MSA: Some Answers

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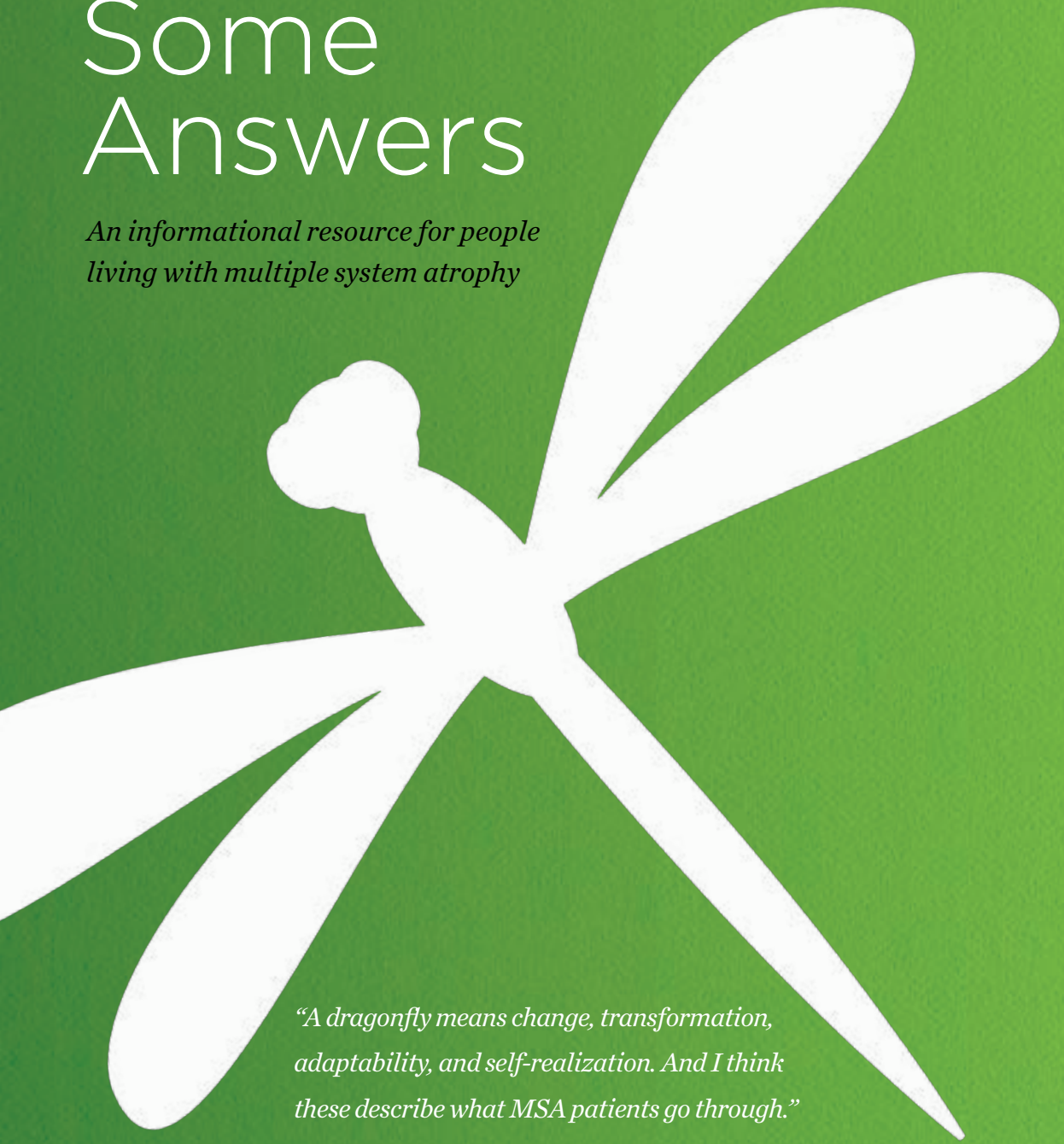
UNLOCKING THE SECRETS OF BRAIN DISEASE®

An informational resource for people living with multiple system atrophy



"A dragonfly means change, transformation, adaptability, and self-realization. And I think these describe what MSA patients go through."

- Jeaninne, person diagnosed with MSA

What is multiple system atrophy (MSA)?

Multiple system atrophy, or MSA, is a rare, adult-onset, neurological disease that impacts movement, coordination, and, often, the autonomic nervous system. MSA is commonly referred to as an atypical parkinsonism, or sometimes as a Parkinson's-plus diagnosis, because of its overlap with certain symptoms of Parkinson's disease.

How many people are diagnosed with MSA?

MSA is considered rare, affecting about two to five individuals for every 100,000 people. Currently, about 13,000 people are diagnosed with MSA in the United States. This compares with about 30,000-40,000 people with progressive supranuclear palsy (PSP), which is a different type of atypical parkinsonism disorder; about 1 million with Parkinson's disease; and 5 million with Alzheimer's disease. This means that in the U.S., about five people are newly diagnosed with MSA each day. However, these figures for MSA are probably underestimates because many people with MSA are misdiagnosed with another condition, such as Parkinson's disease.

At what age does MSA start?

People with MSA often begin to have symptoms anywhere from their late 40s through their early 70s. The average age at which the symptoms of MSA begin is 53. Unlike Parkinson's disease, where symptoms can begin as early as the 20s and as late as the 90s, symptoms of MSA are very unlikely to begin outside this age range.

What are the symptoms of MSA?

MSA involves multiple circuits in the brain, each of which explains one of its several categories of recognizable symptoms. These major symptom groups include:

- Parkinsonism, which refers to slowness, smallness, and stiffness of movement, as well as tremor and changes in gait and balance. Other common problems related to movement in parkinsonism include reduced arm swing with walking, small or cramped handwriting, soft voice, and reduced facial expression.
- Cerebellar ataxia, which is caused by disease in the cerebellum (located at the back of the brain) and its connections. Common symptoms are a staggering, drunken-like gait, imbalance, uncoordinated movements, difficulty reaching for things with the arms, sloppy handwriting, and slurred speech.
- Autonomic nervous system failure, including severe blood pressure fluctuations when changing positions, difficulty with urination, constipation, difficulty swallowing, reduced sweating, and sexual dysfunction.
- Spasticity, which refers to muscle stiffness or tightness that creates resistance to being stretched. When your doctor taps on your arm or leg with a reflex hammer, you may notice that your limb jumps. MSA can exaggerate these reflexes, interfering with voluntary movement.

Are there different types of MSA?

People with MSA may develop some or all of the groups of symptoms listed above. Currently there are two recognized subtypes of MSA, defined by their predominant symptoms. One is the parkinsonian subtype (MSA-P). People with this type of MSA have more parkinsonism symptoms, meaning slow and small movements, tremor, and shuffling gait. Many people with this subtype may be misdiagnosed with Parkinson's disease initially. The other subtype of MSA is the cerebellar subtype (MSA-C). This subtype is diagnosed when someone has a predominance of

cerebellar ataxia symptoms, meaning balance and coordination trouble. People with this subtype may be misdiagnosed with other forms of cerebellar ataxia initially, particularly genetic or inflammatory conditions. Typically, people living with MSA over time will develop at least some degree of symptoms in both subtypes, though one will often remain more prominent. Both of these subtypes share the same pathology in the brain, with abnormal buildup of the same protein (alpha-synuclein) in brain cells. Depending on where in the brain the buildup starts, people will exhibit one MSA subtype or the other.

What other symptoms can occur in MSA?

While each individual with MSA can present with their own unique symptoms and progression, there are commonalities for many people living with this diagnosis.

As the disease progresses, people with MSA often experience mobility and balance problems that can eventually require assistance in walking or even a wheelchair. People can also develop difficulty using their hands to write, button clothing, dress themselves, feed themselves, and perform other activities required for daily living. People with MSA of the parkinsonian type tend to get more muscle stiffness and general slowness. Those with the cerebellar type develop difficulty aiming their limb movements or walking in a straight line.

People with MSA often develop problems with their autonomic nervous system. The autonomic nervous system takes care of things you don't have to think about, such as blood pressure, heart rate, sweating, emptying the bladder or bowels, and sexual function. People with this problem may notice symptoms such as lightheadedness or even fainting with standing and walking, constipation, loss of control of urinary function, or sexual dysfunction.

Sometimes breathing can also be affected. This can include irregular breathing or temporary cessation of breathing while sleeping (sleep apnea) and a loud noise when taking in a breath (inspiratory stridor). Treatment of these symptoms often involves the use of a continuous positive airway pressure (CPAP) or bilevel positive airway pressure (BiPAP) machine, which pushes oxygenated air into the nose or mouth via a mask during sleep. In addition to sleep apnea, some people with MSA experience other sleep disturbances such as abnormal movements during sleep, acting out dreams while asleep, restless leg syndrome, and frequent awakenings during the night. Your doctor may recommend a sleep study to monitor for these symptoms.

People with MSA may develop difficulty with speaking. This difficulty can manifest as soft speech or slurred speech. Swallowing can also become difficult and may require people to alter the consistency of their food or to take special precautions while eating. For these reasons, your doctor may recommend that you participate in regular evaluations and treatment with a speech-language pathologist. In some cases, if swallowing becomes very difficult, people may choose to get a special tube placed into the stomach for feeding.

Visual symptoms can also occur, the most common of these being dry eyes and double vision. These can be addressed with a neuro-ophthalmologist.

One or more limbs can develop uncontrolled muscle contractions that lead to abnormal, fixed postures in a limb or in the neck, which is called dystonia. These issues can be prevented to some degree with stretching exercises and physical and occupational therapy. Dystonia can be treated in some cases using oral medications or with botulinum toxin (Botox) injections into the affected limb. Some people with MSA hold their head bent forward to an extreme degree, a condition called antecollis. This problem may be improved with Botox injected into the neck muscles. Jaw clenching or forced eye closure occur and can also be treated with medication or Botox injections. Botox injections should only be performed by an experienced neurologist to minimize risks and side effects.

Another issue some people experience is sudden, rapid jerks of a limb or of the trunk. This can occur at rest or in reaction to an external stimuli such as a physical touch. This symptom, called myoclonus, is annoying but rarely interferes with normal movement, and it can be treated with medication. MSA can cause a tremor, which is not nearly as prominent as in most people with Parkinson's disease. This tremor generally occurs when the limb is in use rather than at rest as in Parkinson's disease. It may respond to medication but usually is too mild to require treatment.

Do people with MSA develop dementia?

Dementia, or severe memory or cognitive decline, is very unusual in MSA. However, people with MSA may develop milder signs of mental changes, typically after living with the disease for several years. People with MSA can develop difficulty in the aspect of thinking called executive function. This aspect is what allows us to organize information by categories, understand abstractions and instructions, create and follow a plan, and inhibit inappropriate actions and behaviors. Common mental changes that people with MSA may notice include slowed thinking, difficulty with keeping their attention on a task, and difficulty with multitasking. Occasionally, people with MSA may also experience inappropriate or unintentional laughter or crying, a symptom called pseudobulbar affect. These mental changes rarely become functionally limiting for people living with MSA.

What happens to someone with MSA over time?

Unfortunately, MSA is progressive. This means that over time, people with MSA will notice increasing severity of their symptoms and/or onset of new symptoms. Not everyone experiences all of the symptoms of MSA, and the appearance and progression of these symptoms vary greatly among individuals.

Research has shown that someone with MSA lives about eight to ten years after the onset of symptoms, on average. The most common complications in MSA are infections, particularly pneumonia and urinary tract infections. Abnormal breathing, particularly at night, along with severe blood pressure fluctuations, blood clots, and falls are other common and potentially serious complications in MSA. Your doctor may recommend regular examinations of your swallowing function to ensure that food is not entering the lung spaces and causing pneumonia, evaluations by a urologist to test your urinary function, sleep studies to test your nighttime breathing, adaptive

equipment to improve your safety with ambulation, and other preventative measures. Quality of life is enhanced by attentive care, maintaining general health, and perhaps most important, by an optimistic and hopeful attitude of the patient and family.

We recognize this information is scary and overwhelming to learn and to think about. It can be helpful to talk this through with your medical team and your family, including planning for the future and your wishes for quality of life. CurePSP and the rest of your support system are here to help.

How is MSA diagnosed?

To diagnose MSA, a neurologist will gather a person's medical history, including neurological symptoms, and will perform a physical examination. At this time, there is no specific test of body fluids nor imaging test of the brain that makes the diagnosis. A brain MRI can show changes in parts of the brain that would support the MSA diagnosis, but because changes in the brain do not always show up on an MRI, particularly in the first few years of symptoms, brain MRI cannot be relied upon as the sole diagnostic test.

Your neurologist may decide to use other tests, such as a DaTscan, positron emission tomography (PET) scan, or autonomic nervous system testing, to help support the diagnosis of MSA. However, like the brain MRI, these tests can only support the diagnosis but are not sensitive enough nor specific enough to make the diagnosis alone. Given the rarity of the disease, many people with MSA face a long and confusing diagnosis journey. It is common to go through a number of tests, specialists, and diagnoses. It is our hope that better awareness of MSA, especially within the medical community, will lead to earlier and more accurate diagnosis.

How is MSA treated?

At this time, we have no medication to cure MSA or to slow its progression. As research has shown repeatedly that cardiovascular exercise can slow the progression of motor decline in most neurodegenerative conditions, exercise remains a very important piece of disease management for people with MSA.

Some symptoms of MSA can be managed successfully with medications for the same symptoms in other conditions. Examples include medications to raise blood pressure, enhance sleep, improve bladder emptying, stimulate the bowel, treat dystonia and spasticity, and treat anxiety or depression. Drugs for Parkinson's disease that stimulate the brain's dopamine system, particularly carbidopa-levodopa, can be effective in alleviating some of the parkinsonism symptoms in MSA, though the response is typically not as dramatic or long-lasting as in Parkinson's disease. Your doctor will work with you closely to try different medications, timing, and dosages to maximize the benefits for your symptoms while also trying to minimize side effects.

Physical, occupational, and speech therapy are also important pillars of treatment to address many of the symptoms and challenges faced by people living with MSA, such as speaking, swallowing, balance, and daily activity performance. Home safety evaluations performed by trained physical and occupational therapists are extremely useful to help prevent falls and to recommend adaptive equipment such as grab bars, shower chairs, walkers, or wheelchairs.

Does the deep brain stimulation that is done for Parkinson's disease work for MSA?

There have been only relatively small case series as examples of people with MSA undergoing deep brain stimulation surgery, or DBS. Only very few people with MSA who received DBS (because they were misdiagnosed as having Parkinson's disease) had any symptomatic improvement, and in all of those cases, the benefits were very brief. In many cases, people with MSA who underwent DBS noticed worsening of their symptoms after implantation. For these reasons, DBS is not recommended for MSA.

What is happening in the brain and spinal cord cells to cause MSA?

The direct cause of MSA is not fully understood. However, we do know that it has to do with the clumps of alpha-synuclein protein. Alpha-synuclein is a protein that is normally produced in the brain. In MSA, the alpha-synuclein seems to become abnormally folded, which causes it to stick together, and become stuck inside the cell. The areas of the brain that have cells with alpha-synuclein inside of them exhibit impaired neuron function and neuronal death.

One theory of the cause of MSA is that the clumps of misfolded alpha-synuclein are toxic to the brain. There is evidence of higher levels of inflammation in the brains of people with MSA, though it remains unclear whether this is a cause of the disease or a side effect of the disease process. There are also theories related to how MSA spreads through the brain. These include the idea that the diseased cells in the brain have a faulty mechanism for getting rid of waste materials, leading to cell deterioration as well as buildup of waste products such as alpha-synuclein, or that the abnormally folded alpha-synuclein protein itself "infects" other cells.

The same protein, alpha-synuclein, also accumulates in the brain cells in Parkinson's disease, but in a different pattern. In Parkinson's disease, the accumulation of this protein is in the neurons, which are electrically active cells, primarily in the part of the brain that produces the chemical dopamine, which helps to control movement and coordination. In MSA, the alpha-synuclein accumulation and cell loss appear to mainly impact the glial cells, which are the electrically inactive supporting cells of the brain, in addition to the neurons. It is unknown why the alpha-synuclein accumulates differently in these two conditions.

Why is it called "multiple system atrophy"?

Most brain disorders affect more than one set of circuits or areas of the brain, so why does MSA deserve the term "multiple"? It's because it was once three different diseases. The cerebellar type of MSA (MSA-C) used to be known as olivopontocerebellar atrophy (OPCA); the parkinsonian subtype (MSA-P) was called striatonigral degeneration (SND); and MSA with disproportion-

ate autonomic symptoms was called Shy-Drager syndrome. By 1989, scientists discovered that the abnormalities under the microscope in the three conditions were identical except for their locations, which overlapped significantly. They coined the term "multiple system atrophy" as a tribute to the historical notion of three disorders in one. Still, sometimes we still hear these older names used.

Is MSA genetic?

MSA is not considered an inherited disease, as there have been only a very small number of cases of more than one family member being affected. A variant in a gene called GBA, which encodes the enzyme glucocerebrosidase, has been found to be a little more common in people with MSA than in the rest of the population. The same finding is present in Parkinson's disease. However, this cannot be used as a diagnostic test. 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 and has not been confirmed in further studies. Variants in the gene encoding COQ2, an enzyme that helps in the production of coenzyme Q10, which is important to the production of energy by brain cells, were found in family members with MSA in two Japanese families where multiple members had MSA. When testing this finding among large groups of people with MSA, these COQ2 genetic variants were slightly more common among people with MSA compared to those without MSA, though this was only true in studies done in East Asian populations. Still, the vast majority of MSA is not known to have a genetic cause. Additionally, there have not been confirmed clusters of MSA related to occupation, industry, diet, ethnicity, or geography. However, one study done in North America found that occupational exposure to organic solvents, plastic monomers, metals, and pesticides was slightly higher in people with MSA.

Ultimately, it is not yet known why people develop MSA. For someone who is personally impacted by MSA, we recognize that this can be extremely frustrating and confusing. Researchers and doctors are working hard to understand MSA and other neurodegenerative diagnoses, and we hope this will lead to more answers and treatment options soon.

What research is being done to better understand MSA and find more treatment options?

In 2020 alone, almost 500 research papers on MSA were published in scientific journals. As scientists understand more about the various neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, progressive supranuclear palsy, Lou Gehrig's disease, and MSA, many commonalities among them are being revealed. There is hope that as researchers find prevention or ways of halting the progression of any of these diseases, the discovery could apply to MSA as well.

Some drug companies looking for a way to slow or halt the progression of Parkinson's disease are testing their treatments in MSA first, or simultaneously, in relation to the accumulation of the abnormally folded protein, alpha-synuclein. This has brought a wealth of new treatment trials in MSA.

There is also research being done to better understand and manage the low blood pressure challenges associated with MSA.

How can I become involved in research in MSA?

Many people with MSA find that participation in research is a meaningful way to help doctors and scientists understand, diagnose, and treat MSA. Participants in clinical trials may not only benefit from a new treatment that is not generally available; in addition, they often receive detailed care and attention that is not part of the routine, even at excellent medical centers. Equally important research is being done to look for genetic and environmental contributors to the cause of MSA, as well as research on tests that can lead to more accurate diagnosis and improved care of MSA.

In the United States, clinical trials 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. You can also visit *www.curepsp.org* for a list of active and pending treatment trials in MSA. Additionally, you can ask your neurologist if they are offering or are aware of studies in MSA.

Donating your brain to science can be a powerful contribution to the understanding of MSA and other neurodegenerative conditions. Each donated brain is also evaluated by a trained neuropathologist to confirm that the diagnosis of MSA was correct. Setting up brain donation needs to occur early, ideally months or even years prior to someone passing away. Visit *www.psp.org/ineedsupport/braindonation* to learn about CurePSP's brain donation program.

What can I do to support myself and my family with this diagnosis?

Building a support team around you is foundational to quality of care and life with MSA. Your support team may consist of your partner, family, friends, support group, religious community, healthcare team, professional care, and others—people who care about you and show up for you.

When living with a chronic and progressive diagnosis, it is important to find the right medical team to support your needs with MSA over time. MSA needs to be managed by a neurologist. This could be a general neurologist, but, if available in your area, you may also choose to work with a neurologist who has gone through specific training in movement disorders or autonomics. Rehabilitation therapists (physical, occupational, pelvic, and speech therapists) and clinical social workers also play important roles in the care of MSA. As symptoms and needs arise, you may also benefit from adding other specialists to your team, such as a urologist, neuro-ophthalmologist, and palliative care physician. Taking care of your emotional health with MSA is also a priority, and working with a mental health professional to process the experience, foster coping skills, or address other emotional needs can be exceptionally beneficial. When building your care team, it is important that you have providers you have chemistry with and that you trust, and for you to know you have the right and the ability to change your providers if needed.

Completing health care advance directives is an excellent tool for sharing your wishes regarding care with your support team. Health care advance directives address topics such as how aggressive your medical care should be (for example, whether you would want a feeding tube or a machine for breathing if the need arose) and how you define quality of life. These directives should be completed with your family and your doctor, and should be reviewed at least annually in case your wishes change.

Many people living with MSA consider and explore professional care services, such as in-home care, adult day care, or long-term care, depending on their care needs and situation. These services can provide an additional layer of support, including companionship or hands-on help for the person with MSA and assistance and respite for the family.

Additionally, there can be great value in connecting with other people affected by the same diagnosis as you and your family, through support groups or a peer support network. It can feel validating and uplifting to hear the experiences and insights of how others adapt to life with MSA. You can exchange helpful tips on ways to cope physically and psychologically with the diagnosis. There are a handful of support groups specifically for MSA and many more for atypical parkinsonism (which can include progressive supranuclear palsy and corticobasal degeneration) in the United States and other countries. Visit *www.psp.org/ineedsupport/supportgroups* for a list of regional support groups as well as virtual, national support groups facilitated by or in collaboration with CurePSP. Additionally, many local Parkinson's disease support groups welcome members with MSA. If you may be interested in starting your own MSA support group, contact CurePSP to learn more and for help in getting started. Additionally, CurePSP offers educational symposiums and webinars where you can learn about MSA and connect to the community.

We recognize that a diagnosis of MSA can bring up many emotions, changes, and considerations. No matter how you find support, please remember that you do not have to navigate the MSA journey alone.

The mission of CurePSP is to raise awareness, build community, improve care and find a cure for PSP, CBD and MSA.

Please contact CurePSP for additional information and resources:

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