MULTIFOCAL MOTOR NEUROPATHY

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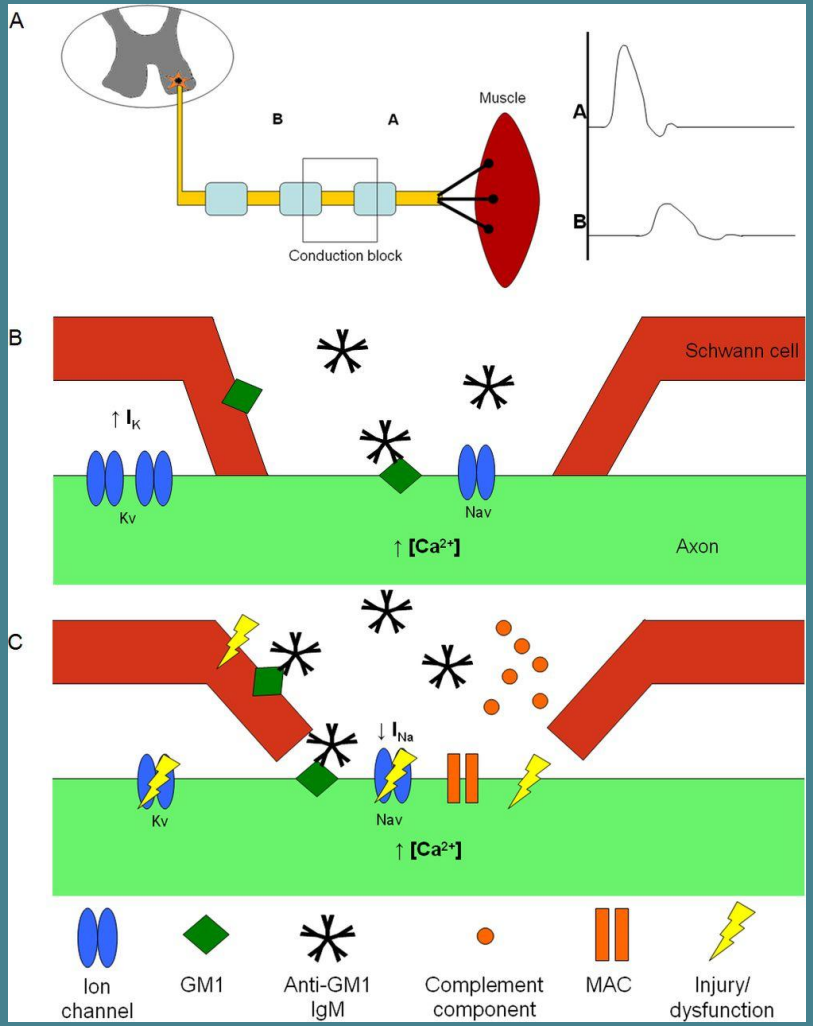
ETIOPATHOLOGY

- Multifocal motor neuropathy (MMN) is characterized by **progressive, asymmetrical distal limb weakness** and **conduction block at non-compressible sites (about 50% of cases)**; without any sensory loss
- It affects males disproportionately (3:1); average age of onset is 40 years
- MMN predominantly affects the upper limbs, and is triggered by cold temperatures (**cold paresis**)
- The exact etiopathology has been under debate, but the **presence of anti-GM1 antibodies (50% of cases)** and **therapeutic response to IVIg** suggests an **autoimmune phenomenon**
- Recent findings suggest a chronic axonal process **(nodopathy)**, with: loss of large myelinated fibers, increased number of regenerating clusters, complete absence of demyelination, and onion-bulb formation



A. Node of Ranvier (black box), and conduction block (b) vs normal amplitude of conduction (a)
B. Direct: Anti-GM1 antibodies bind to GM1 on axon membrane and directly affect calcium homeostasis; increased intracellular calcium alters membrane potential and consequently, Na+ & K+ transport
C. Indirect: Anti-GM1 antibodies bind to GM1 and immune-complex activates complement (C5-C9 MAC) which destroys axonal Na+/K+ channels

Yeh *et al;* 2020

CLINICAL FEATURES

- **Posterior interosseous:** wrist or finger drop
- **Median, ulnar, radial:** dexterity problem and grip weakness
- **Peroneal nerve:** foot drop
- **Musculocutaneous nerve:** biceps weakness
- Muscle atrophy, fasciculations, cramps

DDx

- Multifocal Acquired Motor Neuropathy (MAMA)
- Motor neuron disease (MND)
- Chronic inflammatory demyelinating polyneuropathy (CIDP)
- Lewis-Sumner syndrome (MADSAM)
- Hereditary neuropathy with liability to pressure palsy (HNPP)
- Acute motor axonal neuropathy (AMAN)

Table 1 | Differential diagnosis of multifocal motor neuropathy

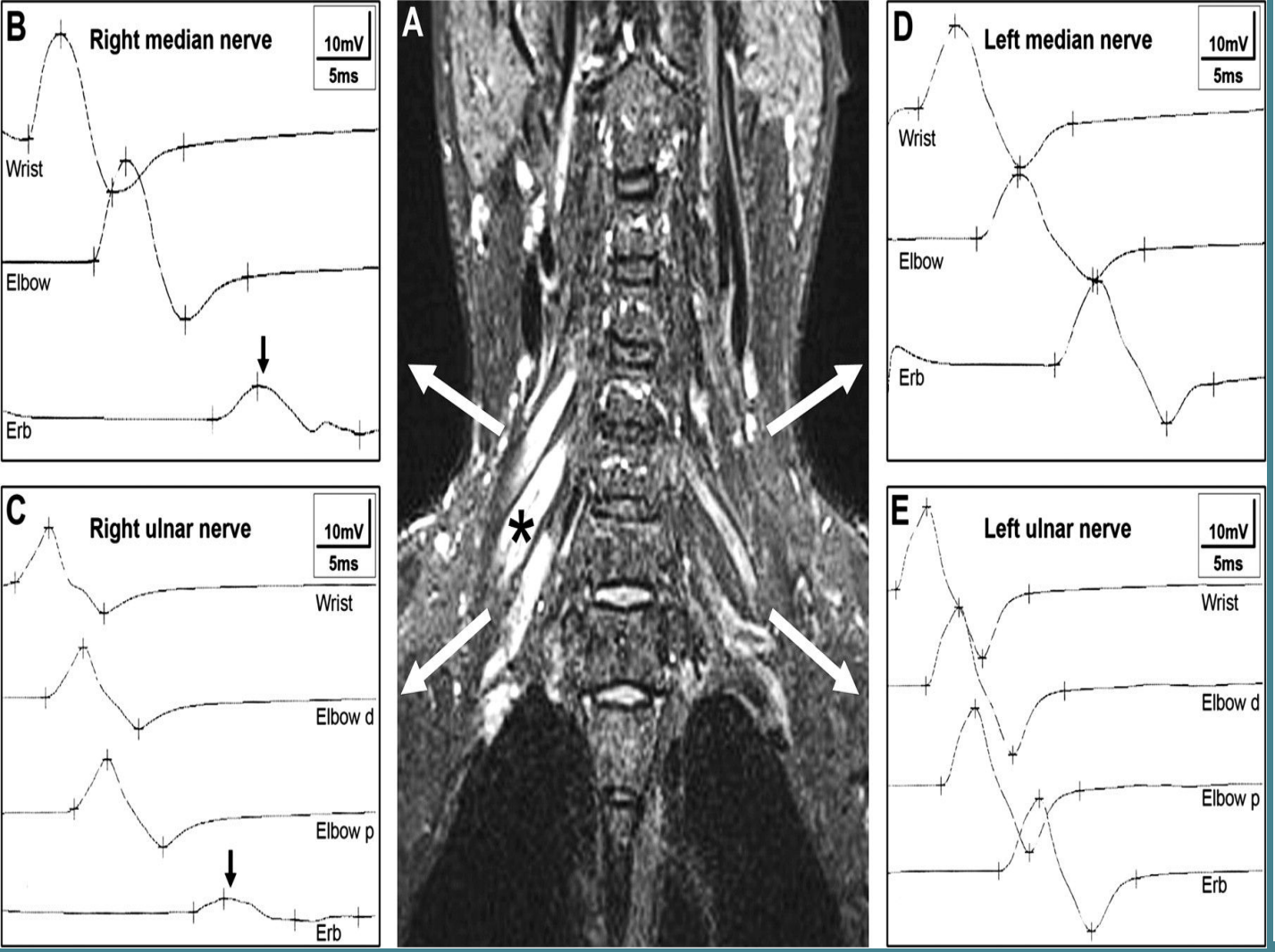
Feature	Multifocal motor neuropathy	Amyotrophic lateral sclerosis	Lower motor neuron disease	Chronic inflammatory demyelinating polyneuropathy	Lewis–Sumner syndrome
Distribution of weakness	Asymmetric	Asymmetric	Asymmetric	Symmetric	Asymmetric
Prominent sensory symptoms	No	No	No	Yes	Yes
Tendon reflexes	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 >1g/l	No	No	No	Yes	Rare
Increased titers of GM1-specific IgM antibodies	Common	Rare	Rare	Rare	Rare
Abnormal MRI signal in the brachial plexus	Asymmetric	No	No	Symmetric	Asymmetric
Response to intravenous immunoglobulin	Yes	No	No	Yes	Yes
Response to corticosteroids	No‡	No	No	Yes	Yes

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

Vlam *et al.*, 2012

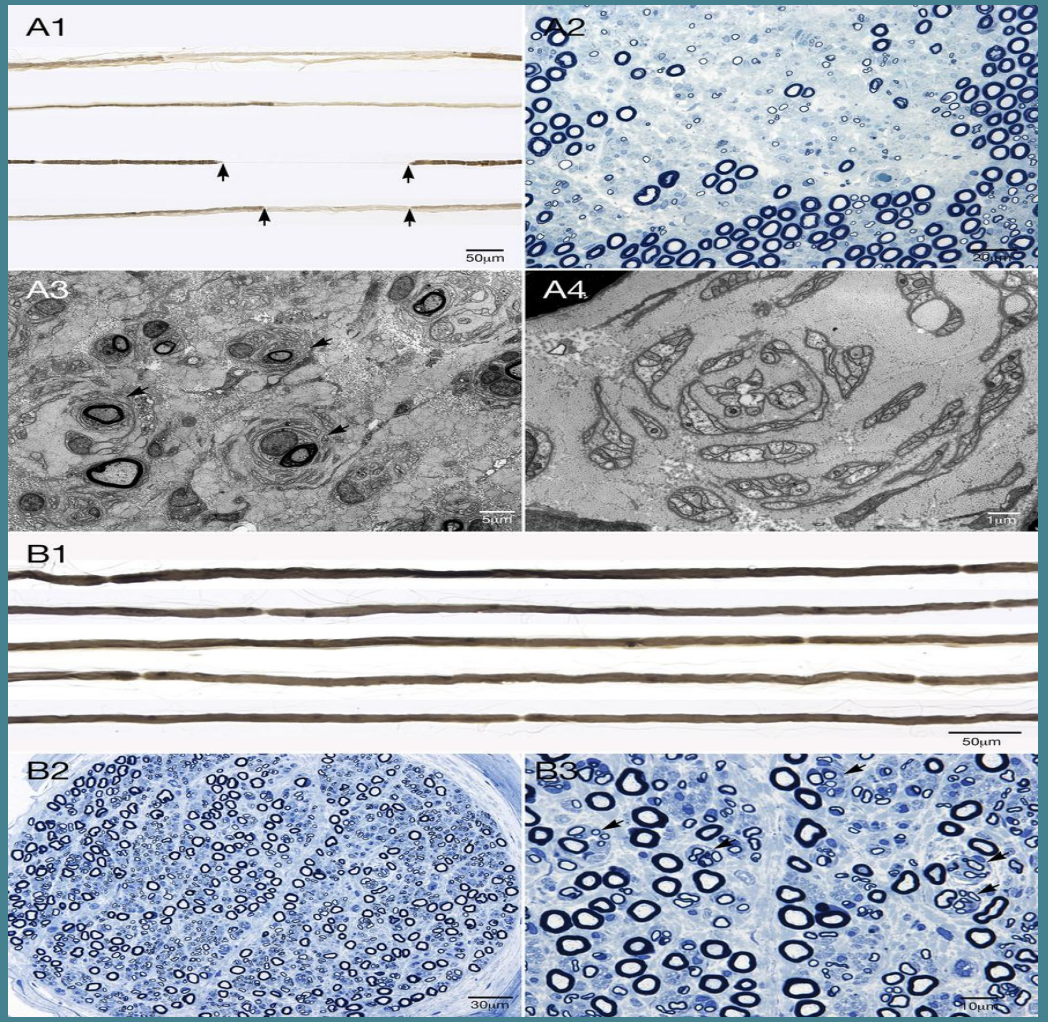
DIAGNOSIS

- **Electrophysiology:** Conduction block (seen in about 50% of cases)
- **Lab testing:** anti-GM1 antibody (seen in about 50% of cases) +/- ↑ creatine kinase
- **Nerve biopsy:** not used routinely; will show loss of large myelinated fibers, increased number of regenerating clusters, complete absence of demyelination, and onion-bulb formation
- **MRI/MRN (of brachial plexus):** shows T2 hyperintensity and diffuse enlargement in affected nerve segments. MRN is more sensitive for peripheral nerves
- **Nerve ultrasound:** recently introduced; shows increased cross-sectional area (CSA)



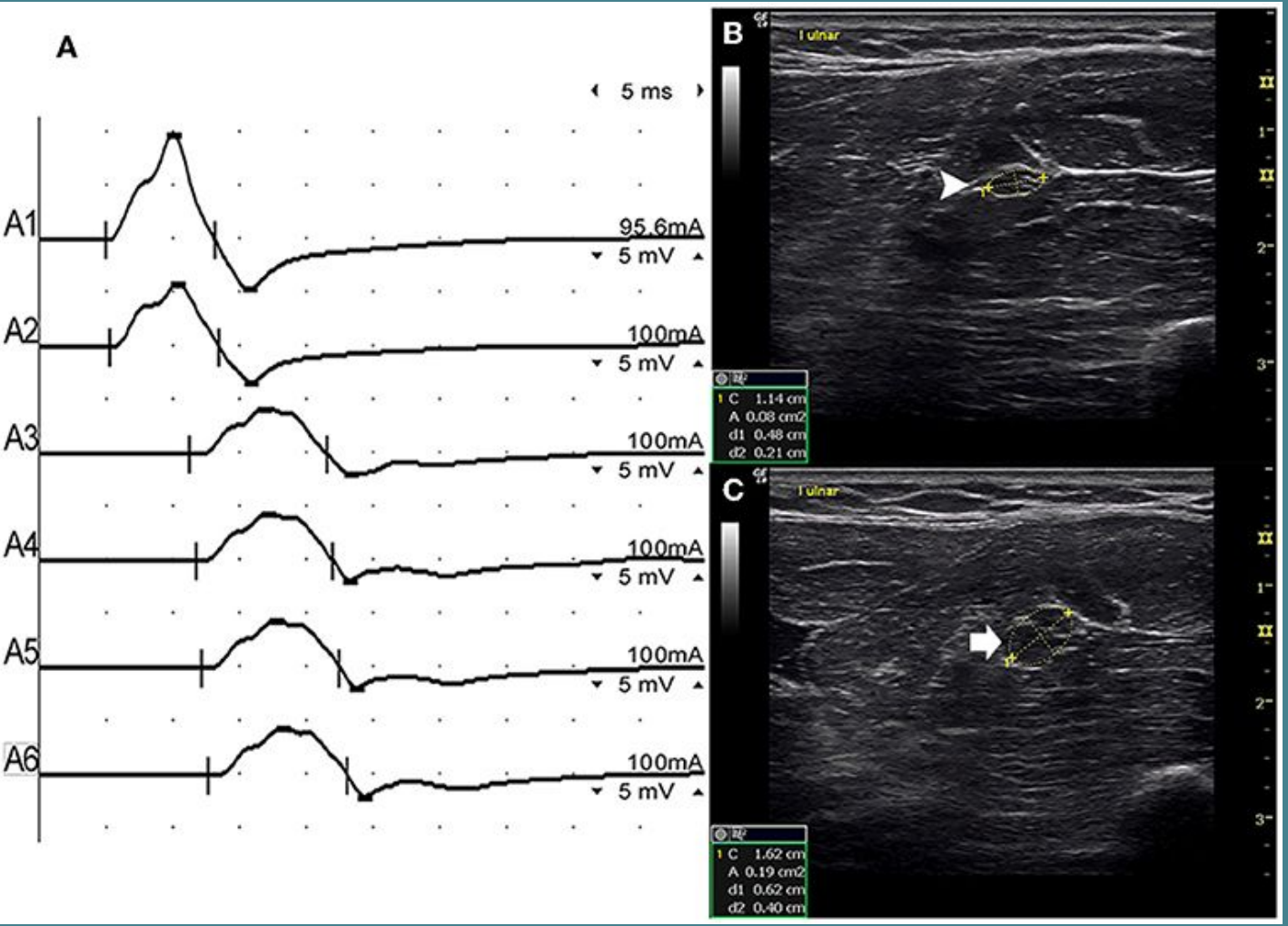
(A) Coronal short tau inversion recovery MRI demonstrates diffuse enlargement and abnormally high signals at the level of the trunks in the right brachial plexus (asterisk). Electrodiagnostic studies reveal partial conduction block in the right median and ulnar nerves, localised between the elbow and Erb's point (B, C; black arrows). No blocks are observed in the left median and ulnar nerves (D, E).

Echaniz-Laguna & Dietemann, 2011



Proximal fascicular nerve biopsies taken from mixed motor and sensory nerves. Both cases had focal motor predominant neuropathies with some imaging abnormalities that allowed selection of nerve biopsy site. Case A (A1–A4) had focal hypertrophic demyelination and so was diagnosed with focal chronic inflammatory demyelinating polyneuropathy whereas case B (B1–B3) had mild neurogenic changes without evidence of inflammatory demyelination. Fascicular nerve biopsy from the left brachial plexus (a). (A1) Teased fibre preparations showing regions of demyelination between arrows. (A2) Semithin epoxy section stained with methylene blue shows apparent focal loss of myelinated fibres. (A3) Electron microscopy from region of fibre loss showing frequent small onion-bulb formations (arrows). (A4) Electron microscopy at a higher power showing a small onion-bulb with no fibre at the centre. Fascicular nerve biopsy from left median nerve at site of conduction block (B). (B1) Teased fibre preparations showing normal myelinated fibres without demyelination. (B2) Semithin epoxy section stained with methylene blue shows normal myelinated fibre density. (B3) On higher power, arrows showing regenerating cluster (arrows) and no onion-bulbs.

Yeh *et al;* 2020



(A) Conduction block was detected between A1 (latency 4.9 ms, duration 8.2 ms, amplitude 14.8 mv, area 38.2 mvms, conduction velocity 66.6 m/s) and A2 (latency 5.2 ms, duration 8.2 ms, amplitude 9.5 mv, area 26.1 mvms, conduction velocity 11.6 m/s). **(B)** The white arrowhead showed that the CSA of A1 was 8 mm_2. **(C)** The arrow shows that the CSA of A2 was 19 mm_2 (A1, elbow-6 cm; A2, elbow-4 cm; A3, elbow-2 cm). CSA, cross-sectional area; CB, conduction block; l, left; r, right.

Li *et al.*, 2019

Core criteria (both must be present)

- Slowly progressive or stepwise progressive, focal, asymmetric limb weakness, that is, motor involvement in the motor nerve distribution of at least two nerves, for more than 1 month. If symptoms and signs are present only in the distribution of one nerve only a possible diagnosis can be made
- No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs

Supportive clinical criteria

- Predominant upper limb involvement
- Decreased or absent tendon reflexes in the affected limb
- Absence of cranial nerve involvement
- Cramps and fasciculations in the affected limb
- Response in terms of disability or muscle strength to immunomodulatory treatment

Exclusion criteria

- Upper motor neuron signs
- Marked bulbar involvement
- Sensory impairment more marked than minor vibration loss in the lower limbs
- Diffuse symmetric weakness during the initial weeks

Table 2: Electrophysiological criteria for conduction block*

Definite motor CB

- Negative peak CMAP area reduction on proximal vs. distal stimulation of at least 50% whatever the nerve segment length (median, ulnar, and peroneal). Negative peak CMAP amplitude on stimulation of the distal part of the segment with motor CB must be >20% of the lower limit of normal and >1 mV and increase of proximal to distal negative peak CMAP duration must be ≤30%

Probable motor CB

- Negative peak CMAP area reduction of at least 30% over a long segment (e.g., wrist to elbow or elbow to axilla) of an upper limb nerve with increase of proximal to distal negative peak CMAP duration ≤30%

  OR

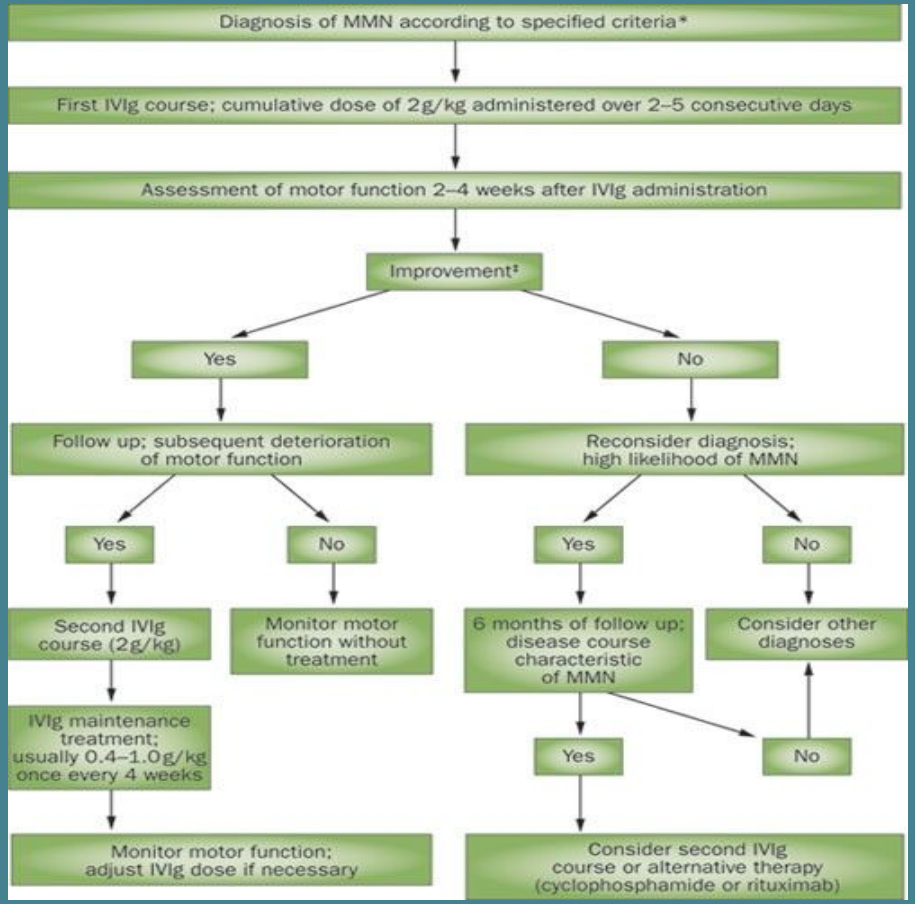
- Negative peak CMAP area reduction of at least 50% (same as definite) with an increase of proximal to distal negative peak CMAP duration >30%

Normal sensory nerve conduction in upper limb segments with CB (see exclusion criteria)

Nguyen & Chaudry, 2011

TREATMENT

- **IVIg:** is the mainstay of tx; dose-dependent
- **SCIg:** similar efficacy to IVIg but more convenient
- **Immunomodulators:** such as cyclophosphamide and rituximab have shown varying effects; high toxicity for cyclophosphamide
- **Eculizumab:** varying effects; better side effect profile

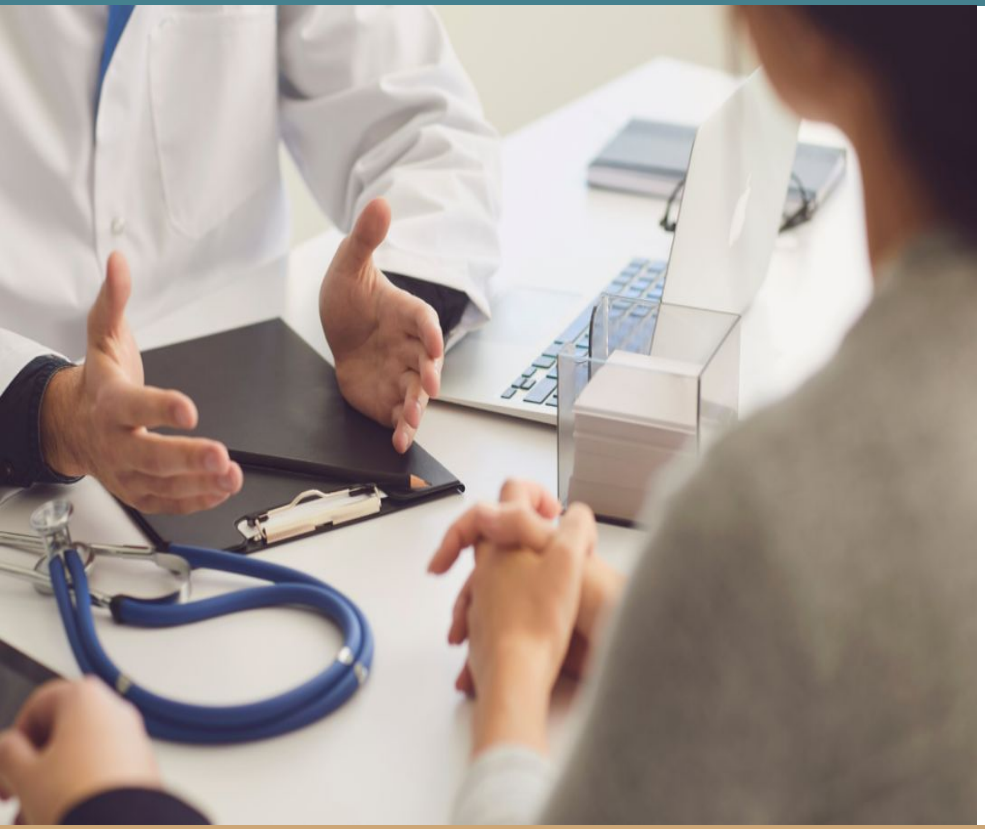


MMN management criteria

‡Increase in strength of at least two muscle groups of ≥1 grade on the Medical Research Council scale without a decrease in other muscle groups, decrease of 1 point in at least two categories of the Self-Evaluation Scale, or decrease of at least 1 point on the Overall Disability Sum Score

Vlam *et al.*, 2012

PROGNOSIS & RECOMMENDATION



- Slowly progressive decline in muscle strength, even with IVIg use
- Number of years w/o IVIg tx and amount of axon loss determine permanent weakness
- Prevention of axon loss should be a goal of future studies


THANK YOU!

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IMAGES

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Page 5: https://www.telegraph.co.uk/money/charity-will-gifting/multifocal-motor-neuropathy-support/

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