MRI and ultrasound in multifocal motor neuropathy with conduction blocks

Poster No.: P-0098
Congress: ESSR 2012
Type: Scientific Exhibit
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Keywords: Neuroradiology peripheral nerve, Musculoskeletal system, MR, Ultrasound, Diagnostic procedure, Inflammation
DOI: 10.1594/essr2012/P-0098

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Purpose

To illustrate the magnetic resonance imaging (MRI) and ultrasound (US) findings in patients with clinical and electrophysiological diagnosis of Multifocal Motor Neuropathy.
Multifocal motor neuropathy (MMN) is a rare disorder characterized by slowly, progressive, asymmetrical and predominantly distal lower motor neuron weakness with minimal or no sensory symptoms, with electrophysiological evidence of motor conduction block, common association with anti-GM1 IgM antibodies, and frequently a good response to high-dose intravenous immunoglobulin (IVIg) therapy.\textsuperscript{1,2,3,4} The long-term prognosis tends to be good, but even in patients who respond to therapy may be found some residual impairment. The pathogenesis of MMN is unclear, but clinical improvement with immunoglobulin therapy suggests an underlying immunemediated mechanism. Histopathological studies of motor or mixed nerves, which are not normally needed for diagnosis, tended to show demyelination, occasionally with onion bulb formation or axonal degeneration, sometimes in areas with conduction block electrophysiological evidence.\textsuperscript{12}

The prevalence is not securely estimated but this disorder, which is more frequent in men than women (2.6:1), probably affects 1-2 per 100,000.\textsuperscript{12} The mean age at onset is around 40 years and the symptoms are generally insidious. Weakness is much more common in the upper limbs, generally affecting the forearm or hand muscles at the first stages of the disease. Weakness may involve the distribution of individual nerves, being the ulnar, median, radial, peroneal and tibial nerves commonly affected. Other possible symptoms are finger or wrist drop, fasciculations and cramps.\textsuperscript{12,3,4} Interestingly, there are patients who report a weakness worsening after exposure to cold, which could be related to the increase in the depolarizing conduction block caused by slowing down of the temperature-sensitive sodium-potassium pump at lower temperatures.\textsuperscript{1}

In some patients, muscle wasting may be mild or even absent, mainly in the first years of illness, which may indicate the presence of conduction block in the afferent nerve, contrasting to permanent axonal degeneration. A particular group of patients is characterized by early amyotrophy, often with poor prognosis related to irreversible axonal loss.\textsuperscript{12}

Cranial nerve involvement can be seen very occasionally, often limited to the X\textsuperscript{th} cranial nerve, and respiratory muscle weakness can rarely occur due to phrenic nerve palsy.\textsuperscript{12}

The essential electrodiagnostic finding of MMN is persistent, multifocal, partial conduction block (CB), the hallmark of the disease.\textsuperscript{14} Its identification is helpful in differentiating MMN from other chronic motor neuron syndromes, but other electrophysiological features
of demyelination may be seen in MMN, including prolonged distal motor latencies and reduced conduction velocities particularly across the affected segments. CB is measured as the distal to proximal reduction in area or amplitude of the compound muscle action potential (CMAP) - usually expressed as a percentage -, in the absence of or with only focal abnormal temporal dispersion. Typically, there's an abrupt drop in the CMAP amplitude (focal conduction block), contrasting to the gradual drop usually seen in chronic demyelinating neuropathy or after chronic axonal loss. In MMN, conduction block is seen along motor nerves, usually outside the usual sites of nerve compression, and is more frequently detected in the arms, sometimes at proximal areas.

There's no absolute consensus about the CB definition, which could reduce sensitivity for electrophysiological diagnosis. Actually, it is common to see patients who report weakness in areas where conduction block cannot be found and there's also some MMN patients with no detectable CB in spite of correct search, probably because the affected segment is too proximal and inaccessible.

Clinical examination and electrophysiological tests are mandatory and constitute the main diagnostic criteria for MMN, according to the guidelines on management of multifocal motor neuropathy of the European Federation of Neurological Societies.

### Clinical criteria

**Core criteria** (both must be present)

1. Slowly progressive or stepwise progressive, focal, asymmetric a limb weakness, i.e. motor involvement in the motor nerve distribution of at least two nerves, for more than one month. If symptoms and signs are present only in the distribution of one nerve only a possible diagnosis can be made.

2. No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs

**Supportive clinical criteria**

3. Predominant upper limb involvement

4. Decreased or absent tendon reflexes in the affected limb (but slightly increased tendon reflexes, in particular in the affected arm have been reported)

5. Absence of cranial nerve involvement (but 12th nerve palsy has been reported)

6. Cramps and fasciculations in the affected limb
7. Response in terms of disability or muscle strength to immunomodulatory treatment

**Exclusion criteria**

8. Upper motor neuron signs

9. Marked bulbar involvement

10. Sensory impairment more marked than minor vibration loss in the lower limbs

11. Diffuse symmetric weakness during the initial weeks

**Electrophysiological criteria**

1. **Definite motor CB:** Negative peak CMAP area reduction on proximal versus 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%.

2. **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%;

3. Normal sensory nerve conduction in upper limb segments with CB.

**Table 1.** Clinical and electrophysiological criteria for MMN, according to the European Federation of Neurological Societies.

- Besides the clinical and electrodiagnostic criteria, there are diagnostic tests recommended for selected patients, mainly whom don't fulfill the custom criteria: cerebrospinal fluid examination (protein must be < 1 g/l), anti-ganglioside GM1 antibodies and MRI scans of the brachial plexus.

- IgM anti-GM1 and other antiganglioside antibodies can be elevated in patients with MMN. The presence of IgM anti-GM1, although helpful, is neither essential nor specific for the diagnosis of MMN. However, in a patient with a pure lower motor neuron syndrome, a raised IgM anti-GM1 level may be strongly predictive of MMN.

- Ultrasound and Magnetic Resonance Imaging (MRI) may be useful in the differential diagnosis with other causes of motor neuropathy and its use has increased in the last years. Ultrasound findings are not specific and there is only one article systematically describing the ultrasound findings in these patients. The most frequent finding is diffuse
nerve enlargements with marked increase in nerve cross sectional areas, a pattern that was consistently seen in our group of patients.

MRI findings are not specific for MMN but may identify asymmetric high signal in T2-weighted of the brachial plexus, contrasting to symmetrical distribution of similar T2-weighted signal changes in chronic inflammatory demyelinating polyneuropathy (CIDP) patients and normal signals in motor neuron disease (MND). There are also reports of focal gadolinium enhancement at the areas of conduction block in consecutive slice T1WI of the median nerve in the forearm. MRI is also helpful in the identification of compressive extrinsic causes, not only at the level of the brachial plexus, but also in more distal potential impingement areas.

Multifocal motor neuropathy is a treatable disorder. Intravenous immunoglobulin (IVIg) therapy is effective in almost 80% of MMN patients and it is usually recommended an infusion of 2g/kg, over 2 to 5 days. The treatment is repeated in cycles and although most responsive patients tend to respond in the first cycle, the need of long-term therapy is frequent and individual cycles of IVIg may be needed every one to eight weeks in the majority of patients. There is a typical pattern of response to IVIg: rapid clinical improvement, with restoration of functional abilities, often within the first 48 hours; best improvements in muscles recently affected with minimal or no wasting. The electrophysiological findings may variably improve ant there's just a little effect on the anti-GM1 levels.

In patients who fail to respond to IVIg, cyclophosphamide (CTX) remains an option. Its intravenous administration was initially used with clinical benefits and progressive reduction in the anti-GM1 levels, but the clinical relapse after discontinuation and the toxicity after long-term use decreased its recommendation. Oral CTX may be advantageous by reducing the frequency of IVIg cycles.

A small group of MMN patients who don't respond to IVIg may benefit from interferon #1a therapy, which may lead to clinical improvement a few weeks after the beginning of the therapy. Other possibilities include azathioprine, ciclosporin and rituximab. Steroids and plasma exchange are usually ineffective.

We report here the ultrasound and MRI findings of several cases of MMN diagnosed primarily by clinical and electrophysiological criteria. All our patients had involvement of the upper limb and the imaging studies were directed to the most affected limb. All patients were examined with an 16.5 MHZ linear ultrasound probe. Nerve cross sectional areas were measured at the different segments of the brachial plexus and the median, ulnar, radial and main branches of these nerves were also examined through their entire length. All patients also had an MRI (not on the same visit) of the brachial plexus and corresponding upper limb.
Results

The most common finding was a thickening of the affected brachial plexus on MRI and US, as well as slight increased enhancement of the plexus after iv contrast on MRI and thickening of several peripheral nerves on US, mainly the median, radial and ulnar nerves. The imaging studies were also useful in excluding other diagnosis and confirming the topographical changes seen in the clinical examination.
Fig. 1: A. Axial T2WI: diffuse thickening and hyperintensity of the left brachial plexus. B. Coronal T2 WI: slight diffuse thickening of the right brachial plexus. C, D, E. Three images of the same patient. Axial T2W1 w/FAT SAT: thickening and hyperintensity of the main trunks of the left brachial plexus. Sagital T2WI w/FAT SAT: diffuse signal hyperintensity of the ventral rami of the nerve roots. Coronal T1WI w/ GAD and FAT SAT: thickening but only slight hyperintensity after iv gadolineum at the level of the main trunks.

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Fig. 2: In this doubtful case, there was clinical and electrophysiological suspicion of MMN, and the MRI helped in the diagnosis of a mechanical compression of the brachial plexus. A. Axial T1WI: diffuse thickening of the right brachial plexus trunks (arrows) with a round hypointense cyst (arrow-heads) that compresses several chords distally. B. Oblique coronal high resolution T2 3D WI shows the cyst originating from the shoulder joint and the compressed chords. The two lower arrows nicely show the flattened chords.

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Fig. 3: The median nerve was the most consistently altered with diffuse increase in nerve cross-sectional areas always above 15 mm² in the arm. In this patient the area was 18 mm² in the arm but decreased to 13 mm³ in the forearm.

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Fig. 4: Radial nerve areas were increased to a maximum of 20 mm² in the arm as in this patient. At the forearm and wrist the nerve thickness was normal.

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Fig. 5: The ulnar nerve cross sectional areas were also increased although to a lesser degree in our group of patients. Areas ranged from 12 mm² to 10 mm² in the arm but were normal at the wrist.

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**Fig. 6:** The musculocutaneous nerve section area was normal in our patients even when there was an increased thickness of the lateral chord of the brachial plexus.

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**Fig. 7:** A. There was a mild generalized increase in the brachial plexus thickness with sectional areas of the trunks increased to a mean 15 mm² at the interscalenic segment. There were no extrinsic compression points identified. B. At the axilla, the mean cord thickness was about 12-13 mm². In our group of patients there was a uniform increase in thickness without significant fascicle asymmetry.

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Conclusion

MMN should be considered in the differential diagnosis of any patient with an insidious asymmetrical limb weakness without objective sensory abnormalities, upper motor neuron or bulbar signs or symptoms. Its diagnosis is fundamentally based on clinical examination and electrophysiological evidence of multifocal conduction block. Nevertheless, in doubtful cases, laboratorial analysis such as anti-GM1 antibodies and imaging tools may be helpful. MRI and US are then useful in confirming the clinical and electrophysiological findings in uncertain cases and in some situations may provide an alternative diagnosis.
References


