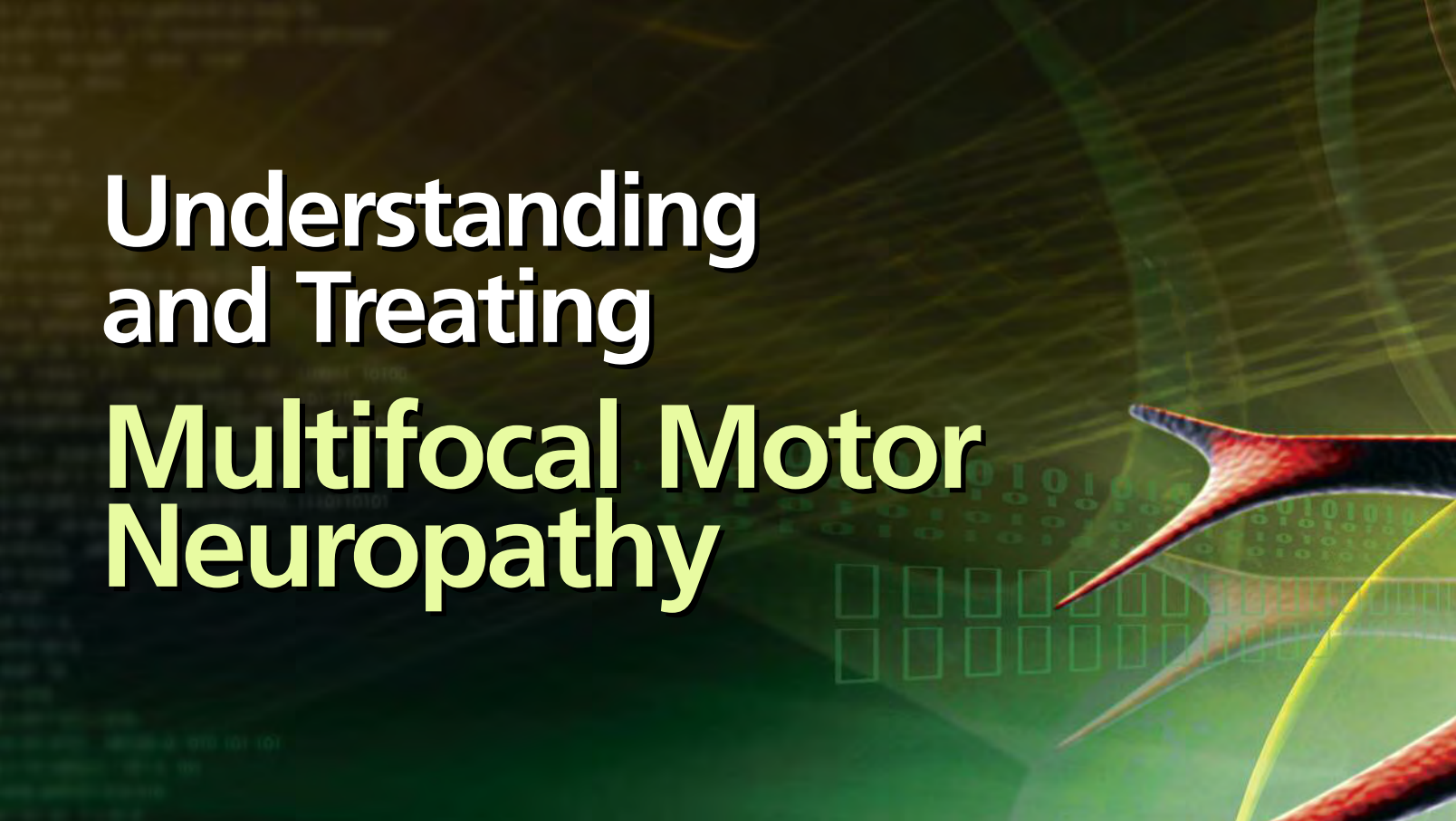


Understanding and Treating Multifocal Motor Neuropathy



This rare disease is typically diagnosed late or misdiagnosed, resulting in permanent disability, but patients still respond to treatment.

By Matthew David Hansen, DPT, MPT, BSPTS

Little is known or understood by most people about a great many immune and autoimmune diseases. Medical conditions such as diabetes, cerebral palsy, hemophilia and muscular dystrophy at least carry an air of familiarity. But, then there are those other diseases with alien-sounding names that are rare, as is the case with multifocal motor neuropathy (MMN).

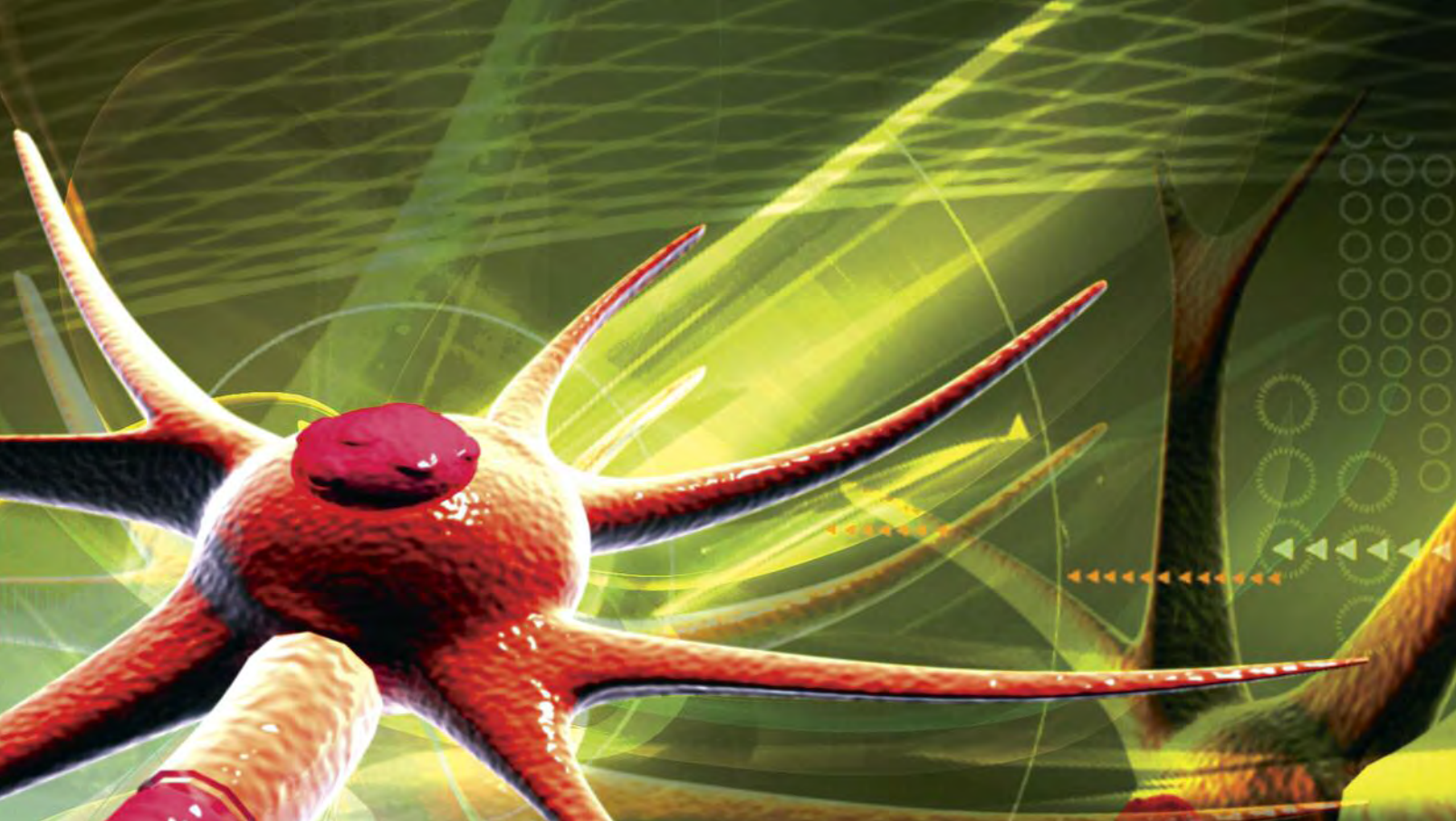
MMN occurs in approximately one in 100,000 people, with men being affected about three times as often as women.¹ Yet, while this is a very rare disease, understanding what the disease is and how to diagnose and treat it can mean the difference between MMN patients being cured or successfully managed, or permanently disabled.

What Is MMN?

The National Institute of Neurological Disorders and Stroke defines MMN as “a [typically slowly] progressive muscle disorder characterized by muscle weakness in the hands, with difference from one side of the body to the other in the specific muscles involved.” Symptoms frequently

include general fatigue, muscle cramping and fasciculation (twitching or involuntary contractions) and, less likely, muscle atrophy (wasting).² The exact pathogenesis (or cause) of the disease is not understood; however, it is now generally accepted that the condition results from an autoimmune disorder. Specifically, it appears that the body’s immune system misidentifies markers on the body’s own nerve cells as foreign, and mounts an attack. Studies have demonstrated injury and/or destruction to the peripheral motor nerve fibers and to the myelin sheath (a fatty covering that protects nerve fibers and allows for a signal to be relayed quickly), resulting in slowed or blocked nerve conduction. Weakness usually follows the distribution of individual peripheral nerves, contributing to the clinical signs of weakness on one side of the body and not the other, or mixed weakness in the same extremity.

Although mild abnormalities are often seen in the sensory nerve fibers of MMN patients as well, sensation is almost never affected. The lack of noticeable sensory involvement with MMN is one of the distinguishing symptoms from



other progressive neuropathies, such as chronic inflammatory demyelinating polyneuropathy (CIDP), Guillain-Barré syndrome and Lewis-Sumner syndrome (multifocal acquired demyelinating sensory and motor neuropathy [MADSAM]). It is not unusual for MMN also to be initially mistaken for the ultimately fatal condition of amyotrophic lateral sclerosis (commonly referred to as ALS or Lou Gehrig's disease) or other disorders. Needless to say, the diagnostic process can be a lengthy and frustrating one for individuals with MMN, while the "duration of disease prior to diagnosis ranges from several months to more than 15 years."³

The Story of Tony Marsalisi

Tony Marsalisi experienced this lengthy diagnostic process firsthand. Marsalisi is a private business owner who first saw a doctor in the fall of 2001 with complaints of unexplained difficulty writing. According to him, "Everything else seemed fairly normal; no strength problems or mobility issues. The doctor pretty much blew me off. I was too young to have anything major wrong with me (33 years old at the time)." After a year of

persisting symptoms, Marsalisi visited another doctor and was referred to a neurologist who suspected multiple sclerosis and who ordered an MRI to be performed. When the results came back negative, Marsalisi was sent home again without concern.

Three years later in 2005, Marsalisi began noticing strength differences between his right and left arm. This time when he saw a neurologist, he was diagnosed with

"writer's cramp," and Botox injections were recommended to "loosen the muscles" in his wrist/forearm. Not trusting the diagnosis, Marsalisi refused the treatments. When pain and numbness isolated to his right arm, wrist and hand developed in the spring of 2006, another MRI was ordered, this time revealing herniated cervical disks at the C5 and C6 levels. After being

told that spinal fusion surgery would cure his problems, Marsalisi optimistically consented. Unfortunately, the operation did not cure the problem. Marsalisi describes the whole diagnosis process as "very frustrating." "I pretty much dealt with it by myself in the beginning due to the lack of severity

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of my symptoms," he says. "They were very hard to explain and, with no pain, people don't take it very serious; they make you feel like it's in your head."

During the latter part of 2007, Marsalisi began having problems in his left thumb and wrist. That's when he decided to enlist the assistance of his wife, whom he describes as being "a lot more demanding [of answers] than I am." Together, they made an appointment to see yet another neurologist, who ordered yet another MRI. After multiple sclerosis was ruled out a second time, the neurologist referred Marsalisi to an ALS specialist who, to the couple's dismay, told them that Marsalisi likely had some variation of ALS, Kennedy's disease or MMN. A follow-up electromyogram (EMG), in which a needle electrode is inserted into a muscle to measure its electrical activity, led the doctor to declare with 85 percent certainty that the cause of Marsalisi's symptoms was MMN. He began intravenous immunoglobulin (IVIG) treatments in April 2008 and has received them ever since (currently four times a month). "Once my symptoms spread to the other side of my body and you could actually see the disability of what I was experiencing, it got much more attention," says Marsalisi. "My wife was great during the time I went to the ALS specialist and my testing, and helped keep me positive till we got some definitive results."

Diagnosing MMN

With upwards of 30,000 people in the United States living with MMN, Marsalisi's experience of delayed and misdiagnosis is not unique. It can be difficult for a doctor to sort through a host of differential diagnoses; most general practitioners have never seen a case of MMN, and it's likely that many neurologists have not either. Nevertheless, besides those signs and symptoms already mentioned, there are several other clues that may help point to MMN. For example, a positive blood test for antibodies to ganglioside GM1 (a fatty substance found within nerve cells) is supportive of MMN, particularly when concentrations are elevated. However, it should be noted that a-GM1 is also implicated in Guillain-Barré syndrome and motor neuron disease. It also should be noted that the lack of a-GM1 does not rule out the diagnosis of MMN.

There also are other things to look for. The mean age of onset for MMN is 40 years old, with 80 percent of patients falling in the age range of 20 to 50. Deep tendon reflexes may be absent (especially in affected limbs) or normal (reflexes may be brisk early in the course). And, muscle tone may be decreased or normal (no clonus, spasticity or pathologic reflexes [e.g., Hoffman or Babinski] are noted).^{1,3} The important thing to remember is that, in the face of real and persistent symptoms, one should not stop looking for an accurate medical explanation.

Treating MMN

Once MMN is diagnosed, most patients will require some form of treatment. The first choice in therapy tends to be IVIG in an attempt to depress the overactivity of the immune response. The Johns Hopkins Medical Institution's Department of Neurology (JHMI) asserts that IVIG:

"... has been found to be effective in patients reported in the literature with 80% of 170 MMN patients treated with IVIg having shown improvement. ... Beneficial effects from IVIg begin within days, and sometimes hours after the infusion, peak at an average of 2 weeks and the effect lasts from several weeks to months. Most patients require periodic maintenance doses of IVIg. The dose and frequency of IVIg administration needs to be individualized depending on the length of benefits received, which appears to vary between patients, but is relatively consistent in individual patients."⁴

A recent study conducted at the Rudolf Magnus Institute of Neuroscience at the University Medical Center in Utrecht, Netherlands, reports that 94 percent of the patients included in the study responded positively to IVIG therapy.⁵ A separate study, conducted at the same institute, suggests that the rapid clinical improvement in strength following an IVIG infusion may be due to the immunoglobulin interfering with antibody binding to gangliosides or preventing access to the antigen (the substance that stimulates an immune response), and not to structural remyelination of the nerve axons (which typically takes much longer). IG antibodies that bind to the ganglioside GM1 could be detected in approximately 50 percent of all MMN patients.⁶

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Although IVIG is the preferred treatment for MMN, it is not the only one. JHMI indicates that cyclophosphamide, a drug used to treat various types of cancer (taken orally or intravenously) “is perhaps the only immunosuppressive agent (besides IVIg) that has shown to have consistent efficacy (50%) in the treatment of multifocal motor neuropathy with 20 of 40 cases showing improvement.” The drug is not routinely used, however, because of associated toxic side effects, including increased risk of infections, bone marrow suppression, nausea and vomiting, an increased risk of hematological malignancies and other concerning conditions.⁴ JHMI reports initial positive results for the use of azathioprine (an immunosuppressant drug) and interferon beta-1a (frequently used in the care of multiple sclerosis); however, study numbers are too small to make any conclusions about their effectiveness or side effects in the MMN population. The usefulness of corticosteroids and plasmapheresis has been limited and, in fact, may worsen the symptoms of some patients after treatment.⁴

Prognosis of MMN

Early treatment of MMN usually leads to enough of a reduction, if not a resolution, of symptoms so that permanent disability is avoided. Still, slow progression of symptoms over the years, which may lead to significant disability, is not unusual⁷ and, unfortunately, many patients aren’t diagnosed with MMN soon after they begin noticing symptoms. On the other hand, the disease may be responsive to treatment even after many years of manifestation. Death as a consequence of MMN is extremely rare, and most patients are able to remain independent with indoor and outdoor activities,⁸ with up to 94 percent remaining employed.⁹

In Marsalisi’s case, he experienced some immediate improvement since beginning IVIG treatments nearly three years ago and has since “leveled off — no worse, no better.” He continues to run the day-to-day operations of his business (scheduling, ordering, bookkeeping, etc.), but he is not responsible for the most physical work. Time missed from the job during infusions and difficulty writing are the most direct effects on Marsalisi’s livelihood. He is quick to note that his employees are very understanding and supportive of his absence, and he explains that he has had to train himself to write with his left hand, “which still leaves a lot to be desired.” Other fine motor skills also can be a struggle.

Outside of work, Marsalisi notes that MMN is a hard disease to explain to people. “How it affects you and how the treatments help is very confusing, and seeing as no one has ever heard of it, they don’t seem to understand [the]

difficulties you have to deal with on a daily basis. My favorite line is: ‘You look good.’”

The gratitude that Marsalisi feels for the people in his life shines through his words. He thanks his wife for her support, especially now that he is receiving his infusions at home; he thanks his three teenage sons, who joke with him about his condition, calling it his “kunk” because he occasionally drops things or misses a short putt when they’re playing golf; he thanks the cancer patients at the infusion clinic and the perspective that visiting with them gives him; and he thanks his IG nurse for her flexibility and consistency.

A Rare, But Important-to-Understand Disease

MMN is but one of many diseases that society knows little about, making it a tough disease to diagnose and an even tougher one for the patient to live with — especially when not diagnosed early enough to prevent permanent disability. Even though it affects only a small population, increased familiarity with it will surely advance the likelihood of earlier diagnoses, leading to improved care and outcomes. ■

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