MINNESOTA PHYSICIAN

JANUARY 2024

THE INDEPENDENT MEDICAL BUSINESS JOURNAL

Volume XXXVII, No. 10

Multiple Sclerosis

Understanding a treatable chronic condition

BY SHELLY L. LARSON-PETERS, MD

Multiple sclerosis (MS), which is now one of the most common chronic diseases of the central nervous system (CNS), is a result of immune-mediated inflammation directed toward the myelin that not only may go on to result in chronic demyelination but also may lead to axonal damage or loss and, ultimately, neuronal cell death. It is an unpredictable disease of the CNS and currently there is no cure. It is estimated that there are more than 2 million cases worldwide, and it can occur in most ethnic groups but is most common amongst white people of northern European descent. Susceptibility rates vary among these groups, with recent findings suggesting that African American women have a higher than previously reported risk of developing MS. It has been described in virtually all ages around the world, although it does have a preference for younger individuals between the ages of 20 and 50, especially women. The youngest reported case of MS in the United States is a 2-year-old girl. The specific triggering mechanism that causes an immune system to attack its own myelin is unknown. There are many environmental/geographic factors, possible hormonal factors and a suspected genetic susceptibility to developing the disease as well. MS is not directly inherited in a simple Mendelian manner; however, approximately 200 genes have been identified that each contribute a small amount to the overall risk of developing MS.

Historical Perspective

Possibly the earliest description of MS was in a woman named Lidwina in Schiedam, Netherlands, in the late 1300s. She was reportedly a healthy child and teenager, but at 15 she developed an acute illness from which she gradually recovered. The following year, she suffered a fall while ice skating that resulted in rib fractures that she also slowly healed from. However, over the next 37 years, she would go on to have relapses and/or progressive symptoms consisting of paralysis of the legs and right arm, facial weakness, blindness of varying degrees in both eyes, sensory disturbances including recurrent facial pain, and swallowing difficulties. Interestingly, Saint Lidwina was canonized by Pope Leo XIII in 1890, and she is also the patron saint of figure skating; the United States Figure Skating Association has a medal featuring a picture of Lidwina. It's important to note that historical descriptions may not perfectly align with the modern understanding of MS, and various neurological conditions might have been grouped together in historical accounts. Since the 14th century, there have been numerous other documented descriptions of similar cases. With the advancement of better clinical examination techniques coupled with autopsy findings and a simultaneous increase in medical meetings, journals and so forth, the devotion for further understanding and categorization of neurological diseases expanded. The most well-known physician who classified a great variety of conditions was Jean-Martin Charcot, a French neurologist and professor who worked at Salpêtrière Hospital in Paris. In 1868, Charcot gave the first definitive description as "la sclerose en plaques." In particular, he made the distinction between the tremor of paralysis agitans (later called Parkinson's disease) and that of multiple sclerosis. Around the same time, J.C. Morris and Silas Weir Mitchell published the first description of MS in North America to the College of Physicians of Philadelphia; however, it was not until the 1950s that the English adopted the name *multiple sclerosis*.

A Wide Range of Symptoms

Depending on the location of the inflammatory lesion in CNS, the symptoms of MS can be vastly different among individuals, which may include but not be limited to weakness, sensory disturbances, vision changes, memory and cognitive impairment, mood disturbances, gait and mobility issues, genitourinary symptoms, debilitating fatigue, neuropathic-type pain and so on. Due to the diversity of symptoms, which vary in severity and frequency, it can be difficult to diagnose this disease at times, especially early in its course. Depending on the location of the inflammatory lesion(s), some individuals may initially be clinically asymptomatic, which prolongs the length of time to diagnosis and treatment. A relapse is defined as new neurological symptoms typical for MS, lasting longer than 24 hours, and without a febrile illness. Relapses may often develop subacutely over hours to days and can plateau for many days to weeks, if not longer, and then may recover either completely or incompletely gradually over time. Cognitive and neuropsychiatric relapses can easily be missed. For individuals with a progressive form of the disease, they may also be diagnosed later in life than those with relapsing MS. Diagnosing MS involves a combination of clinical evaluation, imaging studies with MRI and laboratory tests. With the development and advancement of MRI technology since the 1980s, imaging has become one of the most important tools to aide with the diagnosis and treatment of MS. In addition, there are multiple potential mimickers of the disease, including infectious, vascular, and metabolic etiologies, systemic inflammatory and autoimmune syndromes, other demyelinating or inflammatory CNS syndromes, neoplastic syndromes, and other rare genetic etiologies. The revised McDonald criteria for multiple sclerosis are diagnostic guidelines used to identify and diagnose MS. These criteria have been updated to improve the accuracy and speed of diagnosing the disease. They include clinical and imaging findings, such as the presence of specific symptoms, evidence of lesions in different areas of the CNS, and the dissemination of these lesions over time. Additional supplementary testing such as serum and CSF studies and evoked potentials may also aid in the diagnosis and exclude other possible diseases.

Many individuals with MS lead long and fulfilling lives.

The pathophysiology of MS is limited to the primary CNS with two primary processes that result in microscopic injury and neurodegeneration involving axons, neurons, and synapses; and focal inflammation resulting in macroscopic plaques and injury to the blood-brain barrier. Perivascular lymphocytic infiltrates and macrophages produce degradation of myelin sheaths, resulting in myelin loss, edema and axonal injury, which are the chief components of plaque pathology. There is increasing evidence that inflammation in MS is initiated by peripheral immune cells and CNS-residing immune cells. Acute inflammation is initiated by activation of peripheral T- and B-cells into the CNS and then results in blood-brain barrier disruption and corresponds to enhancement seen on MRI; over time, this inflammatory process will subside, resulting in an astrocytic scar. In the majority of cases, the disease initially starts as a relapsing-remitting course, with attacks of neurological impairment that may resolve entirely or near completely over a length of time. Now, however, a number of subtypes of multiple sclerosis have been classified, including clinically isolated syndrome, radiographic isolated syndrome, primary progressive, progressive-relapsing, and acute and chronic secondary progressive disease. A relatively new and emerging model of "smoldering multiple sclerosis" is unfolding, which is thought to be a chronic compartmentalized inflammation within the CNS that is independent of relapses and is driven by CNS-residing immune cells, such as microglia, that become chronically activated and cause diffuse damage to both white and gray matter in the brain. This results in a slow, progressive accumulation of disability in the absence of clinical relapses and the absence of new lesions on MRI. Researchers have discovered that slowly expanding lesions located in the brain continue to damage the nerves of the CNS, despite treatment with currently approved (as of 2023) disease-modifying therapies. These therapies work outside of the CNS in the blood or lymph systems to slow disease activity by reducing the numbers of relapses and active lesions.

Treatment and Management

The goal of MS treatment is to reduce the frequency and severity of relapses and new inflammatory lesions, slow down disease and disability progression over time, manage symptoms and improve quality of life. Before MS was described, treatment for it was nonspecific and ineffective, if not dangerous or deadly. These treatments may have been herbal concoctions, chloroform, electrotherapy, hydrotherapy, arsenic, cooling therapies, bleeding/leeches, silver nitrate or potassium iodide. By the 1950s and 1960s, the immune nature of the disease process became commonly

accepted and the first clinical trials for MS were evaluating the effects of corticosteroids. Steroid therapies have continued to be useful for treating acute attacks and reducing acute inflammation but have been found to have no beneficial long-term effects on the disease. Because of the evolving disease paradigm, the treatment options for MS have advanced exponentially in the last 20 years, particularly when it comes to disease-modifying therapies. Interferons, discovered in the late 1950s, were initially promoted as a treatment for cancer. The Food and Drug Administration (FDA) approved the first interferon for the treatment of multiple sclerosis in 1993, with other interferons and copolymers following. There are now numerous medications that modify or modulate the immune system and medications that may suppress a portion of the immune system to try to keep MS under control. With evidence now growing that gradual neurodegeneration can be present from the start, there are several medications currently in clinical trials focusing on the chronic secondary progressive forms of the disease, targeting the "smoldering" inflammatory pathway. Currently in the United States, over 20 disease-modifying medications are FDA-approved for treating relapsing forms of multiple sclerosis and one medication approved for primary progressive multiple sclerosis. Medications can be administered by injection, orally or intravenously, and there are several factors that go into selecting which therapy to use. Historically, an escalation strategy has been used when initiating treatment, which may be associated with an increased risk of further relapses and disability early on in some individuals. However, an induction strategy that involves the use of highly effective therapy right from the start has been favored as well, but this may be associated with increased risk including possible serious infections, other systemic adverse effects and/or malignancy. Unfortunately, there are no clear class I evidence-based guidelines that dictate the ideal approach to treatment thus far.

There are no clear class I evidence-based guidelines that dictate the ideal approach to treatment thus far.

In addition to treating the disease itself, there are numerous other medications for symptom management, as well as nonpharmacological and rehabilitative therapies, including noninvasive neuromodulation devices for a variety of MS symptoms. Diet and other lifestyle modifications can play a supportive role in managing symptoms. A healthy and balanced, nutrient-rich diet with the addition of anti-inflammatory foods such as nuts, berries and fatty fish, in addition to adequate hydration throughout the day, is key. Although there is no direct link that vitamin D deficiency causes MS, ensuring that an individual has a sufficient vitamin D level is recommended to help support the immune system. Regular exercise, adequate rest, temperature management and tobacco cessation may also help keep MS symptoms more manageable. Individual responses to diet and lifestyle changes may vary and it is important for individuals with MS to work with health care professionals to develop a personalized plan based on their specific needs and circumstances. Furthermore, symptomatic treatments are important in helping individuals fulfill their personal, social and occupational roles and improve quality of life, for as long as possible.

In Summary

In summary, multiple sclerosis is a treatable disease, for which treatment should begin at the time of diagnosis. It is recommended to start treatment with an FDA-approved disease-modifying therapy as soon as possible, and treatment may be given indefinitely, unless there are other surrounding circumstances that may arise to warrant discontinuation or switching therapy. With the advancement of treatment options, the life expectancy for many individuals with multiple sclerosis is typically similar to that of the general population. Although MS is a chronic condition that may affect a person's quality of life, it is not usually a direct cause of reduced life expectancy. Many individuals with MS lead long and fulfilling lives. In turn, it's important for individuals to continue to address other medical conditions and age-related health issues that may develop over time. It is important that patients are informed and educated and have access to a multidisciplinary approach to help manage the complex symptoms of multiple sclerosis. It is a collaborative effort among a number of health care professionals to address the diverse needs of individuals with MS. This includes the involvement of not only a neurologist but also a primary care physician and a number of other sub-specialist physicians, as well as rehabilitative therapists, mental health practitioners, dietitians, nursing specialists and social workers.

Shelly Larson-Peters, MD, is a board certified neurologist. She is both the director of multiple sclerosis and medical director of infusion at Noran Neurology, offering comprehensive services for individuals with MS, including diagnosis and management of the disease, at several locations in the Twin Cities.