Patient male 45 years-old

Gilbert’s disease

Since 6 months:
- Painful and distal paresthesiae of hind limbs and hands
- Progressive weakness, noticeably for steps
- Loss of weight (7 kgs)

Clinical exam:
- Tactile loss feet
- Reduction in vibration sense on hindlimbs
- Slight ataxia with Romberg
- Proximal motor weakness (4/5)
- Areflexia: achilles and patellar
First line exams

- MNCV studies:
  - Conduction blocks
  - Reduced Motor Nerve Velocities
  - Prolonged Distal Motor Latencies
  - Absent/Prolonged Late Responses
- Sensory potentials more affected in upper limbs
First line exams

CSF
- Cytologie normale
- Proteines 1.21 g/l, glucose normal

Biology:
- ERC : normal. Plaquettes : 493.000/mm3
- Ionogramme sanguin normal. Pas diabetes. CRP<1
- Serologies (hepatitis B, C, HIV, syphilis, Lyme) : négatives
- Antinuclear Ac, anti ENA, ECA : normal
- Cryoglobuline negative
- TSH normale : 4.1 (N : 0.270-4.2)
- Vit B12 normal
Clinical diagnosis of CIDP

Typical CIDP

- Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected, and
- Absent or reduced tendon reflexes in all extremities

EFNS/PNS CIDP GUIDELINES
European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – First Revision

Joint Task Force of the EFNS and the PNS

Clinical diagnosis of CIDP

Atypical CIDP

- One of the following, but otherwise as in A
- Predominantly distal weakness (DADS)
- Pure motor or sensory presentations
- Asymmetric presentations (LSS)
- Focal presentations (i.e., involvement of the brachial plexus or 1 or more peripheral nerves in 1 upper limb)
- CNS involvement (may occur with otherwise typical or other forms of atypical CIDP)
CIDP diagnosis

1. Elevated CSF protein with leukocyte count <10/mm³ (level A recommendation)
2. MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses (level C recommendation)
3. Abnormal sensory electrophysiology in at least one nerve (Good Practice Points):
   a. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes; or
   b. Conduction velocity <80% of lower limit of normal (<70% if SNAP amplitude <80% of lower limit of normal); or
   c. Delayed somatosensory evoked potentials without central nervous system disease
4. Objective clinical improvement following immunomodulatory treatment (level A recommendation)
5. Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fibre analysis (Good Practice Points)
The model of EAN

Ab myelinic P0, P2 Galactocerebroside

Kieseier et al., 2002
Rationale of the treatment of CIDP

Similarities with that of multiple sclerosis

- CIDP is a demyelinating disease affecting the peripheral nerve, clinically and electrophysiologically heterogeneous
- CIDP course is relapsing (1/3 of cases) or progressive (2/3 of cases)
- The natural history is unpredictable
- The prognosis is linked to the severity of secondary axonal degeneration
CIDP: first-line therapy (* RCT)

Corticosteroids: 1982*, 1997
Plasma exchanges: 1986*, 1996*

<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Therapy</th>
<th>No. of Patients</th>
<th>Duration</th>
<th>Design</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyck et al</td>
<td>1994</td>
<td>Plasma exchange vs. Iv. immune globulin</td>
<td>15</td>
<td>42 days</td>
<td>Randomized, observer blinded, crossover</td>
<td>NS</td>
</tr>
<tr>
<td>Hahn et al</td>
<td>1996</td>
<td>Plasma exchange</td>
<td>15</td>
<td>28 days</td>
<td>Double-blind, sham controlled, crossover</td>
<td>Improvement in 80% of patients</td>
</tr>
<tr>
<td>Hahn et al</td>
<td>1996</td>
<td>Iv. immune globulin</td>
<td>30</td>
<td>28 days</td>
<td>Double-blind, placebo controlled, crossover</td>
<td>Improvement in 63% of patients</td>
</tr>
<tr>
<td>Mendell et al.</td>
<td>2001</td>
<td>Iv. immune globulin</td>
<td>53</td>
<td>42 days</td>
<td>Double-blind, randomized, placebo-controlled</td>
<td>Improvement in 76% of patients</td>
</tr>
<tr>
<td>Hughes et al.</td>
<td>2001</td>
<td>Iv. immune globulin vs. oral prednisone</td>
<td>32</td>
<td>14 days</td>
<td>Double-blind, randomized, crossover</td>
<td>NS</td>
</tr>
<tr>
<td>Dyck et al.</td>
<td>1985</td>
<td>Azathioprine in combination with prednisone</td>
<td>30</td>
<td>9 mo</td>
<td>Open, parallel-group, randomized</td>
<td>NS</td>
</tr>
</tbody>
</table>
### IVig vs placebo

<table>
<thead>
<tr>
<th>Study</th>
<th>Ivig n/N</th>
<th>Placebo n/N</th>
<th>Weight %</th>
<th>RR, (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vermeulen 1993(^{39})</td>
<td>4/15</td>
<td>3/13</td>
<td>29.3</td>
<td>1.16, 0.32-4.24</td>
</tr>
<tr>
<td>Hahn 1996(^{36})</td>
<td>19/25</td>
<td>5/25</td>
<td>45.5</td>
<td>3.80, 1.68-8.58</td>
</tr>
<tr>
<td>Thompson 1996(^{38})</td>
<td>2/7</td>
<td>0/7</td>
<td>4.6</td>
<td>5.00, 0.28-88.53</td>
</tr>
<tr>
<td>Mendell 2001(^{37})</td>
<td>11/30</td>
<td>2/23</td>
<td>20.6</td>
<td>4.22, 1.03-17.19</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>36/77</td>
<td>10/68</td>
<td>100.0</td>
<td><strong>3.17, 1.74-5.75</strong></td>
</tr>
</tbody>
</table>

### Prednisolone

<table>
<thead>
<tr>
<th>Study</th>
<th>Ivig n/N</th>
<th>Placebo n/N</th>
<th>Weight %</th>
<th>RR, (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hughes 2001(^{41})</td>
<td>9/16</td>
<td>8/13</td>
<td>100.0</td>
<td>0.91, 0.50-1.68</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>9/16</td>
<td>8/13</td>
<td>100.0</td>
<td><strong>0.91, 0.50-1.68</strong></td>
</tr>
</tbody>
</table>
Corticosteroids

Six weeks of oral prednisolone starting at 60 mg daily produced benefit that was not significantly different from that of IVIg 2g/kg (Hughes et al. 2001)

**Pulsed high-dose dexamethasone versus standard prednisolone treatment for chronic inflammatory demyelinating polyradiculoneuropathy (PREDICT study): a double-blind, randomised, controlled trial**

Ivo N van Schaik, Filip Eftimov, Pieter A van Doorn, Esther Brusse, Leonard H van den Berg, W Ludo van der Poel, Catharina G Faber, Jeroen CH van Oostrom, Oscar JMM Vogels, Rob DM Hadden, Bert U Kleine, Anouk GW van Norden, Jan JM Verschuuren, Marcel GW Dijkstra, Marinus Vermeulen

Dexamethasone
(40 mg/d for 4 days x 6 weeks)
has the same efficacy that oral prednisolone
Plasma exchanges (PE)

- PE might be considered as an initial treatment as neurological disability may improve rapidly
- For stabilization of CIDP, PE needs to be combined with other treatments
- Because adverse events (difficulty with venous access, use of citrate and haemodynamic changes) are not uncommon, either corticosteroids or IVIg should be considered first
Essai multicentrique, randomisé, double insu, contre placebo, 2 groupes parallèles,

Efficacité et tolérance,

Efficacité : variation 1 point ONLS ou Rankin,

IgIV 0,5g/kg/j → 4j /methylprednisolone 0,5g/j → 4j,

Suivi 6 mois,

Critère primaire : nombre de patients en échec pour inefficacité ou intolérance,

Critère secondaire : nombre de patients avec EI ou aggravation à l’arrêt du traitement.
<table>
<thead>
<tr>
<th></th>
<th>Intravenous methylprednisolone (n=21)</th>
<th>Intravenous immunoglobulin (n=24)</th>
<th>Risk difference (95% CI)</th>
<th>Relative risk (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 days</td>
<td>6 (29%)</td>
<td>1 (4%)</td>
<td>0.24 (0.03–0.45)</td>
<td>0.75 (0.56–0.99)</td>
<td>0.0389</td>
</tr>
<tr>
<td>2 months</td>
<td>9 (43%)</td>
<td>3 (13%)</td>
<td>0.30 (0.05–0.55)</td>
<td>0.65 (0.44–0.97)</td>
<td>0.0406</td>
</tr>
<tr>
<td>6 months*</td>
<td>11 (52%)</td>
<td>3 (13%)</td>
<td>0.40 (0.15–0.65)</td>
<td>0.54 (0.34–0.87)</td>
<td>0.0085</td>
</tr>
</tbody>
</table>

Data are number (%) unless otherwise stated, risk difference, or relative risk (95% CI). *Primary outcome.

Table 2: Cumulative treatment failures
Suivi 6 mois :

- 10 patients améliorés par methylprednisolone → pas de rechute,
- 21 patients améliorés par IgIV → 8 (38%) rechutes entre 1 et 5 mois (médiane 4),
- p=0,0317.

A 12 mois :

48% des patients initialement traités par methylprednisolone et 54% des patients traités par IgIV sont améliorés et stables sans traitement (p=0,763).

Intérêt de l'identification de biomarqueurs de réponse thérapeutique dans la PIDC !
Taux plasmatique IgIV : un biomarqueur incontournable,

Stabilité intra-patient versus variabilité inter-patient à prendre en compte.
RESEARCH REPORT

Efficacy and safety of Privigen® in patients with chronic inflammatory demyelinating polyneuropathy: results of a prospective, single-arm, open-label Phase III study (the PRIMA study)

Jean-Marc Léger1, Jan L. De Bleecker2, Claudia Sommer3, Wim Robberecht4, Mika Saarela5, Jerzy Kamienowski6, Zbigniew Stelmak7, Orell Mielke8, Björn Tackenberg9, Amjad Sheblı9, Artur Bauhofer9, Oliver Zenker9, and Ingmar S. J. Merkies10; on behalf of the PRIMA study investigators1

---

**Table 2. Number of responders by the adjusted INCAT score at completion (ITT).**

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>IVIG-pretreated patients</th>
<th>IVIG-naïve patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>28</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>Number of responders, n</td>
<td>17</td>
<td>10</td>
<td>7</td>
</tr>
<tr>
<td>Responder rate (%)</td>
<td>60.7</td>
<td>76.9</td>
<td>46.7</td>
</tr>
<tr>
<td>Wilson-Score 95%</td>
<td>42.4–76.4</td>
<td>49.7–91.8</td>
<td>24.8–69.9</td>
</tr>
</tbody>
</table>

---

# Échelle de l’INCAT

## Bras

<table>
<thead>
<tr>
<th>Niveau</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Pas de problèmes aux membres supérieurs</td>
</tr>
<tr>
<td>1</td>
<td>Symptômes dans l’un ou les deux bras ne gênant pas la capacité à réaliser l’une quelconque des taches suivantes : utiliser l'ensemble des fermetures éclair et des boutons, laver ou coiffer ses cheveux, utiliser un couteau et une fourchette ensemble, manipuler de petites pièces de monnaie.</td>
</tr>
<tr>
<td>2</td>
<td>Symptômes dans l’un ou les deux bras affectant sans l’interdire l’une quelconque des taches sus-citées.</td>
</tr>
<tr>
<td>3</td>
<td>Symptômes dans l’un ou les deux bras empêchant une ou deux des taches sus-citées.</td>
</tr>
<tr>
<td>4</td>
<td>Symptômes dans l’un ou les deux bras empêchant trois ou toutes les taches sus-citées, quelques mouvements intentionnels restant possibles.</td>
</tr>
<tr>
<td>5</td>
<td>Incapacité à utiliser l’un ou l’autre des deux bras pour quelque mouvement intentionnel que ce soit.</td>
</tr>
</tbody>
</table>

## Jambes

<table>
<thead>
<tr>
<th>Niveau</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Marche non affectée.</td>
</tr>
<tr>
<td>1</td>
<td>Marche affectée mais marche indépendante en extérieur possible.</td>
</tr>
<tr>
<td>2</td>
<td>Utilisation habituelle d’une aide unilatérale pour marcher en extérieur (une canne, une béquille, un bras).</td>
</tr>
<tr>
<td>3</td>
<td>Utilisation habituelle d’une aide bilatérale pour marcher en extérieur (deux cannes, deux béquilles, cadre de marche, deux bras).</td>
</tr>
<tr>
<td>4</td>
<td>Utilisation habituelle d’un fauteuil roulant pour les déplacements en extérieur mais possibilité de se tenir debout et de marcher quelques pas avec aide.</td>
</tr>
<tr>
<td>5</td>
<td>Confiné au fauteuil roulant, incapable de se tenir debout et de marcher quelques pas avec aide.</td>
</tr>
</tbody>
</table>

**Handicap Total** = somme du handicap des bras et des jambes.
**Table 4.** Pre- and post-infusion serum IgG levels (ITT).

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Responders</th>
<th>Non-responders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>28</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Serum IgG levels (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-infusion, mean (SD)</td>
<td>1828.4 (547.7)</td>
<td>1881.3 (583.6)</td>
<td>1757.8 (490.9)</td>
</tr>
<tr>
<td>Post-infusion, mean (SD)</td>
<td>3363.5 (880.0)</td>
<td>3592.4 (939.7)</td>
<td>3081.8 (711.7)</td>
</tr>
<tr>
<td>Change from pre-infusion to post-infusion (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1574.0 (725.4)</td>
<td>1759.0 (758.8)</td>
<td>1342.7 (612.2)</td>
</tr>
<tr>
<td>Range</td>
<td>-867 to 3,392</td>
<td>-867 to 3,392</td>
<td>84 to 2,685</td>
</tr>
</tbody>
</table>

The mean and standard deviation (SD) of the pre- and post-infusion serum IgG levels are shown for all patients in the intention-to-treat (ITT) analysis, and for responders and non-responders at completion.

- **IgIV efficace dans la PIDC……!**
- **Différence taux IgIV pré/post < non répondeurs**
- **Savoir attendre un bénéfice non immédiat**
Recommendations for treatment, EFNS 2010

For induction of treatment

- IVIg or corticosteroids should be considered in sensory and motor CIDP in the presence of disabling symptoms
- PE is similarly effective but may be less tolerated
- The presence of relative contraindications to any of these treatments should influence the choice

For maintenance treatment

- If the first-line treatment is effective, continuation should be considered until the maximum benefit has been achieved and then the dose reduced to find the lowest effective maintenance dose
- If the response is inadequate or the maintenance doses of the initial treatment (IVIg, steroids, or PE) result in adverse effects, the other first-line treatment alternatives should be tried before considering combination treatments or adding an immunosuppressors or immunomodulatory drug may be considered, but there is no sufficient evidence to recommend any particular drug
Long-term prognosis of CIDP: a 5 year follow-up of 38 cases

- Retrospective study of 38 patients with CIDP
- 89% treated with steroids, 45% with IVIg and 34% with PE: 58% with association
- After 5 years, 10 (26%) had prolonged remission (> 2 years), 23 (61%) partial remission with (26%) or without (34%) other immunomodulator, 5 (13%) had severe disability (unable to walk)
- An overall good response to treatment was associated with symmetric forms, subacute onset, predominantly distal BC and good response to steroids.

Kuwabara et al. JNNP 2006; 77: 66-70
Immunosuppressant and immunomodulatory drugs that have been reported to be beneficial in CIDP (class IV evidence)

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Cost</th>
<th>Evidence</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CIDP</td>
<td>MMN</td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>broad</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>broad</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>broad</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>broad</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>lymphocyte</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Rituximab</td>
<td>B cell</td>
<td>+++</td>
<td>?</td>
</tr>
<tr>
<td>Beta interferon 1 a</td>
<td>broad</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Alpha interferon</td>
<td>broad</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Etanercept</td>
<td>T cell</td>
<td>+++</td>
<td>?</td>
</tr>
</tbody>
</table>

Mahdi, Cochrane, 2009
• Phase II multicentric trial with Avonex, 30 µg/week, 6 months
• Good tolerability (as in MS)
• 7 patients (35%) improved (NDS, clinical grading scale and grip strength), 10 patients (50%) were stable and 3 (15%) worsened

Bêta-1a interferon has no efficacy as adjuntive therapy during 6 months
Randomised controlled trial of methotrexate for chronic inflammatory demyelinating polyradiculoneuropathy (RMC trial): a pilot, multicentre study

Double blind randomised controlled trial
Parallel group
62 participants

<table>
<thead>
<tr>
<th>Responder</th>
<th>Placebo</th>
<th>Methotrexate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>18 (56%)</td>
<td>13 (48%)</td>
<td>31 (53%)</td>
</tr>
<tr>
<td>Yes</td>
<td>14 (44%)</td>
<td>14 (52%)</td>
<td>28 (47%)</td>
</tr>
<tr>
<td>Total</td>
<td>32 (100%)</td>
<td>27 (100%)</td>
<td>59 (100%)</td>
</tr>
</tbody>
</table>

Lancet Neurol 2009; 8: 158–64

60 patients enrolled from 26 European centres
Clinical diagnosis
Of CIDP

\[\text{EFNS/PNS CIDP GUIDELINES}\]

European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society – First Revision

Joint Task Force of the EFNS and the PNS

(1) Inclusion criteria
(a) Typical CIDP
  Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities, developing over at least 2 months; cranial nerves may be affected; and
  Absent or reduced tendon reflexes in all extremities

(b) Atypical CIDP (still considered CIDP but with different features) One of the following, but otherwise as in (a) (tendon reflexes may be normal in unaffected limbs):
  Predominantly distal (distal acquired demyelinating symmetric, DADS) or
  Asymmetric [multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), Lewis-Sumner syndrome] or
  Focal (e.g., involvement of the brachial or lumbosacral plexus or of one or more peripheral nerves in one upper or lower limb)
  Pure motor or
  Pure sensory (including chronic immune sensory polyradiculopathy affecting the central process of the primary sensory neuron)

(2) Exclusion criteria
  Borrelia burgdorferi infection (Lyme disease), diphtheria, drug or toxin exposure probably to have caused the neuropathy
  Hereditary demyelinating neuropathy
  Prominent sphincter disturbance
  Diagnosis of multifocal motor neuropathy
  IgM monoclonal gammopathy with high titre antibodies to myelin-associated glycoprotein
  Other causes for a demyelinating neuropathy including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy. PNS lymphoma and amyloidosis may occasionally have demyelinating features
<table>
<thead>
<tr>
<th>Table 2. Differential Diagnosis.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neuropathy</strong></td>
</tr>
<tr>
<td>--------------------------------</td>
</tr>
<tr>
<td>Guillain–Barré syndrome</td>
</tr>
<tr>
<td>Inherited neuropathy</td>
</tr>
<tr>
<td>Metabolic neuropathy</td>
</tr>
<tr>
<td>Paraneoplastic neuropathy</td>
</tr>
<tr>
<td>Neuropathy associated with monoclonal gammopathy</td>
</tr>
<tr>
<td>Neuropathy associated with infectious diseases</td>
</tr>
<tr>
<td>Neuropathy associated with systemic inflammatory or immune-mediated diseases</td>
</tr>
<tr>
<td>Toxic neuropathies</td>
</tr>
<tr>
<td>Neuropathy due to nutritional deficiency</td>
</tr>
<tr>
<td>Porphyria-associated neuropathy</td>
</tr>
<tr>
<td>Polyneuropathy associated with critical illness</td>
</tr>
</tbody>
</table>

- Glycemia, renal, hepatic & thyroid functions
- Total body CT scan/PET scan
- Electrophoresis & immuno-electrophoresis
- HIV serology
- Erythrocyte sedimentation rate, C-reactive protein, anemia, white blood cell count and eosinophilia, antineutrophil cytoplasmic antibody levels and hematuria
Clinique typique

ENMG "démyélinisant" ?

A oui

D non

• Jeune
• Poussées
• Proximal
• MS
• Moteur ++
• Aréflexie ++
• Ataxie

C oui

• Signes généraux
• Non réponse au ttt
• Perte axonale précoce
• Adénopathies
• Douleurs osseuses
• Signes cutanés
• Chaîne λ

Évoquer :
• Lymphome
• Sarcoïdose
• POEMS
• Amylose

B oui

• ↓ VC +
• Amp N et déficit
• ↓ SNAP MS ++
• ↓ VCS +++
• SNAP N et troubles sensitifs +++

C non

D oui

ENMG "démyélinisant" ?

E non

Clinique atypique

ENMG "démyélinisant" ?

B oui

E non


• Signes généraux
• Non réponse au ttt
• Perte axonale précoce
• Adénopathies
• Douleurs osseuses
• Signes cutanés
• Chaîne λ

Évoquer :
• Lymphome
• Sarcoïdose
• POEMS
• Amylose

LCR, PES, IRM Biopsie ?

Oui

Non

PIDC

PIDC

PIDC

PIDC

Discuter biopsie dans certains cas ?
Case report. – 45 yo – Day 3 after his admission to the ICU. Weakness in the 4 limbs (MRC 1 to 2); areflexia; no sensory loss; nocturnal pain in the back.

Features required for diagnosis
• Progressive weakness in both arms and legs (might start with weakness only in the legs)
• Areflexia (or decreased tendon reflexes)

Features that strongly support diagnosis
• Progression of symptoms over days to 4 weeks
• Relative symmetry of symptoms
• Mild sensory symptoms or signs
• Cranial nerve involvement, especially bilateral weakness of facial muscles
• Autonomic dysfunction
• Pain (often present)
• High concentration of protein in CSF
• Typical electrodiagnostic features

Features that should raise doubts
• Severe pulmonary dysfunction with limited limb weakness at onset
• Severe sensory signs with limited weakness at onset
• Bladder or bowel dysfunction at onset
• Fever at onset
• Sharp sensory level
• Slow progression (consider CIDP)
• Marked persistent asymmetry of weakness
• Persistent bladder or bowel dysfunction
• Increased number of mononuclear cells in CSF (>50×10⁶/L) or polymorphonuclear cells in CSF

van Doorn et al, Lancet Neurology 2008
Investigations for GBS

Studies related to establishing the diagnosis
Electrodiagnostic studies: a minimum study could include 3 sensory nerves (conduction velocity and amplitude), 3 motor nerves (distal latency, amplitude, and conduction velocity) with F waves and bilateral tibial H-reflexes
CSF examination: a minimum study could include glucose, protein, cell count, and bacterial culture

Studies to be done in special circumstances
Urine porphobilinogen and delta-aminolaevulinic acid concentrations
Antinuclear factor
HIV testing in at risk subjects
Drug and toxin screen

Studies related to general medical care
Urine analysis
Complete blood count
Erythrocyte sedimentation rate
Biochemical screening
Coagulation studies
ECG & Chest radiograph, Pulmonary function tests

Studies related to understanding causation
Stool culture and serology for C jejuni
Stool culture for poliovirus in pure motor syndromes
Acute and convalescent serology for cytomegalovirus, Epstein-Barr virus and M. pneumoniae as a minimum

Antibodies to gangliosides GM1, GD1a, and GQ1b

Table: Spectrum of GBS subtypes and serum antiganglioside antibodies

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Antibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute inflammatory demyelinating Polyradiculoneuropathy</td>
<td>Unknown</td>
</tr>
<tr>
<td>Acute motor (and sensory) axonal neuropathy (AMAN or AMSAN)</td>
<td>GM1, GM1b, GD1a, GalNAc-GD1a</td>
</tr>
<tr>
<td>MFS and GBS overlapping syndrome</td>
<td>GQ1b</td>
</tr>
</tbody>
</table>

van Doorn PA et al, Lancet Neurology 2008
Hughes RAC et al, Lancet 2005
Quelle(s) donnée(s) clinique(s) peuvent vous aider à faire la différence entre un Guillain-Barré et une PIDC subaigüe?

1. Une infection préccessive ?
2. L'existence de douleurs ?
3. L'âge ?
4. Une atteinte de paire crânienne ?
5. La vitesse d'installation des troubles ?
# Distinguishing acute-onset CIDP from fluctuating Guillain-Barré syndrome

A prospective study


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>GBS-TRF (n = 16)</th>
<th>A-CIDP (n = 8)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>12 (75)</td>
<td>6 (75)</td>
<td>1.0</td>
</tr>
<tr>
<td>Age at onset, y, mean ± SD</td>
<td>54 ± 17</td>
<td>47 ± 18</td>
<td>0.37</td>
</tr>
<tr>
<td>Previous GBS-like episode in medical history, n (%)</td>
<td>1 (6)</td>
<td>1 (13)</td>
<td>1.0</td>
</tr>
<tr>
<td>Paresthetic/hypasthetic sensations, n (%)</td>
<td>14 (88)</td>
<td>8 (100)</td>
<td>0.54</td>
</tr>
<tr>
<td>Pure motor, n (%)</td>
<td>1 (6)</td>
<td>2 (25)</td>
<td>0.25</td>
</tr>
<tr>
<td>Pain before onset of weakness, n (%)</td>
<td>6 (38)</td>
<td>4 (50)</td>
<td>0.67</td>
</tr>
<tr>
<td>Pain in acute phase, n (%)</td>
<td>13 (81)</td>
<td>5 (71)*</td>
<td>0.62</td>
</tr>
<tr>
<td>Cranial nerve dysfunction, n (%)</td>
<td>11 (69)</td>
<td>1 (13)</td>
<td>0.03</td>
</tr>
<tr>
<td>III, IV, or VI</td>
<td>6 (38)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>VII</td>
<td>10 (63)</td>
<td>1 (13)</td>
<td></td>
</tr>
<tr>
<td>IX, X, or XII</td>
<td>4 (25)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Clinical preceding infections</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory tract/influenza(-like), n (%)</td>
<td>5 (31)</td>
<td>2 (25)</td>
<td>1.0</td>
</tr>
<tr>
<td>Gastroenteritis/diarrhea, n (%)</td>
<td>4 (25)</td>
<td>2 (25)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Course</th>
<th>GBS-TRF (n = 16)</th>
<th>A-CIDP (n = 8)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Days to reach nadir, median (95% CI)*</td>
<td>8.5 (6-11)</td>
<td>16.5 (5-22)</td>
<td>0.03</td>
</tr>
<tr>
<td>Days to reach first TRF/exacerbation, median (95% CI)*</td>
<td>18 (15-27)</td>
<td>51 (31-63)</td>
<td>0.00</td>
</tr>
<tr>
<td>Days to reach second TRF/exacerbation, median (95% CI)*</td>
<td>38 (31-46)b</td>
<td>105 (52-116)b</td>
<td>0.01</td>
</tr>
<tr>
<td>Days from onset of weakness to inclusion</td>
<td>5 (2-10)</td>
<td>14.5 (5-26)</td>
<td>0.01</td>
</tr>
<tr>
<td>Days from onset of paresthesia to inclusion</td>
<td>8 (5-17)c</td>
<td>12.5 (7-24)</td>
<td>0.04</td>
</tr>
<tr>
<td>Days from onset of hypasthesia to inclusion</td>
<td>6.5 (3-12)d</td>
<td>10 (7-21)*</td>
<td>0.12</td>
</tr>
</tbody>
</table>

L. Ruts, MD  
J. Drenthen, MD  
B.C. Jacobs, MD, PhD  
P.A. van Doorn, MD, PhD  
On behalf of the Dutch GBS Study Group
Quelle(s) donnée(s) biologique(s) peuvent vous aider à faire la différence entre un Guillain-Barré et une PIDC ?

1. La protéinorachie ?
2. La cellularité du LCR ?
3. La VS ?
4. Les données de l’EMG (vitesses - blocs) ?
5. Une dénervation à l’aiguille ?
**PIDC « aiguë » :**

**Nerfs crâniens respectés**
**Moins aigu / PRNA**
**Moins sévère**
**VCM plus altérées**


<table>
<thead>
<tr>
<th></th>
<th>GBS-TRF (n = 16)</th>
<th>A-CIDP (n = 8)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cells, 10⁶/L, median (95% CI)</td>
<td>2 (2–4)b</td>
<td>2 (0–5)c</td>
<td>0.30</td>
</tr>
<tr>
<td>Protein, g/L, median (95% CI)</td>
<td>0.9 (0.4–1.8)</td>
<td>0.7 (0.5–1.6)a</td>
<td>0.68</td>
</tr>
<tr>
<td>Increased protein, &gt;0.55 g/L, n (%)</td>
<td>10 (63)</td>
<td>4 (57)a</td>
<td>1.0</td>
</tr>
<tr>
<td>Antiganglioside antibodies</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IgM reactivity against GM1, GM2, GD1a, GD1b, or GQ1b</td>
<td>2 (13)</td>
<td>1 (13)</td>
<td>1.0</td>
</tr>
<tr>
<td>IgG reactivity against GM1, GM2, GD1a, GD1b, or GQ1b</td>
<td>3 (19)</td>
<td>0</td>
<td>0.53</td>
</tr>
</tbody>
</table>
Two questions

Is there an indication for admission to an intensive care unit?

- Rapid progressive severe weakness often with impaired respiration (vital capacity < 20 mL/kg)
- Need for artificial ventilation
- Insufficient swallowing with high chance of pulmonary infection
- Severe autonomic dysfunction

Consider treatment with IVIg or PE

- Severely affected patients (inability to walk unaided)
- Start IVIg preferably within first 2 weeks from onset: 0.4 g/kg for 5 days; or 4× PE with total exchange volume of five plasma volumes in 2 weeks

Unknown whether IVIg is effective:

- Mildly affected patients

Indications for re-treatment with IVIg:

- No proven effect of re-treatment with IVIg in patients who continue to worsen

Others immunomodulating drugs??
Despite IVIg treatment, many patients only partially recover and have residual weakness, pain, and fatigue.

Fig. 6.1. Recovery from Guillain–Barré syndrome. The points on this diagram represent median disability grades of 100 patients. The figures on the top line represent the cumulative numbers of dead patients at those times. The figures in the box on the right represent the number of disabled survivors after one year. (Data from Winer et al. (1988), with permission.)
Management of GBS during the course of disease diagnosis

**Give good general care**, monitor progression and prevent and manage potentially fatal complications, especially:

- Regularly monitor pulmonary function (vital capacity, respiration frequency), initially every 2–4 h, in stable phase every 6–12 h.
- Regularly check for autonomic dysfunction (blood pressure, heart rate, pupils, ileus), initially continuous monitor heart rate, pulse and blood pressure. If logistically impossible, check every 2–4 h, in stable phase every 6–12 h.
- Check for swallowing dysfunction.
- Recognise and treat pain: acute nociceptive pain, according to WHO guidelines (try to avoid opioids); amitriptyline or antiepileptic drugs.
- Prevent and treat infections and pulmonary embolism.
- Prevent cornea ulceration due to facial weakness.
- Prevent decubitus and contractures.

**Rehabilitation and fatigue**

- Start physiotherapy early during course of disease, as soon as improvement starts.
- Consider a physical training programme for severe fatigue.
- Consider contacting patients’ organisation for additional information and help.

---

**Table 3: The Erasmus GBS outcome score**

<table>
<thead>
<tr>
<th>Categories</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at onset (years)</td>
<td></td>
</tr>
<tr>
<td>≥60</td>
<td>1</td>
</tr>
<tr>
<td>≤40</td>
<td>0.5</td>
</tr>
<tr>
<td>≤40</td>
<td>0</td>
</tr>
<tr>
<td>Ectropion (≤4 weeks)</td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>0</td>
</tr>
<tr>
<td>Presence</td>
<td>1</td>
</tr>
<tr>
<td>GBS disability score (at 2 weeks after entry)</td>
<td></td>
</tr>
<tr>
<td>0 or 1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

---

van Koningsveld R et al. Lancet Neurol 2007
Practical points for Guillain-Barré syndrome:

• The most frequently encountered acute neuropathy
• Patients are in particular need of excellent multidisciplinary care to prevent and manage potentially fatal complications (previous panel), so hospitalize each patient
• After the acute phase, plan to review periodically each patient to prevent and manage chronic complications, such as cramps (quinine), pain (gabapentine & others), weakness and fatigue (physical training programme)
Miller-Fisher Syndrome
Triad: Ophthalmoplegia - Ataxia - Areflexia

Case report: A 31 year old man referred with the chief complaint of diplopia and mild ataxia. Over the next few days he developed ophthalamoplegia, facial palsy, dysesthesia in hands, areflexia and marked unsteadiness of gait. A MRI of the head was normal; CSF was normal.

Anti- GQ1b antibody on admission > 15,000 in serum

• Initial symptoms; n=267
  Ito et al. Rinsho Shinkeigaku 2005
  – Diplopia 63%
  – Gait disturbance 33%
  – Dysesthesia 17%
  – Blepharoptosis 5%
  – Photophobia 3%

• Incidence
  Mori et al. Neurology 2005
  – 5% of GBS in Western countries
  – 0.09 / 100,000 population in Italy
  – 19% of GBS in Taiwan
  – 25% of GBS in Japan

• Anti-GQ1b antibodies in 85 %
Mimétisme moléculaire

1/ Association épidémiologique
   agent infectieux et désordre
   auto-immun

2/ Identification AC dirigés
   contre cibles antigéniques de
   l'hôte

3/ Identification mimétisme
   moléculaire avec Ag de la cible

4/ Reproduction de l'affection
   sur un modèle animal
Les preuves épidémiologiques

Syndrome de Guillain-Barré
Lié à l’infection par *C. jejuni* (20 à 30%)
- Atteinte motrice prédominante
- Évolution axonale fréquente
- Lésions histologiques particulières

Syndrome de Miller-Fisher
Association à des IgG anti-QG1b : 90%
20% d’infection à *C. jejuni*

Yuki et al 2006. étude cas/témoin
AC IgG anti-GM1 et GD1a complexe GM1/GD1a
GBS moteur

C. jejuni et polymorphisme de la sialyltransférase Cst-II

AC IgG anti-GQ1b
Syndrome de Fisher

Risque 1/3000

Modèle in vivo
Plaque motrices MOM GQ1b
Activation du complément C5B9

Modèle animal d’immunisation avec GM1
4/ Reproduction de l'affection sur un modèle animal

Infection CJ et Immunisation LOS purifiées induit une réaction croisée anti-ganglioside Spécificité des AC proche de ceux retrouvés chez l'homme

(Ang, Infect Immun, 2001)

Immunisation lapins avec Ac anti-gangliosides induit neuropathie type GBS
Reproduction tableau avec CJ-LOS

(Yuki, J Periph Nerv Syst, 2003)
A. Study or sub-category
- Greenwood 1984: 14, PE Mean (SD): -0.64 (1.35)
- Mokkann 1985: 322, PE Mean (SD): -2.10 (1.93)
- Raphael 1987: 109, PE Mean (SD): -2.20 (1.85)
- Raphael 1987: 46, PE Mean (SD): -2.00 (2.10)
- Total: 290
  - Test for heterogeneity: CH² = 3.10, df = 3 (P = 0.80), I² = 3.3%
  - Test for overall effect: Z = 2.80 (P < 0.00001)

B. Study or sub-category
- van der Maaij 1992: 74, IVg Mean (SD): -0.66 (1.32)
- Bill 1996: 26, IVg Mean (SD): -1.00 (1.32)
- PGGSBS Group 1997: 130, IVg Mean (SD): -1.80 (2.30)
- Nomura 2000: 23, IVg Mean (SD): 0.00 (0.00)
- Donner 2001: 20, IVg Mean (SD): 0.20 (3.32)
- Total: 273
  - Test for heterogeneity: CH² = 6.82, df = 4 (P = 0.15), I² = 41.3%
  - Test for overall effect: Z = 0.21 (P = 0.83)

C. Study or sub-category
- Oral regimen
  - Bansal 1986: 10, Corticosteroid Mean (SD): -2.20 (2.97)
  - Hughes 1978: 21, Corticosteroid Mean (SD): -0.24 (0.94)
  - Shults 1979: 6, Corticosteroid Mean (SD): -0.67 (1.75)
  - Singh 1996: 24, Corticosteroid Mean (SD): -2.20 (2.00)
  - Subtotal: 293
  - Test for heterogeneity: CH² = 6.16, df = 3 (P = 0.10), I² = 31.3%
  - Test for overall effect: Z = 1.17 (P = 0.13)

- Intravenous regimen
  - GBS Steroid 1993: 124, Corticosteroid Mean (SD): -0.80 (1.14)
  - van Koningsveld 2004: 153, Corticosteroid Mean (SD): -3.3 (2.30)
  - Subtotal: 356
  - Test for heterogeneity: CH² = 6.06, df = 1 (P = 0.01), I² = 21.3%
  - Test for overall effect: Z = 0.21 (P = 0.83)

- Total: 293
  - Test for heterogeneity: CH² = 24.60, df = 5 (P = 0.0002), I² = 76.7%
  - Test for overall effect: Z = 1.35 (P = 0.18)

20% de mortalité ou séquelles par atteinte axonale

Corticoïdes/rien ou placebo

Changement d’un score de handicap 4 à 4 semaines

NP/IVg/EP

EP/placebo

Review Article
Immunotherapy for Guillain-Barré syndrome: a systematic review
Richard A. C. Hughes, Anthony V. Swan, Jean-Claude Raphael, Djiti Ali Amare, Rinke van Koningsveld, and Peter A. van Deem
<table>
<thead>
<tr>
<th>Echanges Plasmatiques</th>
<th>Symptômes légers</th>
<th>Symptômes modérés</th>
<th>Symptômes sévères</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 PE n =46</td>
<td>2 PE n=45</td>
<td>2 PE n=149</td>
</tr>
<tr>
<td>Temps de récupération motrice</td>
<td>8 4 0.0002</td>
<td>6 5 0.1</td>
<td>8 8 0.11</td>
</tr>
<tr>
<td>Marche avec assistance</td>
<td>14 14 0.8</td>
<td>24 20 0.04</td>
<td>56 60 0.89</td>
</tr>
<tr>
<td>Marche sans assistance</td>
<td>28 15 0.4</td>
<td>64 52 0.13</td>
<td>113 103 0.64</td>
</tr>
<tr>
<td>Détérioration clinique</td>
<td>18 2 0.0001</td>
<td>- - -</td>
<td>- - -</td>
</tr>
<tr>
<td>Ventilation</td>
<td>6 1 0.11</td>
<td>42 41 1.0</td>
<td>81 80</td>
</tr>
<tr>
<td>Durée de la ventilation</td>
<td>30 7 -</td>
<td>37 15 0.005</td>
<td>43 34 0.96</td>
</tr>
<tr>
<td>Durée du décubitus</td>
<td>18 13 0.02</td>
<td>26 21 0.04</td>
<td>50 44 0.57</td>
</tr>
<tr>
<td>A 1 an</td>
<td>Patients avec une récupération totale</td>
<td>20 28 0.1</td>
<td>45 67 0.006</td>
</tr>
<tr>
<td>Patient sans séquelle motrice sévère</td>
<td>5 5 -</td>
<td>22 26 -</td>
<td>16 8</td>
</tr>
<tr>
<td>Patients avec séquelles motrices sévères</td>
<td>2 0 0.24</td>
<td>24 12 0.05</td>
<td>15 14 1.0</td>
</tr>
</tbody>
</table>
IgIV vs EP vs Combinaison

379 patients
EP (5 ; 50 ml/kg) : 121
Ig IV (400 ml/kg/j pdt 5 jours) : 130
EP puis IgIV : 128

<table>
<thead>
<tr>
<th></th>
<th>EP</th>
<th>IgIV</th>
<th>EP+IgIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>H/F</td>
<td>61%</td>
<td>61%</td>
<td>56%</td>
</tr>
<tr>
<td>Délai</td>
<td>6.9</td>
<td>6.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Score</td>
<td>3.9</td>
<td>4.0</td>
<td>3.9</td>
</tr>
<tr>
<td>Ventil.</td>
<td>9.9%</td>
<td>11.5%</td>
<td>15.6%</td>
</tr>
<tr>
<td>PGAM bas</td>
<td>13.9%</td>
<td>16.1%</td>
<td>11.7%</td>
</tr>
<tr>
<td>Entérite</td>
<td>24%</td>
<td>18.5%</td>
<td>19.5%</td>
</tr>
</tbody>
</table>
Corticostéroïdes

Guillain-Barré Syndrome Steroid Trial Group
Lancet 1993 ; 341 : 586-590 (242 Patients MP vs Placebo)
Pas d’efficacité
Ventilation : 18j vs 27 j / Marche sans aide : 38j vs 50 j

The Dutch Guillain-Barré Study Group.
Ann Neurol 1994 ; 35 : 749-752 (25 patients MP+IgIV ouvert)
Amélioration : 76% vs 53%

<table>
<thead>
<tr>
<th></th>
<th>IgIV</th>
<th>MP+IgIV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amélior.</td>
<td>27%</td>
<td>52%</td>
</tr>
<tr>
<td>Stable</td>
<td>50%</td>
<td>32%</td>
</tr>
<tr>
<td>Aggrav.</td>
<td>23%</td>
<td>16%</td>
</tr>
</tbody>
</table>

![Graph showing days since start of treatment vs IgIV and MP+IgIV]
Corticostéroïdes

Marche sans aide

Amélioration score fonctionnel

Marche sans aide

- Echanges Plasmatiques
  - 85 jours North American Trial (18% incapables)
  - 70 jours French Trial
- Ig IV
  - 51 jours Dutch Trial (19% incapables)
  - 55 jours Sandobuline GBS Trial
- Corticostéroïdes
  - 38 jours GBS Steroid Trial
  - 28 jours Ig IV et MP (8% incapables)
Characteristics of anti-MAG neuropathy:
• A slowly progressive length dependent demyelinating neuropathy with distal symmetric sensory-motor symptoms
• Tremor and ataxia
• Peripheral neuropathy with IgM gammopathy, & elevated anti-MAG antibodies
Neuropathie avec IgM monoclonale anti-MAG

Élargissement de la ligne dense interne

Dépôts d’IgM dans le nerf du patient

Activation du Complément
L'atteinte myélinique à prédominance distale

Clinique

EMG: index de latence terminale

Dépots d'IgM

Biopsie de peau

+ dépôts de complément

Lombardi et al., 2005
Neuropathies avec IgM anti-MAG: traitement

- Sur 22 études dont deux contrôlées
  - IgIV
  - EP
  - cyclophosphamide
  - chlorambucil
  - fludarabine, adriamicine...
  - interféron alpha
  - Immuno-adsorption
- 50% de répondants à court ou moyen terme

<table>
<thead>
<tr>
<th>Years</th>
<th>Mortality</th>
<th>Disability</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>8%</td>
<td>16%</td>
</tr>
<tr>
<td>15</td>
<td>33%</td>
<td>50%</td>
</tr>
</tbody>
</table>

19/25 traités
9 améliorés
1 de façon durable
**10 effets secondaires graves liés au traitement dont 3 DC**
- **New Treatment**: B-cell depletion with anti-CD 20, Rituximab®, a mouse-human chimeric antibody
- Specific depletion of CD 20+ cells via antibody-dependent cell + complement mediated cytotoxicity
- Intravenous once weekly for 4 weeks, and retreatment is usually necessary
- Effective in the treatment of B cell lymphoma; rheumatoid arthritis;
- Rituximab is the first drug that improves some patients with A-MAG-DP in a controlled study (Ann Neurol 2009 ;65:286-93)

CD20 : molécule de différentiation spécifique des lympho B
- pré B
- B matures
- plasmocytes IgM circulants (20%)

**AC anti-CD20** (Rituximab® 375 mg/m²)

![Graph showing the effect of AC anti-CD20 treatment over time](image)

**Avant anti-CD20**
**3 mois**
**9 mois**
• **Etudes ouvertes**
  - Renaud et al., 2003. 9 cas. 375 mg/m²
    - Baisse de l'activité anti-MAG > 52% chez 8/9.
    - 6 améliorés, 2 stables, 1 aggravé
  - Nobile Orazio et al., 2007: 13 cas. 375 mg/m²
    - 60% améliorés surtout si taux d'IgM bas et diminue avec le ttt
  - **Steck et al. 2006 : 8 cas. 750 mg/m²**
    - 4/8 non ou partiellement répondeurs à 375 mg/m² s'améliorent
• **Etude contre un groupe contrôle non randomisée**
  - Pestronk et al., 2003. 20 IgM M (12 gangliosides-8 MAG). 375 mg/m² et 13 contrôle
    - Force améliorée de 23%
    - taux d'IgM abaissé de 55%
• **Etudes contrôlées randomisée contre placebo**
  - Dalakas AAN 2007: 28 patients 375 mg/m²
    - nb de patients améliorés >= 1 pt INCAT à 8 mois p<0.05
    - baisse du titre des AC de 50%
  - JM Leger : en cours
Peripheral neuropathies with IgM or IgG Gammopathy without anti-MAG activity are heterogeneous...

- Waldenström macroglobulinemia
- Myeloma
- POEMS (peripheral neuropathy, organomegaly, endocrine disorder, monoclonal protein, skin disease)
- Cryoglobulinemia with monoclonal IgM
- Amyloidosis
- Lymphoma
- Neurolymphomatosis

- Hyperviscosity
- Amyloid deposit
- IgM/G
Peripheral neuropathies with IgM or IgG Gammopathy without anti-MAG activity are heterogeneous...

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↑ CSF protein
- Demyelinating NP (efficacy of bevacizumab)
- Osteosclerosis-lysis
Peripheral neuropathies with IgM or IgG Gammopathy without anti-MAG activity are heterogeneous…

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\[\text{Carpal tunnel (1/3)}\]
\[\text{Distal axonal asymmetric neuropathy}\]
\[\text{Dysautonomia (2/3)}\]
\[\text{Amyloid deposit}\]
Peripheral neuropathies with IgM or IgG Gammopathy without anti-MAG activity are heterogeneous...

- Waldenström macroglobulinemia
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- Lymphoma
- Neurolymphomatosis

\[ \text{• Local infiltration} \]
\[ \text{• Castleman’s disease} \]
\[ \text{• In association with HIV} \]
Classification of haematological conditions with a paraprotein:

(1) Malignant monoclonal gammopathies
   (a) Multiple myeloma
   (b) Plasmacytoma (solitary, extramedullary, multiple solitary)
   (c) Malignant lymphoproliferative disease:
       (i) Waldenström’s macroglobulinaemia
       (ii) Malignant lymphoma
       (iii) Chronic lymphocytic leukaemia
   (d) Heavy chain disease
   (e) Primary amyloidosis (AL) (with or without myeloma)
(2) MGUS

Definition of monoclonal gammopathy of undetermined significance (MGUS):

(1) IgM–MGUS is defined by all of the following:
   (a) No lymphoplasmacytic infiltration on bone marrow biopsy
   (b) No symptoms or signs suggesting tumour infiltration (e.g. constitutional symptoms, hyperviscosity syndrome and organomegaly)
   (c) No evolution to malignant lymphoproliferative disease requiring treatment within 12 months from first detection of paraprotein
(2) IgG or IgA–MGUS is defined by the presence of all of the following:
   (a) Monoclonal component <30 g/l
   (b) Bence-Jones proteinuria <1 g/24 h
   (c) No lytic lesions in bone
   (d) No anaemia, hypercalcaemia, or chronic renal insufficiency
   (e) Bone marrow plasma cell infiltration <10%
   (f) No evolution to myeloma or 1c
The clinical and laboratory features of chronic sensory ataxic neuropathy with anti-disialosyl IgM antibodies

H. J. Willison,1 C. P. O’Leary1, J. Veitch,1 L. D. Blumhardt,2 M. Busby,3 M. Donaghy,3 P. Fuhr,10 H. Ford,4 A. Hahn,11 S. Renaud,10 H. A. Katifi,5 S. Ponsford,8 M. Reuber,4 A. Steck,10 I. Sutton,6 W. Schady,7 P. K. Thomas,9 A. J. Thompson,9 J.-M. Vallat12 and J. Winer6

CANOMAD Chronic Ataxic Neuropathy with Ophthalmoplegia, M protein, Agglutination and Disialosyl antibodies

Think about it when there is evidence of « Chronic Miller Fisher syndrome » + anti-ganglioside IgM (kappa) antibodies against the NeuNac(α2-8)NeuNac(α2-3)Gal epitope of gangliosides GD2, GD3, GD1b, GT1b, GT1a et GQ1b

IvIg and Rituximab are the drugs that can improve patients …
At diagnosis onset

Musculocutaneous nerve
\begin{itemize}
  \item Arm \& Erb's point to biceps brachii m.
\end{itemize}

Fat-suppressed, T2-weighted, fast spin-echo image of the brachial plexus: swelling and increased intensity.

4 days after IV Ig infusion 2g/kg

Fasciculations, and grouped fasciculations as recorded from surface electrode from the Bb muscle.

8 years later

Strength [arbitrary Unit]

\begin{itemize}
  \item Dec.1998
  \item May.2006
\end{itemize}

Subcutaneous reservoir

Prednisone
Azathioprine
Sandoglobulines
Endoglobulines
Octagam

80 infusions
Multifocal Motor Neuropathy, diagnostic criteria

Table 1 Clinical criteria for MMN

Core criteria (both must be present)
1. Slowly progressive or stepwise progressive, asymmetric limb weakness, or motor involvement having a motor nerve distribution in at least two nerves, for more than 1 month
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 limbs
5. Absence of cranial nerve involvement
6. Cramps and fasciculations in the affected limb
Exclusion criteria
7. Upper motor neuron signs
8. Marked bulbar involvement
9. Sensory impairment more marked than minor vibration loss in the lower limbs
10. Diffuse symmetric weakness during the initial weeks
11. Laboratory: CSF protein > 1 g/l

The diagnosis of MMN is based on clinical, laboratory, and electrophysiological characteristics, the **CBs are the hallmark of the disease**

Supportive criteria
1. Elevated IgM anti-ganglioside GM1 antibodies
2. Magnetic resonance imaging showing gadolinium enhancement or hypertrophy of the brachial plexuses
3. Clinical improvement following IVIg treatment

100% CB of the musculocutaneous nerve
Arm & Erb’s point to biceps brachii m.

90% CB of the ulnar nerve
Wrist to Erb’s point to ADM m.
Multifocal Motor Neuropathy, treatment

1. IVIg (2 g/kg given over 2-5 days) should be considered as the first line treatment when disability is sufficiently severe to warrant treatment.

2. Prednisone and other corticosteroids are not recommended.

3. If an initial treatment with IVIg is effective, repeated IVIg treatment should be considered in selected patients. The frequency of IVIg maintenance therapy should be guided by the response. Typical treatment regimens are 1 g/kg every 2-4 weeks, or 2 g/kg every 1-2 months.

4. If IVIg is not or not sufficiently effective then immunosuppressive treatment may be considered. Cyclophosphamide, ciclosporin, azathioprine, interferon beta1a, or rituximab are possible agents (good practice point).

5. Toxicity makes cyclophosphamide a less desirable option.
Peripheral nerve hyperexcitability

- Shoulder pain / muscle stiffness
- Cramps, discrete fasciculations at rest that increase clearly by motion
- Briskness of the direct percussion of the muscles whereas deep reflexes are weak
- Excessive sweating and weight loss, and insomnia
- Anti–VGKC antibodies negative (can be detected in about 50% of the cases)

Morvan’s syndrome

Treatment = plasma exchanges (phenytoin-carbamazepin may help)

Fasciculations, myokymias, grouped fasciculations and neuromyotonias recorded from surface electrodes over the EDC muscle:

After-responses as recorded form ADM after stimulation of the R ulnar nerve:
Conclusions

1. Dysimmune neuropathies include diverse neuropathies whose diagnosis and classification are based on the clinical presentations and results of ancillary tests.

2. In some, controlled therapeutic trials demonstrated efficacy for IV g-globulins, corticosteroids, and plasmapheresis.

3. In the other immune-mediated neuropathies, there are no reported controlled therapeutic trials, but efficacy has been reported for some treatments in non-controlled trials on case studies.

1. Usefulness of repeated examinations, extensive nerve conduction studies, blood testings and nerve biopsies.

2. Treat asp and strong.

3. Usefulness of new drugs (monoclonal AB rituximab, alemtuzumab & bevacizumab; TNF alpha blockers etanercept; & newly used immunosuppressors, Fingolimod; cladribine; fumarate; teriflunomide; laquinimod...).
Clinical spectrum of chronic immune-mediated neuropathies

- IgM anti-MAG
- MMN
- Multifocal
- Upper limb
- Lower limb