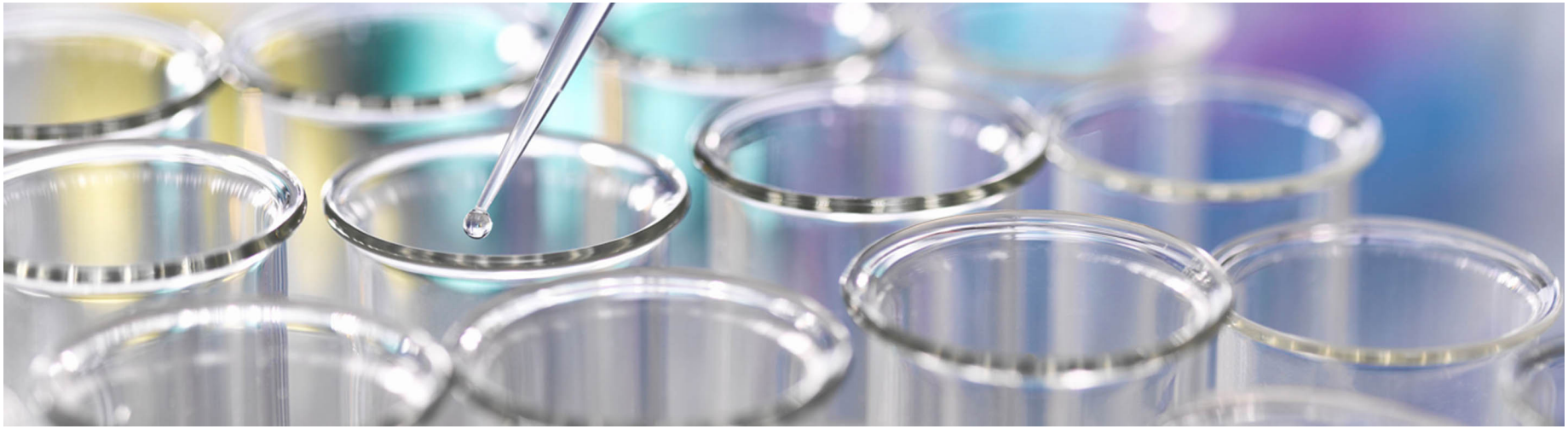
MULTIFOCAL MOTOR NEUROPATHY (MMN) – DISEASE STATE, DIAGNOSIS, AND TREATMENT

RARE DISEASE HUB

C-ANPROM/UK/IG/0026 February 2022



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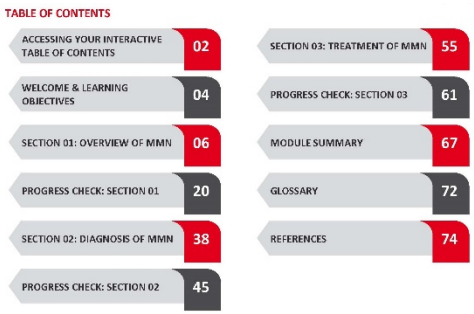

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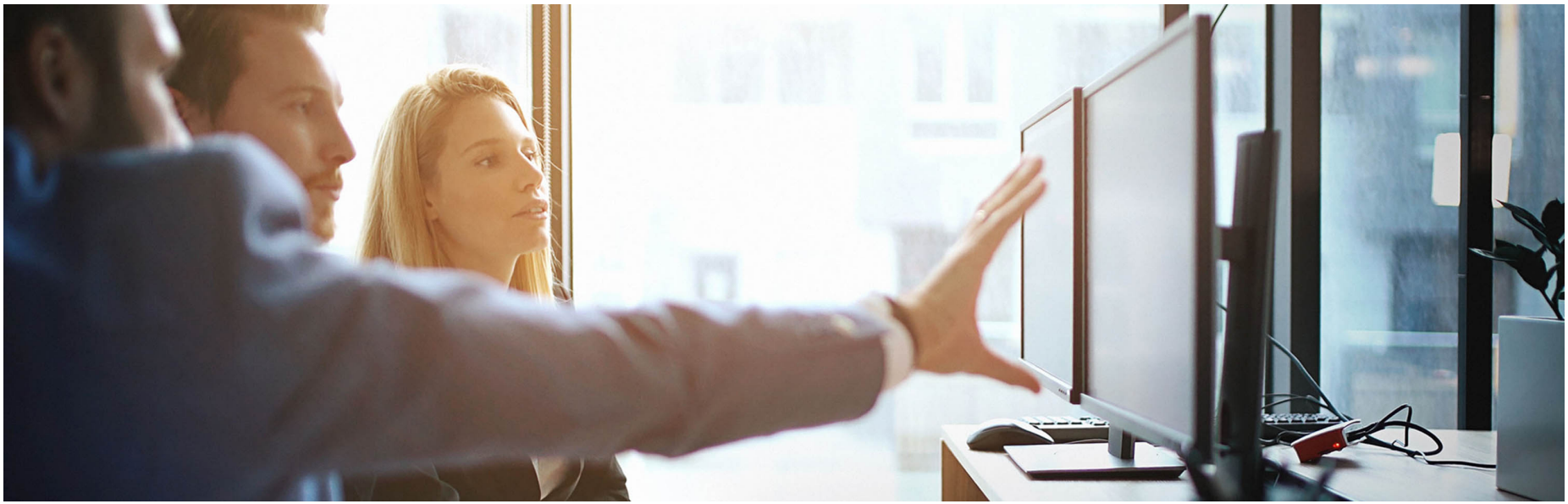
TABLE OF CONTENTS



WELCOME & LEARNING OBJECTIVES

Upon completion of this module, you will be expected to demonstrate that you can…

- Define multifocal motor neuropathy (MMN) and list clinical features and symptoms associated with MMN
- Describe the pathophysiology of MMN
- Discuss the diagnosis of MMN
- List the general treatment options for MMN

Welcome to the Multifocal Motor Neuropathy (MMN) – Disease State, Diagnosis, and Treatment Module!

Dan Lewis is a 38-year-old construction worker. Two years ago, he started feeling weakness and getting muscle cramps in his hands. These symptoms are making it difficult for him to do his job. Dan's family doctor referred him to a neuromuscular neurologist, Dr Caroline Murphy, who is an expert in the diagnosis and treatment of peripheral neuropathies. She suspects that Dan may have multifocal motor neuropathy (MMN). During this course, she will be guiding Dan through the process of diagnosing and treating his condition.

So, what is MMN, how is it diagnosed, and how is it treated? Answering these questions will be the focus of this module.

SECTION 01:
OVERVIEW OF MMN

Peripheral Neuropathies

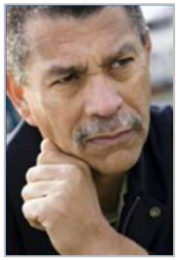
- Nerve disorders that involve the peripheral nervous system and affect muscle strength and control
- More than 100 types of peripheral neuropathies, all of which have different symptoms and prognoses
- May be inherited or acquired
- Causes of acquired neuropathy include physical injury (trauma), diabetes, vascular and blood problems, **autoimmune** diseases, hormonal imbalances, toxins, nutritional imbalances, alcoholism, tumours, and infection
- **Multifocal motor neuropathy (MMN)** is an immune-mediated peripheral neuropathy

Autoimmune
A disease that occurs when the body has an immune reaction to its own cells.

Multifocal motor neuropathy (MMN)
A treatable but incurable, autoimmune-mediated motor neuropathy.

Definition of MMN

MMN is a treatable but incurable disease of the motor nervous system.




- Caused by an immune-mediated motor neuropathy in which autoantibodies and complement react against cells within the body
- Causes weakness in the forearm, hands, and occasionally the distal leg without evident sensory loss
- Progresses slowly and is **asymmetric**, which means that it typically affects one side of the body more than the other
- Characterised by the involvement of two or more nerves

Asymmetric
A lack of correspondence in shape, size, and relative position of parts or problems on opposite sides of a body or structure i.e., the brachial plexus.

DID YOU KNOW?

MMN can affect a person's ability to perform many of the tasks of daily life, from cooking and eating a meal to dressing or brushing one's teeth or hair.

Epidemiology and Prevalence of MMN

- MMN is rare, occurring in only 1 or 2 people per one hundred thousand
- It occurs more often in men than women, in a ratio of 2.7 to 1; onset generally occurs at a younger age for men than women
- The range in age of onset is 20 to 70 years
  - Mean age of onset is 40 years
  - Two-thirds of patients are younger than age 45
- MMN is rarely seen in childhood and onset has never been reported in a person over 70

Clinical Presentation of MMN

- Patients with MMN usually experience limb weakness that follows the distribution of individual nerves
- The disease does not generally affect the **sensory nerves**; therefore, there are no sensory deficits. Sensory nerve **conduction** is preserved, and **conduction block** is confined to motor nerve **axons**
- MMN typically progresses slowly over months to years; it can also advance in steps in which periods of stability are followed by deterioration
- MMN patients have a normal life expectancy and rarely have complete immobility

Sensory nerve
A nerve that transmits impulses from receptors to the central nervous system.

Conduction
The transmission of excitation through living tissue and especially nervous tissue; conduction of impulses to the brain.

Conduction block
Interruption in the transmission of electrical impulse along a nerve; the inability of motor axons to propagate action potentials.

Axon
The part of the neuron that conducts impulses away from the cell body.

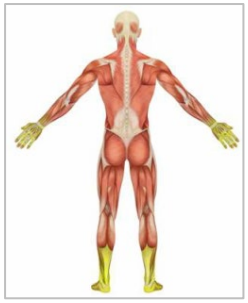
Clinical Presentation of MMN (Cont.)

Initial Symptoms of MMN

- **Wrist drop**
- **Foot drop**
- Grip weakness

Wrist or foot drop is an inability to extend the hand or lift the front part of the foot due to injury of the nerves resulting in muscle weakness in the wrist or ankle.

Weakness usually starts in the forearm or hand muscles. However, about 20–30% of patients with MMN first experience weakness in the lower leg, and 5% of patients first experience weakness in the upper arm.



HERE'S THE CONNECTION

These symptoms might manifest as difficulty performing activities of daily living, such as holding a pencil.

Wrist drop
A condition in which the hand is flexed at the wrist and cannot be extended; may be due to injury of the radial nerve or paralysis of the extensor muscles of the wrist and hand.

Foot drop
General term for difficulty lifting the front part of the foot. Foot drop is a sign of an underlying neurological, muscular, or anatomical problem.

Clinical Presentation of MMN (Cont.)

Later-stage Symptoms of MMN

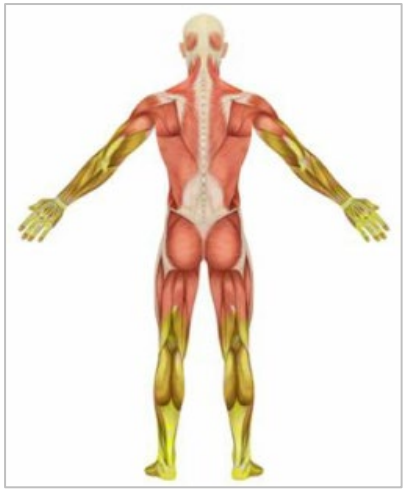
In patients with MMN who experience leg weakness initially, arm weakness frequently follows. Arm weakness usually then becomes the main MMN symptom. In time, weakness may spread from the lower to upper arm, but rarely occurs in the upper leg. Many patients with MMN complain of increased weakness in cold conditions.

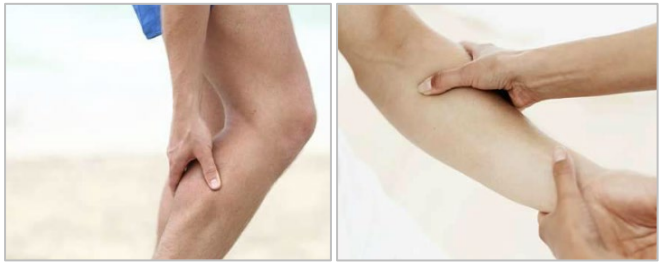
Other symptoms of MMN include:

- Muscle cramps
- **Fasciculations**

These symptoms often occur after exercise.

When patients have extreme weakness in their arms and legs, muscle bulk is initially normal. **Muscle atrophy**, or loss, is typically mild during the early stages of MMN, but can become significant in patients who have had MMN for a long time.





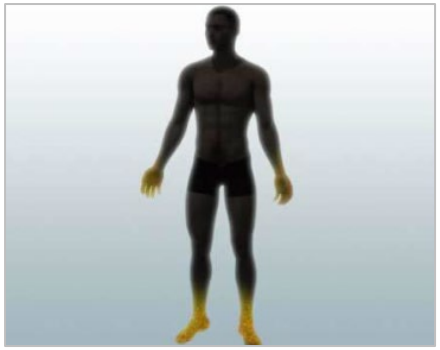
Fasciculation
Involuntary contraction or twitching of muscle fibres, visible under the skin.

Muscle atrophy
Atrophy of muscle tissue, especially due to lack of use or nerve damage or loss.

Clinical Presentation of MMN (Cont.)

Other Symptoms of MMN

- In patients with MMN, **tendon reflexes** are usually low or absent in weak muscles
- Patients may have minor, temporary **paraesthesias**, which are burning sensations or tingling in the weakened muscles
- Sensory deficits are rare, but if present, they typically affect only small patchy areas in the lower part of the limbs



Tendon reflexes
A deep reflex obtained by sharply tapping the skin over the tendon of a muscle; it is exaggerated in upper neuron disease and diminished or lost in lower neuron disease.

Paraesthesia
Abnormal or unpleasant sensation that results from injury to one or more nerves, often described by patients as numbness or as a prickly, stinging, or burning feeling.

Autonomic nervous system
A branch of the motor division of the peripheral nervous system that controls involuntary bodily functions; the autonomic nervous system connects to organs and glands in the body.

DID YOU KNOW?

The autonomic nervous system is not involved in MMN, so involuntary body functions such as breathing, heartbeat, and digestion are not affected.

Clinical Presentation of MMN (Cont.)

Patient & Clinician Perspectives: Symptoms, Disease Progression and Disability

I'm very concerned about how this is affecting my work, because I support my family using my hands. I'm dropping tools at my construction job and trying to make sure no one notices. I'm also slower in the morning with activities of daily living, such as not being able to button my shirts and tie my boots. I've even started having trouble holding a pencil. I don't like feeling less able to do all the things I need to do in my life.

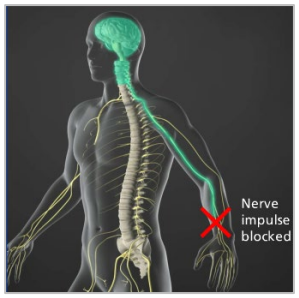
Now my feet are being affected. I trip on doorsteps and uneven sidewalks. I'm afraid that if things get worse, I'll have a hard time supporting my family, working around the house, and raising my kids.

MMN usually progresses steadily but can advance in steps. Most patients experience a slow, progressive decline in muscle strength that may cause serious disability. Twenty percent of patients with MMN have severe arm function impairment. More than half report severe fatigue that interferes with their jobs or daily life. However, despite their disability, patients with MMN have a normal life expectancy.

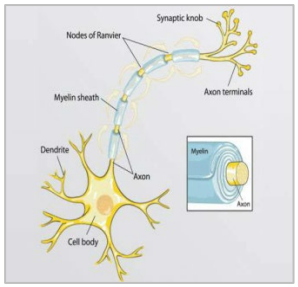
Pathophysiology of MMN

The mechanism of nerve impairment in MMN is not fully understood. Here is some information on what is known about the pathophysiology of MMN:

- Motor nerve conduction block, which is considered the hallmark of MMN, is frequently found in patients with MMN; however, some investigators report some patients with similar clinical presentation who lack conduction block but respond equally well to the **intravenous immunoglobulin (IVIG)** treatment



- Problems with **hyperpolarisation** and **depolarisation** at nodes of Ranvier or abnormalities of the **myelin sheath**



DID YOU KNOW?

The nodes of Ranvier are normally occurring gaps in the myelin sheath that help to transmit **action potentials** rapidly along the axon. Dysfunction at the nodes of Ranvier can therefore cause blocking of the action potential.

Intravenous immunoglobulin (IVIG)
An intravenous formulation of highly purified IgG antibodies.

Hyperpolarisation
An increase in the resting potential of a cell membrane (e.g., a cell membrane of a neuron), causing the inside of the cell to become more negative.

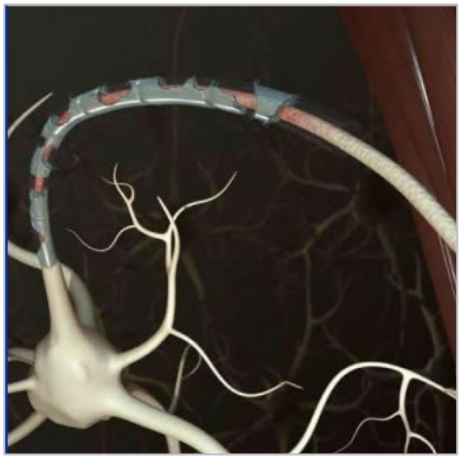
Depolarisation
An electrical change in an excitable nerve or muscle cell that causes the inside to become positive relative to the outside, due to an influx of sodium ions.

Myelin sheath
Layers of the cell membrane of Schwann cells (peripheral nervous system) that wrap nerve fibres, providing electrical insulation and increasing the velocity of impulse transmission.

Action potential
A local reversal of charge across a muscle or nerve cell axon membrane that is propagated along its length.

Pathophysiology of MMN (Cont.)

Pathology studies of motor nerves in patients with MMN are scarce with contradictory results. Some studies have shown signs of axon degeneration and demyelination, which may contribute to conduction block. However, the exact pathophysiological mechanism is not yet fully understood due to the scarcity of pathology from patients with MMN.



Demyelination
Destruction or loss of the myelin sheath around axons, seen in many neurological diseases.

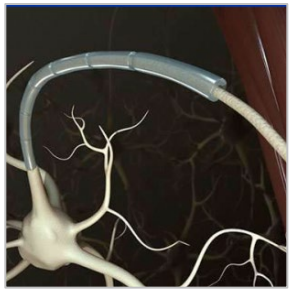
HERE'S THE CONNECTION

Since axon loss is frequently found in MMN, it is likely to be the most important factor influencing whether permanent weakness and disability occur. It has been reported in the literature that in MMN, weakness and disability become more extreme with increasing axon loss that occurs without treatment. Axon loss can occur with treatment but to a lesser degree. Therefore, it is extremely important for a patient with MMN to be properly diagnosed and treated as early as possible.

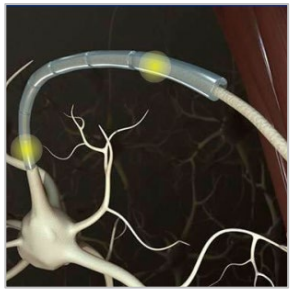
Pathophysiology of MMN (Cont.)

Axon Demyelination

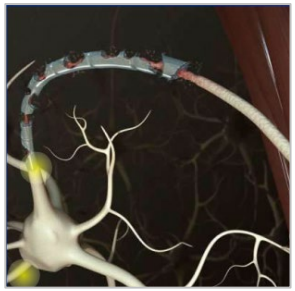
The myelin sheath protects and insulates the motor nerve axon and allows rapid action potential transmission in a normal functioning nerve cell.



A myelinated motor nerve axon transmits nerve impulses faster than an unmyelinated one.



Demyelination, or loss of the myelin coating around a motor nerve axon, will cause action potentials to slow.

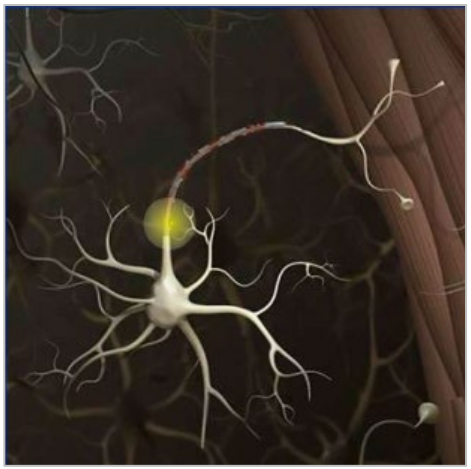


Pathophysiology of MMN (Cont.)

Axon Degeneration

Motor neuron (motor nerve) axons transmit nerve impulses that allow the voluntary control of skeletal muscles.

Axon degeneration causes restriction of nerve impulse transmission along with decline in skeletal muscle strength.



Motor neuron
A neuron that carries impulses from the central nervous system either to muscle tissue to stimulate contraction or to glandular tissue to stimulate secretion.

Pathophysiology of MMN (Cont.)

Clinician Perspective

As a result of the motor nerve conduction block, demyelination, and axonal degeneration issues in the pathophysiology of MMN, patients with MMN experience a range of problems from profound muscle weakness and disability to problems performing the tasks of everyday life, including something as simple as using a fork or tying a shoe.

PROGRESS CHECK

QUESTION ONE

Think about how you would complete the following question, then select the Check Your Answer button.

Match each item to the most appropriate description.

Mean age of onset of MMN is 40 years in these patients	
Prevalence of MMN	
Ratio of MMN in males vs females	
Two-thirds of patients with MMN are below this age	
Usual age range (years) for onset of MMN	

20–70 **2.7:1** **Males** **45** **1 or 2 per 100,000**

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION ONE

Match each item to the most appropriate description.

Mean age of onset of MMN is 40 years in these patients	**Males**
Prevalence of MMN	**1 or 2 per 100,000**
Ratio of MMN in males vs females	**2.7:1**
Two-thirds of patients with MMN are below this age	**45**
Usual age range (years) for onset of MMN	**20–70**

PROGRESS CHECK (CONT.)

QUESTION TWO

Think about how you would complete the following question, then select the Check Your Answer button.

How would you define or describe MMN?

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION TWO

Match each item to the most appropriate description.

MMN is a treatable but incurable disease of the motor nervous system. It is caused by an autoimmune-mediated reaction against cells within the body. MMN primarily causes weakness in the lower arms and legs. It progresses slowly and is asymmetric, meaning that it typically affects one side of the body more than the other. MMN is characterised by the involvement of two or more nerves.

MMN can affect a person's ability to perform many of the activities of daily living, from cooking and eating a meal to dressing or brushing one's teeth or hair.

Patients with MMN usually experience limb weakness that follows the distribution of individual nerves. The disease does not generally affect the sensory nerves, so there are no sensory deficits. Sensory nerve conduction is preserved, and conduction block is confined to motor nerve axons. MMN typically progresses slowly, over months to years. Less often, the disease advances in steps – that is, periods of stability, followed by deterioration. It rarely causes complete immobility.

PROGRESS CHECK (CONT.)

QUESTION THREE

Think about how you would complete the following question, then select the Check Your Answer button.

Which of these are typically symptoms of MMN?

A Fasciculations

B Muscle atrophy

C Increased muscle bulk

D Muscle cramps

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION THREE

Which of these are typically symptoms of MMN?

A Fasciculations

B Muscle atrophy

C Increased muscle bulk

D Muscle cramps

PROGRESS CHECK (CONT.)

QUESTION FOUR

Think about how you would complete the following question, then select the Check Your Answer button.

Which statement describes sensory deficits in MMN?

A They are common

B They worsen as the disease progresses

C They occur more often in males

D They are rare

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION FOUR

Which statement describes sensory deficits in MMN?

A They are common

B They worsen as the disease progresses

C They occur more often in males

D They are rare

PROGRESS CHECK (CONT.)

QUESTION FIVE

Think about how you would complete the following question, then select the Check Your Answer button.

Which factors are associated with MMN and its symptoms?

A Autoimmune mediated reaction

B Demyelination

C Aging

D Conduction block

E Axon degeneration or loss

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION FIVE

Which factors are associated with MMN and its symptoms?

A Autoimmune mediated reaction

B Demyelination

C Aging

D Conduction block

E Axon degeneration or loss

PROGRESS CHECK (CONT.)

QUESTION SIX

Think about how you would complete the following question, then select the Check Your Answer button.

What is the most important factor that determines permanent weakness and disability in MMN?

A Gender

B Conduction block

C Axon loss

D Demyelination

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION SIX

What is the most important factor that determines permanent weakness and disability in MMN?

A Gender

B Conduction block

C Axon loss

D Demyelination

PROGRESS CHECK (CONT.)

QUESTION SEVEN

Think about how you would complete the following question, then select the Check Your Answer button.

What percentage of MMN patients report severe fatigue?

A <25%

B >30%

C >40%

D >50%

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION SEVEN

What percentage of MMN patients report severe fatigue?

A <25%

B >30%

C >40%

D >50%

PROGRESS CHECK (CONT.)

QUESTION EIGHT

Think about how you would complete the following question, then select the Check Your Answer button.

Which symptoms are typically observed at the onset of MMN?

A Wrist drop

B Foot drop

C Grip weakness

D Upper leg weakness

E Hand and forearm weakness

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION EIGHT

Which symptoms are typically observed at the onset of MMN?

A Wrist drop

B Foot drop

C Grip weakness

D Upper leg weakness

E Hand and forearm weakness

PROGRESS CHECK (CONT.)

QUESTION NINE

Think about how you would complete the following question, then select the Check Your Answer button.

How does early diagnosis and treatment impact MMN?

A It has no effect

B It reduces permanent weakness

C It reduces conduction block

D It reduces paraesthesias

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION NINE

How does early diagnosis and treatment impact MMN?

A It has no effect

B It reduces permanent weakness

C It reduces conduction block

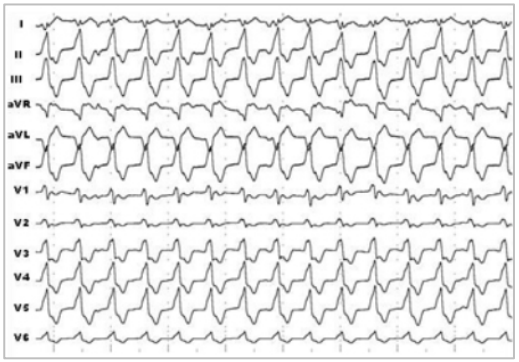
D It reduces paraesthesias

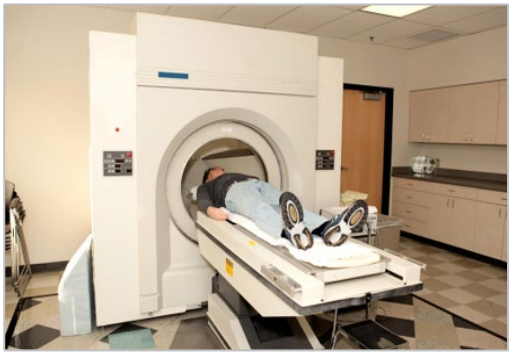
SECTION 02:
DIAGNOSIS OF MMN

Diagnosis of MMN

When doing a diagnostic work-up for MMN, physicians rely on the following:

- Medical history
- Clinical symptoms and criteria
- **Electrophysiological** studies
- Laboratory tests
- **Magnetic resonance imaging (MRI)**





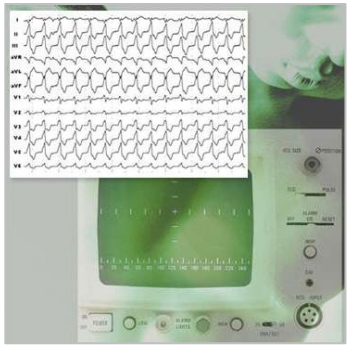
Electrophysiological
Related to the field of study that deals with the relationships of body functions to electrical phenomena (e.g., the effects of electrical stimulation on tissues, the production of electric currents by organs and tissues, and the therapeutic use of electric currents); includes test to determine motor conduction block and nerve dysfunction.

Magnetic resonance imaging (MRI)
A type of medical imaging that uses the characteristic behaviour of protons when placed in powerful magnetic fields to make images of tissues and organs.

Diagnosis of MMN (Cont.)

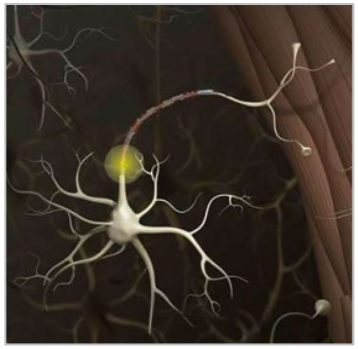
Electrophysiological Tests

- Electrophysiological studies measure electrical signals in the body
- Nerve conduction velocity measures how fast electrical signals travel through a nerve
- Electromyography (EMG) measures the electrical activity in muscles and in the nerves that control them



Conduction block:

Motor nerve conduction block is the electrophysiological hallmark of MMN. It is the inability to propagate action potentials, outside of common sites of **entrapment** or compression. Definite conduction block is defined as >50% reduction in **compound muscle action potential (CMAP)** amplitude over long distances, or ≥30% reduction in CMAP amplitude over short distances.



HERE'S THE CONNECTION

Extensive nerve conduction studies are important for finding **proximal** conduction blocks in the upper arms and legs, which are less accessible by routine conduction studies. A skilled electromyographer and patient cooperation help to detect easily overlooked conduction blocks and avoid misdiagnosis.

Entrapment
Compression of a nerve or nerves, resulting in nerve damage.

Compound muscle action potential (CMAP)
Method for indirectly assessing nerve conduction characteristics of muscle fibres following stimulation.

Proximal
Nearer to the centre (trunk of the body) or to the point of attachment to the body. Proximal is the opposite of distal.

Diagnosis of MMN (Cont.)

Laboratory Tests

Blood and urine tests

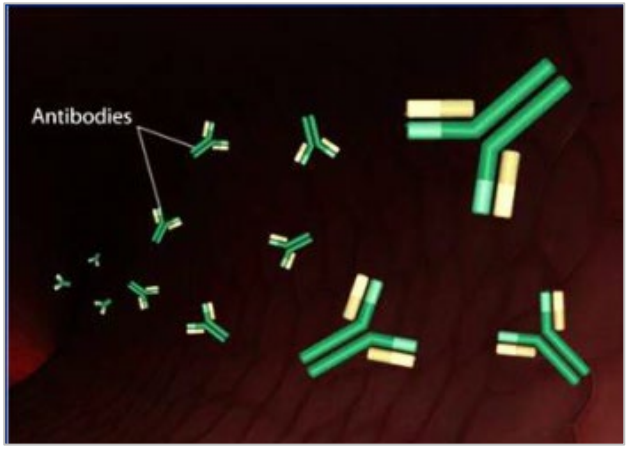
- Routine blood and urine test results are generally normal in MMN
- The exception is elevated **creatine kinase** level, which is observed in up to two-thirds of MMN patients

Cerebrospinal fluid (CFS)

- 30% of patients with MMN show a slight increase in CFS protein levels
- Findings for CSF analysis in the remaining 70% of MMN patients are normal

GM_1-specific immunoglobulin M (IgM) antibody levels can act as a marker for MMN

- About 50% of patients have levels that reach the standard for diagnosis
- The prevalence of GM_1-specific IgM antibodies can range from 20–85% in MMN patients depending on the methodology used
- This test is neither specific to, nor required for, a diagnosis of MMN



Creatine kinase
An enzyme that can be used in differential diagnosis of certain conditions in which it is present in the bloodstream.

Cerebrospinal fluid (CFS)
The sodium-rich, potassium-poor fluid of the brain and spinal cord, which supplies nutrients and removes waste products; it is also a watery cushion that absorbs mechanical shock to the central nervous system.

GM_1
One of a particular class of glycosphingolipid molecule present in nerve tissue and in the spleen.

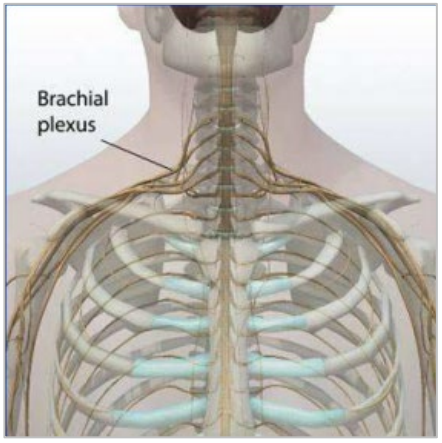
Immunoglobulin M (IgM)
An immunoglobulin formed in almost every immune response during the early period of the reaction; in the case of MMN, GM1-specific IgM antibody titres could suggest MMN.

Diagnosis of MMN (Cont.)

MRI

An MRI scan uses strong magnetic fields to produce a cross-sectional image of the internal organs and structures of the body.

An abnormal MRI signal in the **brachial plexus** has been reported for 40–50% of patients with MMN. These abnormalities include increased signal intensities in the brachial plexus and **ventral rami** of the roots on **T2-weighted images**. These findings correspond with the distribution of MMN symptoms and are associated with nerve inflammation and swelling and demyelination.



Brachial plexus
A network of the anterior branches of the last four cervical and certain thoracic spinal nerves supplying the arm, forearm, and hand.

Ventral rami
Singular ramus; a branch of a spinal nerve that carries motor axons to and sensory axons from all parts of the body except the deep muscles of the back and their overlying skin.

T2-weighted images
Type of MRI images in which fluids appear bright. Generally speaking, T2-weighted images provide information about pathological conditions.

Differential Diagnosis

Other peripheral neuropathies share some signs and symptoms with MMN. These diseases include:

- **Amyotrophic lateral sclerosis (ALS)**
- **Chronic inflammatory demyelinating polyneuropathy (CIDP)**
- **Lewis-Sumner syndrome (LSS)**
- **Lower motor neuron disease (LMND)**

It is important to rule out other peripheral neuropathies in order to avoid an incorrect diagnosis. This can be done with clinical symptoms and criteria, and laboratory, MRI, and electrophysiological results. An incorrect diagnosis could result in improper treatment that could harm the patient, delay proper treatment, and the wrong prognosis.

HERE'S THE CONNECTION

Many patients with MMN are initially misdiagnosed with ALS. This diagnosis is significant because the symptoms of ALS are rapidly progressive and invariably fatal, whereas MMN symptoms are slowly progressive. However, patients with ALS may have bulbar involvement, upper motor neuron signs, and respiratory muscle weakness, which are not present in MMN. Motor conduction block is rare with ALS.

Misdiagnosing MMN as LSS or CIDP can be harmful, since the treatments for LSS or CIDP, such as corticosteroids (any of several steroid hormones manufactured synthetically for use as a drug) and plasmapheresis (removal of plasma from a patient and its replacement with normal plasma) can worsen MMN.

Differential diagnosis
Identification of a disease by comparison of illnesses that share features of the presenting illness but differ in some critical ways.

Amyotrophic lateral sclerosis (ALS)
A progressive neurological disease that involves the neurons responsible for controlling voluntary muscles (such as those needed for chewing, walking, and talking).

Chronic inflammatory demyelinating polyneuropathy (CIDP)
A gradually progressing autoimmune muscle weakness in the legs and arms caused by inflammation of the myelin sheath covering axons in the peripheral nervous system.

Lewis-Sumner syndrome (LSS)
A demyelinating motor and sensory neuropathy.

Lower motor neuron disease (LMND)
A disease that affects the motor neuron axons that control skeletal muscles; initial symptoms often include difficulty speaking and swallowing, as well as facial weakness.

Differential Diagnosis (Cont.)

Feature	MMN	ALS	LMND	CIDP	LSS
Distribution of weakness	Asymmetric	Asymmetric	Asymmetric	Symmetric	Asymmetric
Prominent sensory symptoms	No	No	No	Yes	Yes
Tendon reflexes	Normal or decreased in weakened muscles*	Increased in weakened muscles	Decreased in weakened muscles	General hyporeflexia or areflexia	Decreased in weakened muscles
Disease course	Slowly progressive	Rapidly progressive	Slowly or rapidly progressive	Progressive or relapsing	Progressive or relapsing
Cerebrospinal fluid protein >1 g/L	No	No	No	Yes	Rare
Increased titres of GM_1-specific IgM antibodies	Common	Rare	Rare	Rare	Rare
Abnormal MRI signal in the brachial plexus	Asymmetric	No	No	Symmetric	Asymmetric
Response to IVIG	Yes	No	No	Yes	Yes
Response to corticosteroids	No**	No	No	Yes	Yes

*In some patients, reflexes are brisk. **May aggravate symptoms.

PROGRESS CHECK

QUESTION TEN

Think about how you would complete the following question, then select the Check Your Answer button.

Match each description to the most appropriate diagnostic tool.

Match Items	Match Descriptions
MRI	
Laboratory tests	
Clinical evidence	
Electrophysiological studies	

Options:
- Muscle weakness, wrist drop, foot drop, weak grip
- Nerve conduction velocity test, electromyography
- Creatine kinase, CSF protein, GM_1-specific IgM antibody levels
- Strong magnetic fields produce a cross-sectional image of body organs and structures

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION TEN

Match each description to the most appropriate diagnostic tool.

Match Items	Match Descriptions
MRI	**Strong magnetic fields produce a cross-sectional image of body organs and structures**
Laboratory tests	**Creatine kinase, CSF protein, GM_1-specific IgM antibody levels**
Clinical evidence	**Muscle weakness, wrist drop, foot drop, weak grip**
Electrophysiological studies	**Nerve conduction velocity test, electromyography**

PROGRESS CHECK (CONT.)

QUESTION ELEVEN

Think about how you would complete the following question, then select the Check Your Answer button.

Dan exhibits classic MMN initial-muscle weakness. In which parts of the body does this occur in MMN?

A Hand

B Forearm

C Facial muscles

D Lower leg

E Upper leg

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION ELEVEN

Dan exhibits classic MMN initial-muscle weakness. In which parts of the body does this occur in MMN?

A Hand

B Forearm

C Facial muscles

D Lower leg

E Upper leg

PROGRESS CHECK (CONT.)

QUESTION TWELVE

Think about how you would complete the following question, then select the Check Your Answer button.

Which single laboratory test would be most useful in providing possible evidence for making a diagnosis of MMN?

A Complete blood count

B Lipid panel

C Liver enzymes

D GM_1-specific IgM antibodies

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION TWELVE

Which single laboratory test would be most useful in providing possible evidence for making a diagnosis of MMN?

A Complete blood count

B Lipid panel

C Liver enzymes

D GM_1-specific IgM antibodies

PROGRESS CHECK (CONT.)

QUESTION THIRTEEN

Think about how you would complete the following question, then select the Check Your Answer button.

What type of test should be ordered to measure electrical signals in muscles and nerves?

A X-ray

B Non-stress test

C Electromyography (EMG)

D Magnetic resonance imaging (MRI)

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION THIRTEEN

What type of test should be ordered to measure electrical signals in muscles and nerves?

A X-ray

B Non-stress test

C Electromyography (EMG)

D Magnetic resonance imaging (MRI)

PROGRESS CHECK (CONT.)

QUESTION FOURTEEN

Think about how you would complete the following question, then select the Check Your Answer button.

Which single electrophysiological test would be most useful in providing evidence for making a diagnosis of MMN?

A X-ray

B Echocardiogram

C Motor nerve conduction block

D Electroencephalogram (EEG)

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION FOURTEEN

Which single electrophysiological test would be most useful in providing evidence for making a diagnosis of MMN?

A X-ray

B Echocardiogram

C Motor nerve conduction block

D Electroencephalogram (EEG)

SECTION 03:
TREATMENT OF MMN

Patient and Clinician Perspectives

I just came back from my appointment with Dr Murphy. She told me that based on my symptoms, lab results, and muscle and nerve tests, I have a disease called MMN. I asked her about treatment for my symptoms and about how it will affect my health in the future. Dr Murphy told me that although MMN isn't curable, there are treatments that may help alleviate my symptoms.

MMN is a progressive disease and early diagnosis and treatment of MMN has the potential to reduce disease progression, especially in light of the link between treatment delay and permanent disability.

It has been reported in the literature that in MMN, weakness and disability become more extreme with increasing axon damage that occurs without treatment. Axon damage can occur with treatment but to a lesser degree.

Therefore, it is extremely important for a patient with confirmed MMN to be properly treated as early as possible.

Overview of Treatment Options

Clinical evidence supports the use of IVIG as first-line treatment for MMN. Treatments other than IVIG have also been used for MMN.




KEY POINT

Corticosteroids and plasmapheresis are contraindicated for MMN treatment and may make MMN symptoms worse.

Overview of Treatment Options (Cont.)

IVIG

IVIG is an intravenous formulation of highly purified IgG antibodies and it is an evidence-based treatment for MMN.

A retrospective analysis of 4 randomised, double-blind, placebo-controlled clinical trials including a total of 34 suitable MMN patients demonstrated the beneficial effects of IVIG treatment in patients with MMN. Significant improvement in strength was observed in 78% of patients treated with IVIG versus only 4% of placebo-treated patients (p=0.61). Improvement in disability was also seen although not significant.

In addition, 3 larger retrospective studies have confirmed the favourable response to initial IVIG treatment in 70–90% of patients.

Despite the beneficial effects of IVIG, and even when the IVIG dose is increased, many patients experience a progression of neurological deficits and slow decline in muscle strength after several years.

Overview of Treatment Options (Cont.)

Cyclophosphamide

Cyclophosphamide is an **immunosuppressant** and was the first drug used to treat patients with MMN. Although it has demonstrated some or significant improvement in several case studies, the substantial adverse effects associated with it restrict its long-term use.

Immunosuppressant
An agent that decreases or inactivates the immune response to antigens present on cells or tissues.

Overview of Treatment Options (Cont.)

Rituximab

Rituximab is a **monoclonal antibody** directed against the B cell specific antigen CD20. Several case reports and small uncontrolled studies in patients with MMN have found clinical improvement, but results are inconsistent.

Monoclonal antibody
An antibody that is highly specific to a single type of antigen cell.

PROGRESS CHECK

QUESTION FIFTEEN

Think about how you would complete the following question, then select the Check Your Answer button.

If Dan receives early treatment for MMN, which of the following can occur?

A Reduce disability

B Slow axon degeneration

C Slow demyelination

D Reverse axon damage

E Cure disease

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION FIFTEEN

If Dan receives early treatment for MMN, which of the following can occur?

A Reduce disability

B Slow axon degeneration

C Slow demyelination

D Reverse axon damage

E Cure disease

PROGRESS CHECK (CONT.)

QUESTION SIXTEEN

Think about how you would complete the following question, then select the Check Your Answer button.

Match each description to the most appropriate treatment options for MMN.

Treatment	Descriptions
IVIG	
Immunosuppressants	
Rituximab	

Options:
- No consistent pattern of evidence to support use in MMN
- Long-term adverse effects
- Clinical evidence to support use in MMN

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION SIXTEEN

Match each description to the most appropriate treatment options for MMN.

Treatment	Descriptions
IVIG	**Clinical evidence to support use in MMN**
Immunosuppressants	**Long-term adverse effects**
Rituximab	**No consistent pattern of evidence to support use in MMN**

PROGRESS CHECK (CONT.)

QUESTION SEVENTEEN

Think about how you would complete the following question, then select the Check Your Answer button.

IVIG is going to be Dan's first-line treatment. Describe what you know about IVIG treatment for MMN.

CHECK YOUR ANSWER

PROGRESS CHECK (CONT.)

ANSWER: QUESTION SEVENTEEN

IVIG is going to be Dan's first-line treatment. Describe what you know about IVIG treatment for MMN.

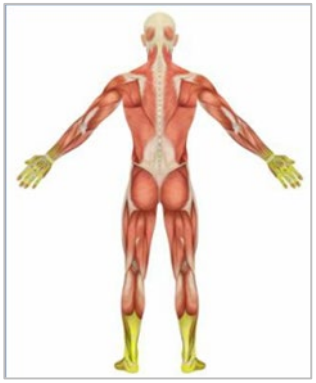
IVIG is an intravenous formulation of highly purified IgG antibodies. IVIG is an evidence-based treatment for MMN. A retrospective analysis of 4 published randomised, double-blind, placebo-controlled clinical trials involving a total of 34 suitable patients have demonstrated the beneficial effects of IVIG treatment in patients with MMN. These trials showed that improvement in muscle strength was significantly greater after IVIG therapy than after placebo. However, there was no significant improvement in disability. In addition, 3 larger retrospective studies have confirmed the favourable response to initial IVIG treatment in 70–90% of patients.

MODULE SUMMARY

Overview of MMN

MMN Features

- Treatable but incurable disease
- Caused by an autoimmune-mediated motor neuropathy in which autoantibodies and complement react against cells within the body
- Weakness usually starts in the forearm, hands, and occasionally the distal leg, without evident sensory loss
- Progresses slowly and is asymmetric



Prevalence and Disease Course

- More common in men than women
- Mostly affects people younger than 45 years of age
- Causes severe functional disability, but not complete immobility
- Normal life expectancy

Initial Symptoms

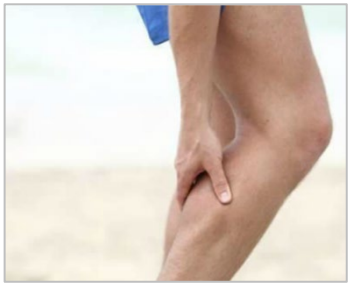
- Wrist or foot drop, grip weakness are often initial symptoms
- Muscle weakness usually starts in the forearm or hand
- Muscle weakness starts in the lower leg in 20–30% of patients, and in the upper arm in 5% of patients

MODULE SUMMARY (CONT.)

Overview of MMN (Cont.)

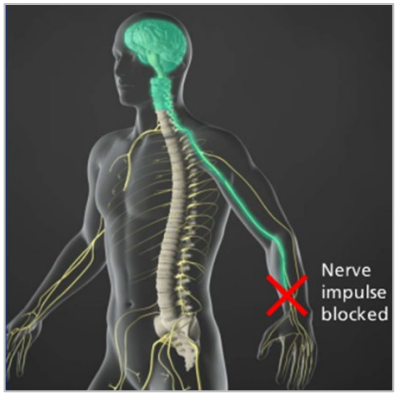
Other Symptoms

- Muscle cramps, twitching
- Tendon reflexes are low or absent
- Minor, temporary paraesthesias
- Rarely involves sensory nerves; no effect on autonomic nervous system
- Muscle atrophy



Pathophysiology

- Motor neuron conduction block is considered the hallmark of MMN
- Motor nerves from patients with MMN may:
  - Be demyelinated
  - Have axon loss, which is the most important factor in permanent weakness and disability

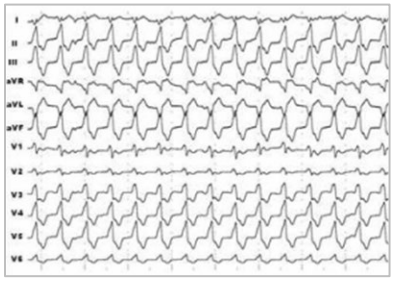


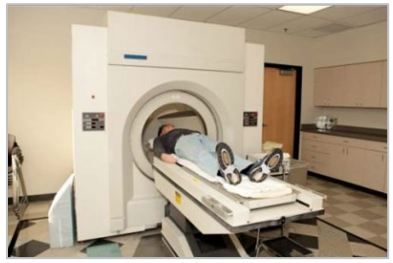
MODULE SUMMARY (CONT.)

Diagnosis of MMN

Evidence for Diagnosis

- MMN diagnosis relies on:
  - Medical history
  - Clinical symptoms and criteria
  - Laboratory tests
  - MRI scan
  - Electrophysiological studies
- Initial symptom of asymmetric weakness in:
  - Hand
  - Forearm
  - Lower leg
  - Upper arm (rare)





Evaluating Test Results

- Laboratory tests
  - Slightly elevated creatine kinase
  - Slightly elevated CSF protein levels
  - Elevated serum GM_1 IgM antibodies
- MRI scan - Abnormal, asymmetric signal
- Electrophysiological tests
  - Conduction block if CMAP levels reduced by:
    - >50% over long distances
    - ≥30% over short distances
- Motor conduction block is the electrophysiological hallmark of MMN

MODULE SUMMARY (CONT.)

Diagnosis of MMN (Cont.)

Differential Diagnosis

- Peripheral neuropathy disorders with similar symptoms:
  - ALS
  - CIDP
  - LMND
  - LSS
- Similar diseases ruled out with:
  - Clinical symptoms and criteria
  - Laboratory, MRI, and electrophysiological results

MODULE SUMMARY (CONT.)

Treatment of MMN

Early Treatment of MMN

- Early treatment of MMN has the potential to reduce disability
- Empirical link between treatment delay and permanent weakness and disability

Contraindicated Treatments for MMN, which may worsen symptoms

- Corticosteroids
- Plasmapheresis

Treatments Used in Management of MMN

- Cyclophosphamide has demonstrated efficacy but is not a good long-term treatment option due to adverse effects
- Initial studies involving rituximab in the treatment of MMN have found mixed results

Clinical Evidence Supporting IVIG

- Retrospective analysis of 4 randomised clinical trials demonstrated beneficial effects of IVIG treatment in patients with MMN
- Three larger retrospective studies have confirmed favourable response to initial IVIG treatment in majority of patients
- Neurological and muscle strength decline after several years, despite IVIG treatment

GLOSSARY

Action potential
A local reversal of charge across a muscle or nerve cell axon membrane that is propagated along its length.

Amyotrophic lateral sclerosis (ALS)
A progressive neurological disease that involves the neurons responsible for controlling voluntary muscles (such as those needed for chewing, walking, and talking).

Asymmetric
A lack of correspondence in shape, size, and relative position of parts or problems on opposite sides of a body or structure i.e., the brachial plexus.

Autoimmune
A disease that occurs when the body has an immune reaction to its own cells.

Autonomic nervous system
A branch of the motor division of the peripheral nervous system that controls involuntary bodily functions; the autonomic nervous system connects to organs and glands in the body.

Axon
The part of the neuron that conducts impulses away from the cell body.

Brachial plexus
A network of the anterior branches of the last four cervical and certain thoracic spinal nerves supplying the arm, forearm, and hand.

Cerebrospinal fluid (CFS)
The sodium-rich, potassium-poor fluid of the brain and spinal cord, which supplies nutrients and removes waste products; it is also a watery cushion that absorbs mechanical shock to the central nervous system.

Chronic inflammatory demyelinating polyneuropathy (CIDP)
A gradually progressing autoimmune muscle weakness in the legs and arms caused by inflammation of the myelin sheath covering axons in the peripheral nervous system.

Compound muscle action potential (CMAP)
Method for indirectly assessing nerve conduction characteristics of muscle fibres following stimulation.

Conduction
The transmission of excitation through living tissue and especially nervous tissue; conduction of impulses to the brain.

Conduction block
Interruption in the transmission of electrical impulse along a nerve; the inability of motor axons to propagate action potentials.

Creatine kinase
An enzyme that can be used in differential diagnosis of certain conditions in which it is present in the bloodstream.

Demyelination
Destruction or loss of the myelin sheath around axons, seen in many neurological diseases.

Depolarisation
An electrical change in an excitable nerve or muscle cell that causes the inside to become positive relative to the outside, due to an influx of sodium ions.

Differential diagnosis
Identification of a disease by comparison of illnesses that share features of the presenting illness but differ in some critical ways.

Electrophysiological
Related to the field of study that deals with the relationships of body functions to electrical phenomena (e.g., the effects of electrical stimulation on tissues, the production of electric currents by organs and tissues, and the therapeutic use of electric currents); includes test to determine motor conduction block and nerve dysfunction.

Entrapment
Compression of a nerve or nerves, resulting in nerve damage.

Fasciculation
Involuntary contraction or twitching of muscle fibres, visible under the skin.

Foot drop
General term for difficulty lifting the front part of the foot. Foot drop is a sign of an underlying neurological, muscular, or anatomical problem.

GLOSSARY (CONT.)

GM_1
One of a particular class of glycosphingolipid molecule present in nerve tissue and in the spleen.

Hyperpolarisation
An increase in the resting potential of a cell membrane (e.g., a cell membrane of a neuron), causing the inside of the cell to become more negative.

Immunoglobulin G (IgM)
An immunoglobulin formed in almost every immune response during the early period of the reaction; in the case of MMN, GM_1-specific IgM antibody titres could suggest MMN.

Immunosuppressant
An agent that decreases or inactivates the immune response to antigens present on cells or tissues.

Intravenous immunoglobulin (IVIG)
An intravenous formulation of highly purified IgG antibodies.

Lewis-Sumner syndrome (LSS)
A demyelinating motor and sensory neuropathy.

Lower motor neuron disease (LMND)
A disease that affects the motor neuron axons that control skeletal muscles; initial symptoms often include difficulty speaking and swallowing, as well as facial weakness.

Magnetic resonance imaging (MRI)
A type of medical imaging that uses the characteristic behaviour of protons when placed in powerful magnetic fields to make images of tissues and organs.

Monoclonal antibody
An antibody that is highly specific to a single type of antigen cell.

Motor neuron
A neuron that carries impulses from the central nervous system either to muscle tissue to stimulate contraction or to glandular tissue to stimulate secretion.

Multifocal motor neuropathy (MMN)
A treatable but incurable, autoimmune-mediated motor neuropathy.

Muscle atrophy
Atrophy of muscle tissue, especially due to lack of use or nerve damage or loss.

Myelin sheath
Layers of the cell membrane of Schwann cells (peripheral nervous system) that wrap nerve fibres, providing electrical insulation and increasing the velocity of impulse transmission.

Paraesthesia
Abnormal or unpleasant sensation that results from injury to one or more nerves, often described by patients as numbness or as a prickly, stinging, or burning feeling.

Proximal
Nearer to the centre (trunk of the body) or to the point of attachment to the body. Proximal is the opposite of distal.

Sensory nerve
A nerve that transmits impulses from receptors to the central nervous system.

T2-weighted images
Type of MRI images in which fluids appear bright. Generally, speaking, T2-weighted images provide information about pathological conditions.

Tendon reflex
A deep reflex obtained by sharply tapping the skin over the tendon of a muscle; it is exaggerated in upper neuron disease and diminished or lost in lower neuron disease.

Ventral rami
Singular ramus; a branch of a spinal nerve that carries motor axons to and sensory axons from all parts of the body except the deep muscles of the back and their overlying skin.

Wrist drop
A condition in which the hand is flexed at the wrist and cannot be extended; may be due to injury of the radial nerve or paralysis of the extensor muscles of the wrist and hand.

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