Multifocal Motor Neuropathy
Description of multifocal motor neuropathy (MMN)

- MMN is a rare, chronic, asymmetric motor neuropathy affecting predominantly distal extremities, arms and legs\(^1\)
  - MMN patients have focal block of motor nerve conduction
- The disease course is slowly progressive, extending over decades without spontaneous remission\(^2,3\)
- Usually presents before age 45; prevalence rates range from 1 to 2 cases per 100,000 with men being affected more often than women (2.6:1)\(^3\)

Signs and symptoms of MMN

• MMN presents as weakness without sensory loss, with asymmetric involvement of two or more nerves and absence of motor neuron signs\(^1\)

• Common signs and symptoms include:\(^2,3\)
  – General fatigue
  – Muscle cramping
  – Fasciculations
  – Conduction blocks

• Lack of sensory involvement with MMN is one of its distinguishing features\(^2,3\)
  – Although mild sensory symptoms are noted, significant sensory abnormalities in the region of motor weakness are not present

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Prognosis for MMN patients

• If left untreated, MMN patients are likely to experience progressive muscle weakness that may result in serious functional impairment and impaired quality of life

• Delayed diagnosis may also have implications for response to IVIG
  – Early initiation of treatment may help to postpone axonal degeneration and permanent deficits

IVIG: intravenous immunoglobulin

Diagnostic guidelines for MMN

- The joint task force of the EFNS and PNS developed guidelines on MMN and updated them in 2011

**Diagnosis (summary)**

- Two core criteria and all exclusion criteria must be met
  - See next slide
- Definite or probable conduction block should be present in at least one nerve
- Supportive diagnosis:
  - MRI
  - CSF
  - Treatment response
  - Anti-GM1 antibodies

CSF: Cerebrospinal fluid, EFNS: European Federation of Neurological Societies, GM1: ganglioside GM1, MRI: Magnetic Resonance Imaging, PNS: Peripheral Nerve Society

### Diagnostic guidelines for MMN continued

<table>
<thead>
<tr>
<th>Clinical criteria</th>
<th>Features</th>
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</table>
| **Core criteria**                 | 1. Slowly or stepwise progressive, focal, asymmetric limb weakness for more than one nerve  
2. No objective sensory abnormalities except for minor vibration sense abnormalities in the lower limbs |
| **Supportive clinical criteria**  | 1. Predominant upper limb involvement                                  |
|                                   | 2. Decreased or absent tendon reflexes in the affected limb             |
|                                   | 3. Absence of cranial nerve involvement                                 |
|                                   | 4. Cramps and fasciculations in the affected limb                       |
|                                   | 5. Response in terms of disability or muscle strength to immunomodulatory treatment |
| **Exclusion criteria**            | 1. Upper motor neuron signs                                              |
|                                   | 2. Marked bulbar involvement                                            |
|                                   | 3. Sensory impairment more marked than minor vibration loss in the lower limbs |
|                                   | 4. Diffuse symmetric weakness during the initial weeks                   |

Diagnostic considerations

- MMN must be distinguished from other degenerative motor neuron diseases and CIDP due to differences in prognosis and therapy\(^1\)
  - Certain therapies may exacerbate weakness in MMN patients

- Increased levels of IgM antibodies to GM1 are typically used as biomarkers for MMN\(^1\)
  - As anti-GM1 IgM is found in 30–80% of patients, there may be antibodies of other specificities that perform a similar function
  - Sensitivity of current assays may affect antibody detection

- Nerve ultrasound can be considered as a complementary tool for the diagnosis of MMN with atypical characteristics\(^2\)

CIDP: chronic inflammatory demyelinating polyneuropathy, IgM: immunoglobulin M

Treatment guidelines for MMN

- Options are limited to IVIG as MMN patients do not usually respond to plasma exchange or corticosteroids
  - Patients may worsen if they receive these treatments

- Recommended treatment:
  - Induction: 2 g/kg bw IVIG given over 2–5 days
    - If the initial dose is effective, consider repeat dosing in selected patients
  - Maintenance: 1 g/kg bw every 2–4 weeks or 2 g/kg bw every 1–2 months

- During long-term IVIG treatment, effectiveness declines as muscle strength decreases, even when dosage is increased due to ongoing axonal degeneration

bw: bodyweight

Treatment options

• IVIG
  – Randomized controlled trials have shown a positive effect;\textsuperscript{1} however, a maintenance dose is required every 2–4 weeks or every 1–2 months, depending on the dose\textsuperscript{2}
  – IVIG limits disease progression but does not prevent it\textsuperscript{3}
  – In 2012, a 10\% IVIG was approved by FDA for the treatment of MMN\textsuperscript{4}
    • Approved for use in Europe in 2011

• Cyclophosphamide: reported to be effective in several case studies\textsuperscript{3}
  – Potential toxicity requires a careful risk:benefit analysis in each patient

FDA: Food and Drug Administration

Evidence for effect of treatment

- In 2012 the FDA approved a 10% IVIG treatment for MMN\textsuperscript{1}
  - Approval was based on the results of a randomized controlled trial in 44 MMN patients:\textsuperscript{2}

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Results</th>
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<tbody>
<tr>
<td>Grip strength in the more affected hand</td>
<td>Mean maximal grip strength of the more affected hand declined by 31.38% with placebo and increased 3.75% with IVIG (p=0.005)</td>
</tr>
<tr>
<td>Upper limb sub-section of the Guy’s Neurological Disability Scale</td>
<td>Fewer patients experienced deterioration in the drug-treated group compared to placebo; 11.9% vs. 35.7%, respectively (p=0.021)</td>
</tr>
</tbody>
</table>

Evidence for effect of treatment continued

- Other randomized controlled trials have also shown IVIG to be an effective treatment in MMN patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azulay JP et al. Neurology 1994;44:429–432</td>
<td>Compared to placebo, IVIG induced a significant increase in muscle strength in patients with CB</td>
</tr>
<tr>
<td>Van den Berg LH et al. J Neurol Neurosurg Psychiatry 1995;59:248–252</td>
<td>IVIG can lead to improvement in muscle strength of MMN patients</td>
</tr>
<tr>
<td>Federico P et al. Neurology 2000;55:1256–1262</td>
<td>IVIG improved CB as well as subjective and objective clinical measures of function (grip strength and NDS)</td>
</tr>
<tr>
<td>Léger JM et al. Brain 2001;124:145–153</td>
<td>IVIG is a promising therapeutic option for MMN (based upon MRC score in 28 muscles and self-evaluation scale)</td>
</tr>
</tbody>
</table>

CB: conduction block, MRC: Medical Research Council, NDS: neurological disability score
### SCIG in MMN

- Studies investigating the use of SCIG for the treatment of MMN have shown it comparable to IVIG*

<table>
<thead>
<tr>
<th>Study</th>
<th>Results/Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Misbah SA et al. J Peripher Nerv Syst 2011;16:92–97</td>
<td>MMN patients with stable clinical course on regular IVIG can switch to SCIG at the same monthly dose without deterioration and with a sustained overall improvement in HRQL</td>
</tr>
<tr>
<td>Harbo T et al. Neurology 2010;75:1377–1380</td>
<td>Patients were able to maintain function over 2 years and showed no change in impairment or disability scores</td>
</tr>
<tr>
<td>Harbo T et al. Eur J Neurol 2009;16:631–638</td>
<td>SCIG and IVIG were equally effective. Mean change in muscle strength: Post-SCIG: 3.6%; Post-IVIG: 4.3%</td>
</tr>
<tr>
<td>Eftimov F et al. J Peripher Nerv Syst 2009;14:93–100</td>
<td>SCIG therapy was feasible, safe and as effective as IVIG (based upon MRC sum score from 10 muscle groups)</td>
</tr>
</tbody>
</table>

HRQL: health-related quality of life, SCIG: subcutaneous immunoglobulin

*SCIG is not currently approved for the treatment of MMN. Please check the label for specific information on approved indications.
Summary

- MMN is a rare disorder characterized by asymmetric, predominantly distal limb weakness without sensory loss

- Diagnosis of MMN is based on clinical and electrodiagnostic criteria, and may be supported by laboratory and ultrasound testing

- IVIG is the first-line treatment for MMN patients
  - Corticosteroids are not recommended
  - SCIG therapy has been reported as a feasible, safe and effective therapy for MMN patients, which could be considered as an alternative option to IVIG*

*SCIG is not currently approved for the treatment of MMN. Please check the label for specific information on approved indications.