movements (dyskinesias) after prolonged levodopa use. Levodopa may also lower blood pressure, which is problematic for patients with autonomic dysfunction.

For patients with autonomic dysfunction, there are treatments that lessen the drop in blood pressure when upright. These treatments include increasing the amount of

salt in the diet, fludrocortisone (a steroid hormone), midodrine, pyridostigmine and droxidopa (drugs that stimulate the autonomic nervous system), and the daytime use of stockings to decrease pooling of blood in the legs. Because these methods can increase blood pressure to undesirably high levels when the patient is lying down, the head of the patient's bed should be elevated at least 30 degrees. Continuous Positive Airway Pressure (CPAP) breathing machines at night may be helpful for those patients with MSA who have sleep apnea. Increased urinary frequency due to an overactive bladder usually improves with solifenacin (Vesicare), tolterodine (Detrol) or similar medications. Sildenafil (Viagra) and related drugs may be effective for erectile dysfunction but can unmask dizziness (orthostatic hypotension) and should be used with caution. Urological consultation is recommended in most cases of MSA. Because of swallowing problems some patients require placement of a feeding tube (PEG) directly into the stomach to maintain adequate nutrition and prevent aspiration pneumonia.

Non-drug treatments for MSA include physical therapy and stretching exercises designed to maintain strength and flexibility. Devices which make walking safer, such as a cane or walker, can also be helpful.

At present, there are no therapies that can reverse or slow the progression of MSA. Animal model research has not identified any neuroprotective treatments. Research in animal models may determine if drugs that reduce the abnormal alpha-synuclein accumulation might be promising treatments for MSA. Furthermore, as MSA is rare, clinical drug trials are sometimes not available for affected patients. Nonetheless, there is reason for hope. Because the biology of MSA may be related to other neurodegenerative diseases, like Parkinson's disease, it is possible that therapies designed for other conditions will also prove helpful for patients with MSA.

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Helpful Organizations

Multiple System Atrophy Coalition™
<https://www.multiplesystematrophy.org/>

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Appendix

- Multiple System Atrophy - Medscape Reference
- Multiple System Atrophy – NIH factsheet

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