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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

MMN in Practice: A Rare Motor Neuropathy Often Misdiagnosed

Announcer:
Welcome to *Neurofrontiers* on ReachMD. This medical industry feature, titled "MMN in Practice: A Rare Motor Neuropathy Often Misdiagnosed," is sponsored by Argenx. Here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is ReachMD, and I'm your host Dr. Jennifer Caudle. Today, we're diving into a rare but impactful condition—multifocal motor neuropathy, or MMN for short. It's a chronic, immune-mediated motor neuropathy that can mimic other neuromuscular disorders.[1-3]

Joining me today to discuss the diagnosis and management of this condition is Dr. Katie Beadon, a neurologist and neurophysiologist specializing in inflammatory and hereditary neuropathies. She's the Co-Director of St. Paul's Hospital Immunotherapy in Neurology Clinic, as well as an Assistant Clinical Professor at the University of British Columbia, in Vancouver.

Dr. Beadon, welcome to the program.

Dr. Beadon:
Thank you for having me.

Dr. Caudle:
Of course. So, Dr. Beadon, let's start at the clinical level. What are the hallmark signs and symptoms that should put MMN on our radar?

Dr. Beadon:
Well, for context, MMN is a very rare disorder. Estimates suggest that it has a global prevalence of about 0.6 per 100,000,[4,5] which is lower than conditions like myasthenia gravis or chronic inflammatory demyelinating polyneuropathy, also called CIDP,[6,7] which in and of themselves are quite rare.

Most MMN patients present with slowly progressive, asymmetric weakness that mainly affects the distal limbs and usually starts in the hands.[4] But what sets it apart from other neuromuscular disorders is that this weakness occurs without sensory loss.[3] Because of this, patients might describe cramping, fatigue, fasciculations, and difficulty walking. Reflexes can also be reduced or absent, and in some cases, there's visible muscle atrophy. Often, weakness is worse in cold temperatures.[3,4]

While MMN, generally, patients have a normal life expectancy, up to 20 percent may develop severe disability, particularly involving the arms.[4] And individuals with MMN report broad impacts on their daily activities, work, social life, and overall wellbeing.[8] Given this impact, recognizing MMN early is critical, especially since it can be mistaken for other neuro-muscular disorders.[3,9,10]

Dr. Caudle:
So with that in mind, could you tell us about some of the neuromuscular conditions MMN can be mistaken for?

Dr. Beadon:
Certainly. A common misdiagnosis is ALS, or amyotrophic lateral sclerosis, especially in its early stages when patients have focal weakness and fasciculations with retained reflexes. But unlike ALS, MMN has no bulbar involvement or respiratory muscle weakness, and its progression is usually slower.[3]

MMN may also be mistaken for asymmetrical variants of CIDP and for lower motor neuron disease such as segmental distal spinal muscular atrophy.[3]

MMN is one of the few motor neuron disorders that is treatable. So making the diagnosis—particularly an early diagnosis—matters.[11]

Fortunately, we have a combination of diagnostic tools to help us differentiate these conditions. Electrophysiological testing is central, but we may also use serology, CSF analysis, or even spinal cord imaging.[11] It's really about pulling together the full clinical picture and using these tools to zero in on MMN. That helps us avoid delays and get patients on the right treatment path as early as possible.[9,10]

Dr. Caudle:
Now you've talked a bit about how critical it is to recognize MMN early. So given that importance, what impact could delays in diagnosis have?

Dr. Beadon:
Even though MMN awareness has improved, earlier studies have estimated a median delay of about two years from symptom onset to diagnosis.[9] And in some cases – for example – a 2010, retrospective study out of the Netherlands found a median delay of five years from symptom onset to first treatment, with some patients waiting decades to get the right diagnosis and management.[9]

And that's concerning because we know that disease severity correlates with the length of time a patient remains untreated. The longer the delay, the greater the risk of irreversible axonal damage leading to functional decline, especially in the arms, where weakness tends to be the most disabling. So early recognition and treatment initiation isn't just ideal—it's essential for preserving long-term motor function.[9,10]

Dr. Caudle:
So let's dive into the diagnostic work-up. How do you approach confirming a diagnosis once you suspect MMN clinically?

Dr. Beadon:
Once MMN is suspected, the diagnostic approach really centers around a combination of clinical, electrophysiological, and supportive criteria. These are outlined in the European Federation of Neurological Societies and Peripheral Nerve Society, or EFNS/PNS, Joint Task Force Guidelines. In addition to guiding the diagnosis, these criteria help to establish the level of certainty to classify a case as definite, probable, or possible, depending on how much supporting evidence we have.[12]

A clinical exam is absolutely essential as a starting point. To meet the core diagnostic criteria, patients must have both of the following[12]:

First, there has to be slowly progressive or stepwise progressive, focal, asymmetric limb weakness—so motor involvement in the distribution of at least two nerves that lasts at least a month.[12]

Second, there should be no objective sensory abnormalities, apart from possibly some minor vibration sense changes in the feet.[12]

So what we're really looking for is a pattern of motor-predominant neuropathy without sensory loss, most commonly affecting multiple nerves in the arms first. And it's important to note that there should be no signs of upper motor neuron involvement. Keeping that in mind helps distinguish MMN from other motor neuron diseases.[12]

Dr. Caudle:
Now, you mentioned electrophysiology—can you walk us through what we should be looking for in nerve conduction studies?

Dr. Beadon:
Of course. Once your patient's clinical presentation and exam raises the suspicion for MMN, the next step is confirming the diagnosis with electrophysiological testing. With MMN, the hallmark finding here is conduction block in motor nerves outside of typical compression sites. And identifying definite or probable conduction block in at least one nerve is required for the diagnosis based on EFNS/PNS criteria.[12]

Conduction block means that when you stimulate a nerve further away from the recording site, you get a smaller response than when you stimulate the same nerve closer to the recording site. Conduction block is referred to as definite if you lose 50 percent of the signal and probable if you lose 30 percent. To qualify as true conduction block, that drop has to occur without major signal spreading, which helps us rule out more widespread demyelination.[12]

In MMN, conduction blocks are typically focal, abrupt, and limited to motor fibers, with normal sensory conduction in the same nerve. The ulnar and median nerves are most commonly affected, and early on, conduction distal to the block may still appear normal, making it easy to miss.[11]

That's why conduction blocks might not always show up on routine electrodiagnostics—especially in early or patchy disease. So even when the tests are inconclusive, clinical suspicion remains essential.[2]

Dr. Caudle:
Now, let's switch gears now and talk about serology. How can antibody testing support an MMN diagnosis?

Dr. Beadon:
Of the antibodies observed in MMN, anti-GM1 IgM is the most clinically relevant. It's detected in at least 40 percent of patients and is associated with greater weakness and more axonal loss.[2,13] Higher titers may correlate with increased disease severity, suggesting a pathogenic role rather than just serving as a diagnostic marker.[3,13]

Mechanistically, GM1 is widely expressed, but is more abundant on motor nerves than sensory nerves. It's concentrated at the node of Ranvier, where it organizes ion channels and anchors the myelin sheath.[4] When anti-GM1 IgM antibodies bind to these sites they disrupt nodal function through complement activation and formation of the membrane attack complex, or MAC, all of which contribute to membrane and axonal damage, and lead to conduction block.[2-4]

Although other ganglioside antibodies—have been identified in MMN, they tend to be less specific. So when anti-GM1 IgM is present—especially at higher titers—it not only supports the diagnosis but also gives insight into disease activity.[13]

Beyond the core clinical and electrophysiologic features, there are several supportive criteria that can help strengthen the diagnosis, especially in borderline cases.[12]

A typical work-up includes laboratory testing for anti-GM1 antibodies as well as for serum and urine immunofixation, thyroid function, and creatine kinase to rule out other coexisting or overlapping conditions.[12] If the patient still doesn't meet full clinical or electrophysiologic criteria after common differential diagnoses have been ruled out, then other supportive tests such as CSF analysis, needle EMG, and imaging can be performed.[12]

Nerve biopsies are now rarely done, unless they can help to rule out other diagnoses such as vasculitis or infiltrative processes.[12]

And importantly, if a patient shows objective improvement after intravenous immunoglobulin therapy, or IVIg, that response can support the diagnosis—even when other findings are inconclusive.[12]

Dr. Caudle:
For those of you who are just tuning in, you're listening to *Neurofrontiers* on ReachMD. I'm your host Dr. Jennifer Caudle, and today I'm speaking with Dr. Katie Beadon about early diagnosis, differentiation, and evolving treatment strategies for MMN.

So, Dr. Beadon, let's move beyond diagnosis now. Although it's essential to assess muscle strength, how can we also best evaluate other outcomes such as functionality and quality of life?

Dr. Beadon:
That's an important question. One tool we have is the MMN-RODS, which is the Rasch-built overall disability score, which is a disease-specific scale that captures activity limitations, especially in the upper limbs. It's made up of 25 items related to real-world functioning—things like buttoning a shirt, opening jars, or typing. Each item is scored on a zero-to-two scale, with a total score ranging from zero to 50.[14]

This is a valuable way to assess the functional impact of treatment, particularly in a disease where standard disability scales may not reflect the asymmetric or hand-focused impairments we often see in MMN.

I also use patient-reported measures to assess fatigue—such as the Fatigue Severity Scale[15]—and a standardized quality of life measure to capture a patient's status over time and as we change treatments.

Dr. Caudle:
I'd like to focus now on how we're managing MMN in practice. What can you tell us about the current treatment landscape?

Dr. Beadon:
Immunoglobulin therapy is the standard of care treatment for MMN. Several randomized controlled trials and a Cochrane meta-analysis have reported improvements in muscle strength and function in patients treated with IVIg.[11,16]

More specifically, in that meta-analysis, about 78 percent of patients treated with IVIg showed improved muscle strength, compared to just 4 percent with placebo. There was also a 39 percent improvement in disability, although that outcome didn't reach statistical

significance—likely due to small sample size and the lack of a disease-specific disability scale at the time.[16]

One smaller study focused on grip strength—a key functional issue in MMN—and found that IVIg led to a 3.8 percent improvement, while the placebo group saw a 31 percent decline.[17]

So while responses can vary, immunoglobulin therapy may help stabilize or improve motor symptoms in many cases, at least over the short-to-medium term.[11,16]

Immunoglobulins have traditionally been administered intravenously, a process that can take several hours. More recently, subcutaneous immunoglobulin have become available, which appear equally effective and may offer patients increased autonomy and reduced side effects compared to IVIg.[11]

Dr. Caudle:
Are there any considerations with immunoglobulin therapy that we should be aware of?

Dr. Beadon:
Yes, it's important to note that while immunoglobulin therapy can be beneficial, most patients with MMN end up needing long-term maintenance therapy to prevent clinical deterioration. And even with ongoing treatment, the majority still experience gradual disease progression, including continued loss of muscle strength over time.[9,11]

We also see that the IVIg dosage often needs to increase to maintain the same clinical benefit.[9,11]

All of this points to a real need for continued investigation into understanding how we may be able to help these patients.

Dr. Caudle:
Before we come to the end of our program, Dr. Beadon, I'd like to look ahead for a moment. What can we anticipate in the MMN treatment landscape moving forward?

Dr. Beadon:
So while MMN is treatable, the range of effective options is still quite limited.[12]

Steroids and plasma exchange typically don't work well in MMN, and in some cases, they can actually worsen symptoms, which is important to recognize when differentiating this condition from other immune-mediated neuropathies.[12,18,19]

Currently, immunoglobulin therapies—including IVIg and subcutaneous immunoglobulins, or SCIg—are among the most studied approaches and are used in many clinical settings. That said, treatment strategies can vary widely, and there's no consensus on dosing schedules, duration, or when to adjust therapy.[11,16,19,20]

There's also interest in immunosuppressants and immunomodulators, but they haven't shown definitive evidence of altering the natural history of MMN in clinical trials.[11,19]

The challenge, of course, is that MMN is rare, making it difficult to conduct large, well-powered trials, which is why our understanding of long-term treatment efficacy is still evolving.[11,19]

That said, several therapeutic strategies are under active investigation. One area of particular interest is complement pathway inhibition, based on the proposed role of complement in MMN pathogenesis. Interim phase II trial data of a complement inhibitor showed encouraging signs of clinical activity in adults with MMN, suggesting this class may warrant further exploration in future trials.[21]

Other approaches being explored include B-cell–directed therapies and T-cell–modulating strategies, though these agents remain early in development.[21]

So while the current therapy is often centered around immunoglobulin treatment, future options may expand how we manage MMN at a more targeted, mechanistic level.[21]

Dr. Caudle:
As those final insights bring us to the end of today's program, I'd like to thank my guest, Dr. Katie Beadon, for sharing her insights on early diagnosis and evolving management strategies for MMN.

Dr. Beadon, it was great working with you today.

Dr. Beadon:

Thank you for having me.

Dr. Caudle:
For ReachMD, I'm Dr. Jennifer Caudle.

Announcer:
This medical industry feature was sponsored by Argenx. If you missed any part of this discussion or to find others in this series, visit *Neurofrontiers* on ReachMD.com, where you can Be Part of the Knowledge.

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