September 2019 Newsletter

Accelerating research towards a cure for multiple sclerosis

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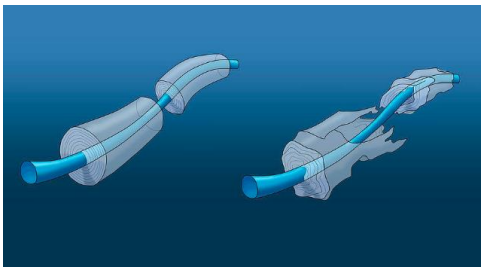
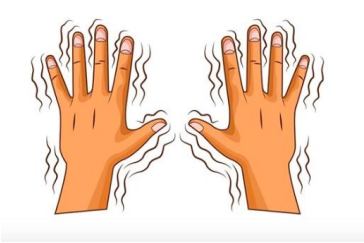
What are the symptoms of MS and how is it diagnosed?



MS is a progressive, autoimmune disorder where the system designed to keep the body healthy (the immune system) mistakenly attacks the nerves in the brain and spinal cord. The protective covering of nerve cells (myelin sheath) is damaged, which interferes with the conduction of signals. This nerve damage can cause a myriad of symptoms that can be variable and unpredictable, depending on the location and extent of nerve damage. People with MS tend to have their first symptom between the ages of 20 and 40. No two people have exactly the same symptoms, and they can change over time. One person may experience only one or two symptoms while another person may experience many more. Some symptoms may come and go, while others linger. People with MS may have a single symptom that resolves for months or even years, without any other symptoms. On the other hand, some individuals experience multiple MS symptoms that worsen within weeks or months. Many MS symptoms are heat-related. For example, some may notice more symptoms in hotter weather, or as they warm up during exercise. These often go away when one gets out of the heat, or rests and cools down.

MS symptoms can be classified in three categories: primary, secondary and tertiary. Primary MS symptoms are caused by ongoing damage to the myelin sheath. Two primary MS symptoms that are often initial symptoms in those living with the disease are visual problems, as well as numbness and tingling. Visual problems (blurred vision, double vision or loss of vision) occur when the optic nerve is affected. MS can also damage other nerves in the brain and spinal cord, causing it to send conflicting signals around the body, or no signals at all, which results in tingling and numbness. Common sites of these altered sensations include the face, arms, legs, and fingers. Chronic pain is another common primary MS symptom, occurring in 65% of those living with the disease. As discussed in our March 2019 newsletter, 80% of people with MS experience fatigue and over half rank it as one of their most troubling symptoms. In some cases, it may be the most prominent symptom in a person who is otherwise minimally affected.



When nerve damage occurs along nerve pathways responsible for coordination of movement, a number of symptoms can occur. Spasticity is a feeling of stiffness and involuntary muscle spasm that most commonly occurs in the legs (but can occur in any limb). Tremor, or uncontrollable shaking, can also occur in various parts of the body. Weakness may be the result of nerve damage, or deconditioning of unused muscles. Nerve demyelination may cause a person to feel off balance or lightheaded. Less frequently, one may have the sensation that they or their surroundings are spinning (vertigo), most frequently upon standing up. Bladder dysfunction is another common primary MS symptom. Difficulties that may occur include frequent urination, strong urges to urinate, or incontinence. Constipation, as well as a loss of bowel control, may also occur in people with MS. As discussed in our March 2019 newsletter, up to 65 percent of people with MS struggle with cognitive dysfunction. This can include difficulties with memory, attention or organization.

Some less common primary MS symptoms include difficulties with speech, such as slurring (dysarthria), loss of volume (dysphonia) and stuttering. These typically occur later in the disease course and during periods of extreme fatigue. Problems with swallowing (dysphagia) may also occur as a result of damage to the nerves controlling the muscles in the mouth and throat. According to the National MS Society, seizures occur in 2-5 percent of people with MS. These are

the result of abnormal electrical signals in an injured or scarred area of the brain. Breathing problems, such as shortness of breath and difficulty breathing deeply, can occur in people whose chest muscles have been weakened by damage to the nerves that control those muscles. Other uncommon symptoms include hearing loss, headaches and sudden, intense itching.

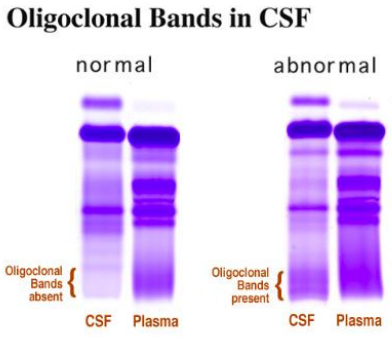
While the primary symptoms of MS are the direct result of nerve damage, secondary MS symptoms are complications that can arise as a result of primary symptoms. For example, bladder dysfunction can lead to repeated urinary tract infections. Becoming less mobile can result in weakness and decreased bone density. While secondary symptoms can be treated, the best approach is to avoid them by treating the primary symptoms. Tertiary symptoms are a result of the social and psychological consequences of the disease. For example, a person who becomes unable to walk or drive may lose his or her job. The strain of dealing with chronic illness may disrupt personal relationships. Problems with bladder control, tremor or swallowing may cause people to withdraw from social interactions and become isolated. Some MS symptoms may have multiple causes. For example, sexual response can be affected by nerve damage. It also has the potential to be affected by other MS symptoms, such as fatigue and spasticity, as well as psychological factors in living with the disease. As discussed in our April 2019 newsletter, depression is common among people with MS. This can be a reaction to the stresses of living with MS as well as the result of neurologic and immune changes that occur due to the disease itself.

As discussed in our March 2019 newsletter, sleep is often disturbed in people with MS as a result of primary, secondary and tertiary MS symptoms. Lesions and nerve damage to key brain structures, as well as disruption of key neurotransmitters involved in sleep have the potential to interfere with getting a good night's rest. People with MS are also prone to vitamin D deficiency, which has been linked to sleep disorders. However, additional research is needed to assess the relationship between vitamin D and sleep in people living with the disease. MS also causes a number of symptoms that indirectly disrupt sleep, such as restless legs, muscle cramps, pain, or urinary/bowel problems. People with MS often report becoming easily overheated. Awakening due to such temperature discomfort may also disturb one's slumber. Insomnia may be a side effect of medications used to treat MS and its symptoms. For example, it is a common

side effect of steroid treatments (used to treat MS relapses). Stimulant medications often prescribed to treat MS-related fatigue can cause restlessness and sleep disruption. Increased napping during the day due to fatigue can interfere with a good night's sleep, as well. Reduced physical activity due to fatigue and MS-related disability can have the same effect. In addition, those living with MS often struggle with depression, stress and anxiety, all of which have the potential to keep one awake at night.

Because MS affects every individual differently, it can be very difficult to diagnose. For many people, the first episode of what is often later diagnosed as MS is called clinically isolated syndrome (CIS). CIS is a single episode of neurologic symptoms due to demyelination of nerves in the brain and spinal cord. Symptoms depend on the location of the lesions and can range from barely detectable to disabling. The most common CIS symptoms are optic neuritis, Lhermitte's sign (an electric, shock-like feeling that goes from the back of the neck to the spinal column), numbness and tingling. There are two types of CIS – a monofocal episode (individuals experience one symptom) or a multifocal episode (individuals experience more than one symptom). To be classified as CIS, the episode must last at least 24 hours and it can't be associated with fever, infection, or other illnesses. It's hard to distinguish CIS from MS based on symptoms alone. The big difference is that CIS is a single episode while MS involves multiple episodes, or flare-ups. CIS is sometimes the first clinical episode of MS, but not everyone with CIS develops MS.

To determine a diagnosis of MS, a neurologist typically performs a neurological exam (to check for impaired nerve function) and an eye exam (to evaluate vision and check for eye diseases). While no single laboratory test can confirm or rule out MS, tests to check for specific biomarkers associated with the disease are currently under development and may aid diagnosis in the future. One's neurologist may order blood tests to help rule out other diseases with symptoms similar to MS. He or she may recommend a spinal tap (or lumbar puncture). In this procedure, a needle is inserted into the spinal column and spinal fluid is removed for analysis. The presence of white blood cells in the fluid may indicate an inflammatory reaction resulting from MS. The presence



of a pattern of antibodies called oligoclonal bands in the spinal fluid may also lead to an MS diagnosis. In addition, more specialized diagnostic procedures may be performed such as evoked potential tests which record the electrical signals produced by the nervous system in response to visual, auditory or painful stimuli. Electrodes measure how quickly this information travels down nerve pathways. Neurologists use magnetic resonance imaging (MRI) to look for damage to the central nervous system (CNS), as well as rule out other conditions. MRI provides specialized cross-sectional images of the brain and spinal cord using a powerful magnetic field and radio waves.

The McDonald Criteria is the guideline neurologists use to determine a diagnosis of MS. This guideline takes into consideration information from clinical evaluation as well as MRI scans to establish a diagnosis of MS. It requires evidence of damage over time (occurring on different dates) and in two or more parts of the CNS. The McDonald Criteria was first established in 2001 by neurologist Ian McDonald and has been revised over the years to reflect a better understanding of MS and improved MRI techniques. This guideline was developed using a white and Western patient population. Recent revisions have also improved the criteria's applicability to other populations (pediatric, Asian and Latin Americans).

MS is very challenging to diagnose because it can vary both in severity and how it affects different people. Research shows early recognition and accurate diagnosis of MS are key to delaying disease progression as much as possible and improving outcomes. Early treatment helps to prevent accumulation of disability and irreversible neurologic damage. Unfortunately, misdiagnosis often occurs. A recent study looking at 241 people with an established diagnosis of MS concluded that almost 20 percent of them were misdiagnosed and, more likely, had another health condition.

Four disease courses have been identified in MS – CIS (described above), relapsing-remitting MS (RRMS), secondary progressive MS and primary progressive MS (PPMS). Most people with MS have a relapsing-remitting disease course, where they experience periods of new symptoms or relapses that develop over time and usually improve partially or completely. These relapses are followed by quiet periods of disease remission that can last months or even years. Most people with RRMS will eventually transition to a

secondary progressive course in which there is a progressive worsening of neurologic function (accumulation of disability) over time. Some people with MS experience a gradual onset and steady progression of MS symptoms without any relapses, which is known as PPMS. Of note, although it is not part of the classification of MS, the term "benign MS" is used when people have had MS for many years without developing significant disability. Recent research suggests benign MS cannot be predicted early in the disease. As a result, the term is usually only used retrospectively, after people have done very well with the disease for many years.

MS has the potential to cause a variety of symptoms, many of which can be managed effectively with medication, rehabilitation and other management strategies. Recognizing the early symptoms of MS is key to improving outcomes. A number of disease modifying therapies have been shown effective in slowing disease progression and reducing the number of relapses an individual with MS may have. Those experiencing symptoms typical of MS should report them to their doctor immediately, as early diagnosis and treatment can help counter the disease's intensity and progression.