curePSP®
UNLOCKING THE SECRETS OF BRAIN DISEASE®

MSA: Some Answers

Lawrence I. Golbe, MD

Professor of Neurology,
Rutgers Robert Wood Johnson Medical School,
New Brunswick, NJ

Director of Clinical Affairs and
Scientific Advisory Board Chairman, CurePSP

July 2016

What is Multiple System Atrophy (MSA)?

Multiple system atrophy is a disease of the brain and spinal cord. It is often classified as one of the "parkinsonian" conditions because it often resembles Parkinson's disease, at least for the first few years. The resemblance is in the general slowness, stiffness and balance loss. But MSA usually has at least two other important categories of symptoms to some degree. One is impairment of the cerebellum, producing a coarse tremor, drunken-appearing walk and slurred speech. The other is impairment of the autonomic nervous system, which maintains such things as blood pressure, sleep, bowel action and bladder emptying. The result can be fainting, insomnia, constipation and urinary urgency or incontinence. Many other less common symptoms can occur, too.

How common is MSA?

MSA is rare, with about 13,000 sufferers in the United States, most of whom have not yet received a correct diagnosis. This compares with about 20,000 with progressive supranuclear palsy (PSP), which is a similar condition, about 500,000 with Parkinson's disease and five million with Alzheimer's disease.

New cases of MSA arise in about six persons per million per year. This means that in the U.S., about five people are newly diagnosed with MSA each day.

Are there different types of MSA?

There are three types that grade into one another. MSA emphasizing slowness and stiffness was once called *striatonigral degeneration*. MSA emphasizing autonomic problems was called *Shy-Drager syndrome* and cases emphasizing cerebellar problems were called *sporadic olivopontocerebellar atrophy*. These terms were discarded in 1989, when all three were found to be variants of the one disease, which then received its current name. What they all have in common is a type of protein that forms clumps in the same types of cells in the three. The differences among the three types of MSA are dictated by which parts of the brain or spinal cord are most involved.

What is the cause of MSA?

The ultimate cause (called the *etiology* of the disease) is not known. MSA almost never occurs twice in a family and there are no confirmed clusters related to occupation, industry, diet, ethnicity or geography. A variant in a gene called alpha-synuclein (SNCA) occurs more often in people with MSA than in the rest of the population, but this accounts for only a small fraction of the overall cause of the disease. Various chemical toxins have also been implicated, but these results have not been confirmed in multiple studies.

What's going wrong in the brain and spinal cord cells?

The direct cause of the loss of brain and spinal cord cells (the *pathogenesis* of the disease) in people with MSA is not fully understood. However, it has to do with the clumps of alpha-synuclein protein mentioned above. Alpha-synuclein is a normal protein that is necessary for brain cells to signal to one another. The current favored theory is that too much alpha-synuclein is made. Once it reaches a certain concentration in the cell, it starts to stick together. The resulting blobs, when they are still too small to be seen with a microscope, are toxic. The larger clumps seen under the microscope, called *glial cytoplasmic inclusions*, may actually be the brain's attempt to solidify the tiny, toxic clumps floating around inside the cell into a hard, relatively harmless form.

The same protein, alpha-synuclein, accumulates in the brain cells in Parkinson's disease, but in somewhat different parts of the brain. Also, in MSA, the initial accumulation and cells loss appears to be in the *glia*, the electrically inactive supporting cells of the brain. In Parkinson's disease, on the other hand, the problem starts in the *neurons*, the electrically active cells.

At what age does MSA start?

The average age at which the symptoms of MSA begin is only 53. This is younger than the averages of 59 for Parkinson's and 63 for PSP.

What happens to someone with MSA?

All three kinds of MSA feature important balance problems that can eventually require assistance in walking or even a wheelchair. All three types can also display difficulty in the aspect of thinking called *executive function*. This is what allows us to organize information by categories, understand abstractions and instructions, create and follow a plan and inhibit inappropriate actions. These things often decline to some extent in people with MSA.

Some other features occur in all three types of MSA. Perhaps the most important is difficulty swallowing, which obliges one to modify the diet to exclude thin liquids or tough solids. All three types can also have difficulty in moving the eyes, which can interfere with reading; and in speaking, which may require speech therapy and communication devices.

People with MSA of the parkinsonian type tend to get more muscle stiffness and general slowness. Those with the cerebellar type develop a coarse tremor when moving the limbs and difficulty aiming their limb movements or walking in a straight line, much like someone who is drunk. Those with MSA that emphasizes the autonomic problem have a variety of symptoms including urinary urgency and incontinence, constipation, erectile disturbance in men, lightheadedness or even fainting upon standing, noisy or irregular breathing, sleep disruption and difficulties with temperature regulation. Most people with MSA have some combination of the three types rather than a pure form.

Some other problems with movement can occur in MSA. The hands can gradually assume abnormal, fixed postures called *dystonia*. This can be prevented to some degree by stretching exercises and can be treated in some cases by botulinum toxin (Botox) injections into the hands or forearms. Some people with MSA hold their heads bent forward to an extreme degree, a condition called *antecollis*. This may respond to Botox injected into the neck muscles, although care must be taken not to exacerbate the swallowing problems via leakage of the Botox to the immediately adjacent muscles. Another issue in some people is sudden, rapid jerks of a limb or of the trunk that is annoying but almost never large enough to interfere with normal movement. This called *myoclonus* and can be treated with medication. Finally, a tremor, which is not nearly as prominent as in most people with Parkinson's, can occur in MSA. This tremor generally occurs when the limb is in use rather than at rest as in PD. It may respond to medication, but usually is too mild to require treatment.

Some people with MSA develop *obstructive sleep apnea*. This is where the upper airway tends to close during sleep, which causes insomnia and sometimes insufficient blood oxygen levels. It can be treated by wearing a mask during sleep that connects to a kind of air pump that keeps the airway open, called *continuous positive airway pressur*e or CPAP. This is usually best managed by a specialist in sleep medicine or pulmonary medicine rather than a neurologist.

Is MSA a fatal disease?

On average, someone with MSA lives about seven or eight years after the onset of symptoms. This short survival is not a direct effect of the disease, but of complications of the difficulties in swallowing safely and moving around. The most common of these complications are pneumonia, urinary tract infections and blood clots in the legs that lodge in the lungs. Other potentially dangerous complications of MSA are low blood pressure, slow heart rate, sleep apnea and injuries from falls.

How is MSA treated?

We have no treatment or prevention for the underlying brain disorder, but some of the individual symptoms can be managed successfully with medication that raise blood pressure, enhance sleep, inhibit bladder emptying or stimulate the bowel. Drugs for PD that stimulate the brain's dopamine system sometimes work for a few years for the general slowness and stiffness in MSA.

What happens eventually?

Unfortunately, the progression of MSA is almost as rapid as that of PSP, with the average time from initial symptom to requiring a wheelchair of five years. Death occurs an average of seven to eight years after the initial symptom, usually from complications of the immobile state such as pneumonia or other infections. Keep in mind that this is only an average duration of survival. Many people with MSA survive longer.

What research is being done?

A critical defect in the brain cells in MSA is accumulation of the normal protein "alpha-synuclein." The same protein accumulates in Parkinson's disease, but in a different set of brain cells. In 2010 alone, 227 research papers on MSA were published in scientific journals. As scientists understand more about the various brain degenerative disorders such as Alzheimer's, Parkinson's, PSP, Lou Gehrig disease and MSA, many commonalities among them are being revealed. That means that any breakthrough in one could benefit the others. It is entirely realistic to expect that after researchers find a prevention or a way of halting the progression of one of these diseases, the others will benefit similarly.

How can I help research in MSA?

One way is to be alert for trials of new medication or new diagnostic tests. These are listed on a website maintained by the National Institutes of Health, www.clinicaltrials.gov. You simply enter "Multiple System Atrophy" into the search box. Participants in clinical trials may not only benefit from a new treatment that is not generally available, they also often receive detailed care and attention that is not part of the routine, even at excellent medical centers. They also get the satisfaction of helping in the fight against their illness. Other trials may look for new genetic or environmental contributors to the cause of MSA. Discovering these could also point to potential preventative measures or treatments.

More information on research is available from CurePSP (*www.curepsp.org* or 1-800-457-4777), which includes MSA among the disorders for which it provides education and support for patients and their families.

curePSP®

UNLOCKING THE SECRETS OF BRAIN DISEASE®

404 5th Avenue
3rd Floor
New York, NY 10018
347-294-2873 (CURE)
Canada: 844-287-3777
www.curepsp.org
Facebook.com/curepsp.foundation