

Multifocal Motor Neuropathy

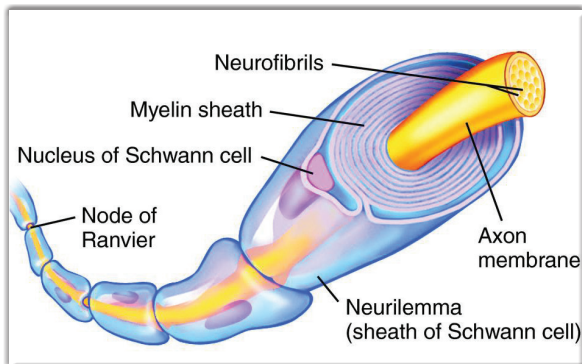
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What is Multifocal Motor Neuropathy?

Multifocal Motor Neuropathy (MMN) is a rare condition in which multiple motor nerves are attacked by one's immune system. This causes weakness without loss of sensation. The specific nature of the attack is unique and perplexing, since motor and sensory fibers are intermingled within the nerve trunks of the arms and legs, but only the motor nerves become involved.

To understand MMN it is important to understand how nerves transmit impulses. Nerve fibers are similar to electric wires, in that they are composed of axons (the wires) and myelin (the insulation). Unlike wires, however, the myelin is spaced along the nerves with gaps called Nodes of Ranvier. These nodes sit between segments of nerve that are wrapped with myelin (figure below). Nerves propagate electrical current, called action potentials by "jumping" from one Node of Ranvier to the next. This remarkable arrangement allows microscopic axons to transmit impulses at very high speeds; in adult humans, at rates of 50 meters/second.



A defining feature of MMN is conduction block; Conduction block is when the impulse fails to travel all the way down the nerve. There are many reasons for this but the exact one responsible in MMN is unknown. The encouraging aspect of conduction block is that it is potentially reversible, restoring function without any significant long term effects.

In MMN, it is thought, although not proven, that antibodies directed against a constituent of the Node of Ranvier (GM 1 ganglioside) cause the sodium channels at the nodes to stop functioning.

Although conduction block is reversible, continued attacks on the nodes can cause destruction of the myelin and axons. These different mechanisms explain why some people with MMN respond to therapy very quickly, while others may develop prolonged or permanent weakness and shrinking of muscles from damage to the nerve (atrophy). As such, the goals of any treatment are to prevent the axonal degeneration and reverse the conduction block.

Incidence and Demographics

MMN is a rare disease probably affecting no more than 1-2 in 100,000 people. Men are twice as likely as women to be affected. Most patients are in their 40's to 60's, although MMN has been described between the ages of 20 and 80. The disorder can cause significant disability but does not shorten life. It is extremely rare for MMN to cause problems with breathing or swallowing. It is rare that MMN will go into remission. In some cases, MMN will initially respond to treatment (see "Therapy" section) but then stop responding to treatment and remain stable.

Cause of MMN

MMN is thought to be caused by alterations in the immune system, such that certain proteins (antibodies) that would normally protect one from viruses and bacteria begin to attack constituents of peripheral nerves. Antibodies may be directed against "GM-1", a ganglioside located at the Node of Ranvier. These antibodies have been detected in at least one third of MMN patients. More recent studies also sug-

gest that newer tests for antibodies directed against GM-1 combined with a number of related gangliosides, are positive in over 80% of MMN patients. Thus, there are increasing reasons to believe these antibodies are the cause of MMN.

MMN Signs and Symptoms

By definition MMN causes weakness. There is essentially no numbness or tingling, and pain is not a significant factor. MMN usually develops asymmetrically and tends to begin in the hands. Frequently, the weakness can be recognized as fitting a specific nerve territory. For example, someone who develops a wrist and finger drop has a problem in the radial nerve, and when new weakness occurs, a different nerve is likely to be involved. The attack on multiple single nerves is called a multiple mononeuropathy syndrome. This pattern can be seen in other diseases, but MMN is the only condition where the attack is isolated to the motor nerve fibers. It follows that this is the most important clinical finding to diagnose MMN.

Patients with MMN can have other symptoms including twitching, or small random dimpling of the muscle which neurologists call fasciculations. Fasciculations are the spontaneous firing of a motor unit (the collection of all the muscle fibers that are innervated by a single motor neuron). Fasciculations are also characteristic of ALS (Amyotrophic lateral sclerosis) and this is one reason many patients with MMN are initially misdiagnosed with ALS. Other lower motor neuron signs such as atrophy, decreased tone and absent reflexes occur in both diseases, although in MMN these tend to affect the territories of single nerves, while in ALS they affect all of the muscles in the limb. In contrast to MMN, patients with ALS may have “upper motor neuron signs” (UMN) caused by damage to motor control in the brain. These signs include increased muscle tone and reflexes and pathologic reflexes such as a Babinski sign.

Diagnosing MMN

The diagnosis of MMN depends on demonstrating that a patient has a purely motor disorder affecting individual nerves, that there are no UMN signs, that there are no sensory deficits, and that there is evidence of conduction block. These criteria are designed to differentiate the disorder from ALS (purely motor but with UMN signs), the Lewis-Sumner Syndrome variant of Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (similar to MMN but usually with significant sensory loss), and “vasculitis” (a type of multiple mononeuropathy syndrome caused by inflammatory damage to the blood vessels in nerves that also causes sensory and motor symptoms).



A neurologist is usually needed to determine the diagnosis, which is based on the history and physical examination along with the electrodiagnostic study, which includes nerve conduction studies (NCS) and needle electromyography (EMG).

The NCS usually demonstrate conduction block. This can be done by showing that the nerve signal cannot conduct past a “lesion” at some point along the nerve. For example, if the nerve is

blocked in the forearm, an electrical impulse can easily get from the wrist to the hand if the stimulus is placed at the wrist. However, the signal will be blocked from reaching the hand if the stimulus is applied at the elbow. In MMN, sensory conduction along the same path should be normal. The EMG portion of the test looks for signals in the way muscles fire. In MMN it will most likely reveal abnormalities suggesting that some percentage of the motor axons have been damaged.

Laboratory testing for GM1 antibodies is frequently done, and can be very helpful if they are abnormal. However, since only a third of patients with MMN have these antibodies, a negative test does not rule out the disorder. Spinal fluid examination is not usually helpful.

Therapy

It is now established that intravenous immunoglobulin (IVIg) provides benefit to patients with MMN. IVIg can lead to improvement in most patients with MMN, with the response varying from minimal to very large. The treatment usually does not completely reverse all of the symptoms and those patients who do respond will require repeated treatments to keep their improvements. The exact timing and dosing needs to be individualized and there is no single formula for success. Dosing may need to be adjusted if the response begins to wear off, or if symptoms worsen despite maintenance therapy.

IVIg is not a cure for MMN and currently no other therapy has proven effective. It is fairly clear that corticosteroids are ineffective and can actually make the disease worse. Other immunosuppressants have been used, but have greater side effects and risks. For example, there are a number of reports suggesting that cyclophosphamide controls the disease in some patients, while results for Rituximab are not encouraging. It is clear that newer therapies are needed, and

many investigators around the world are working towards a better understanding of MMN and the development of more definitive treatments.



Additional Resources

For additional information, resources or if you are having difficulties obtaining IVIg please contact:

Neuropathy Action Foundation

1950 Old Tustin Avenue
Santa Ana, CA 92705
Toll free: 877.512.7262
www.neuropathyaction.org

GBS | CIDP Foundation International

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