# The alphabet soup of inflammatory neuropathies

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Diagnostics</th>
<th>Treatments</th>
<th>Research</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute</strong></td>
<td>• LP</td>
<td>• IVIg</td>
<td>• IGOS</td>
</tr>
<tr>
<td>• GBS</td>
<td>• CSF</td>
<td>• PE</td>
<td>• I-SID</td>
</tr>
<tr>
<td>• AIDP</td>
<td>• EMG</td>
<td></td>
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<tr>
<td>• AMAN</td>
<td>• MAG</td>
<td></td>
<td></td>
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<tr>
<td>• MFS</td>
<td>• GM1</td>
<td></td>
<td></td>
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<tr>
<td>• A-CIDP</td>
<td>• GD1a</td>
<td></td>
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<tr>
<td><strong>Chronic</strong></td>
<td>• GD1b</td>
<td></td>
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<tr>
<td>• CIDP</td>
<td>• GQ1b</td>
<td></td>
<td></td>
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<tr>
<td>• MMN</td>
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<td></td>
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<tr>
<td>• LSS</td>
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<td></td>
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<tr>
<td>• DADS</td>
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<td></td>
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<tr>
<td>• MADSAM</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• CANOMAD</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>• MGUS-NP</td>
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</tbody>
</table>
Peripheral nervous system

Axon

Myelin (insulation)

Neuron

Nerve

Myelin sheath
**Normal nerves**

- Muscle strength
  - limbs, face
  - breathing
  - swallowing

- Sensation
  - touch
  - pain
  - coordination

- Reflexes

**Neuropathy**

- Weakness
  - limbs, face
  - respiratory failure
  - swallowing

- No or abnormal sensation
  - numbness
  - pain, cold
  - ataxia

- Low or absent reflexes
Reflex hammer
Knee jerk reflex
Lumbar puncture (LP) and cerebrospinal fluid (CSF)
Nerve electrophysiology and myogram (EMG)

- Myelin damage (demyelination)
- Axon damage (degeneration)
Patients with inflammatory neuropathies in USA
estimations based on data from The Netherlands

<table>
<thead>
<tr>
<th></th>
<th>New this year</th>
<th>Total alive with/after disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBS</td>
<td>3,000 - 4,000</td>
<td>60,000 - 80,000</td>
</tr>
<tr>
<td>MFS</td>
<td>100 - 200</td>
<td>2,000 - 4,000</td>
</tr>
<tr>
<td>CIDP</td>
<td>400 - 500</td>
<td>8,000 - 10,000</td>
</tr>
<tr>
<td>MMN</td>
<td>100 - 200</td>
<td>2,000 - 4,000</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>3,500 - 5,000</strong></td>
<td><strong>70,000 - 100,000</strong></td>
</tr>
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Population: 320 million
Guillain-Barré syndrome (GBS)


G. Guillain  |  J-A. Barré  |  A. Strohl
Guillain-Barré syndrome (GBS)

- All ages, but increasing with age
- More frequent in males than females
- Rapidly progressive and potentially life-threatening
- Symmetrical weakness and sensory symptoms in legs and arms
- Frequently painful
- 25% respiratory failure requiring ventilation at ICU
- 15% autonomic dysfunction
- Large variation in clinical course between patients
Two main subtypes of GBS

- Damaged myelin
  - Acute inflammatory demyelinating polyneuropathy (AIDP)
- Damaged axon
  - Acute motor (sensory) axonal neuropathy (AMAN) (AMSAN)
Miller Fisher syndrome (MFS)

- Three typical characteristics
  - Weakness muscles for eye movements (double vision)
    - Often with drooping eyelids and facial weakness
  - Poor balance and coordination with clumsy walking (ataxia)
  - On physical examination: loss of tendon reflexes

- Variant of GBS, but no weak of the limbs
Typical clinical course of GBS

- Progression
- Plateau phase
- Recovery phase
- Disability

- <4 weeks
- weeks
- months
- years

Recovery phase
Disability
Treatment of GBS

• Supportive care
  • Artificial ventilation
  • Pain medication
  • Prevention complications

• Specific treatments
  • Immunoglobulins (IVIg)
  • Plasma exchange (PE)

• Rehabilitation and physiotherapy
Infections that can cause GBS

- Campylobacter bacteria
- Cytomegalovirus
- Epstein-Barr virus
- Mycoplasma bacteria
- Hepatitis E virus

Infectious mononucleosis ('kissing disease')

- Gastro-intestinal infection: 30%
- Respiratory tract infection: 15%
- Infectious mononucleosis ('kissing disease'): 10%
- Respiratory tract infection: 5%
- Hepatitis: 5%

GBS
Infections that trigger immune responses to nerves
Infections that trigger immune responses to nerves
## Erasmus GBS outcome score (EGOS)

<table>
<thead>
<tr>
<th>Predictors</th>
<th>Categories</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>≤40</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>41-60</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>&gt;60</td>
<td>1</td>
</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td>absent</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>present</td>
<td>1</td>
</tr>
<tr>
<td><strong>GBS disability score</strong></td>
<td>0-1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>3</td>
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<tr>
<td></td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>5</td>
</tr>
</tbody>
</table>

**EGOS** 1 - 7

## Chance unable to walk at 6 months according to EGOS (N=762)

![Graph showing the predicted fraction not walking at 6 months against EGOS score with AUC 0.85.](image)

AUC 0.85
Chronic inflammatory demyelinating poly(radiculo)neuropathy (CIDP)
CIDP

• **Clinical features:**
  - Slow onset (disease progression > 8 weeks)
  - Symmetrical weakness and sensory deficits
  - Legs more involved than arms
  - Sometimes cranial nerve involvement

• **Diagnosis:**
  - Neurological exam
  - Blood tests (to exclude other diseases)
  - Spinal tap
  - Nerve electrophysiology

• **Treatments:**
  - Immunoglobulins (IVIg)
  - Corticosteroids
  - Plasma exchange (PE)
Typical clinical course of GBS and CIDP

- GBS: <4 weeks (Acute onset) A-CIDP
- CIDP: weeks, months, years
Peripheral nerves of a patient with CIDP

Myelin damage

‘Union bulbs’

Bosboom et al., 2001
Right diagnosis and treatment?

- Important to excluded other causes of neuropathy:
  - Hereditary neuropathy
  - Diabetes-related polyneuropathy
  - Paraprotein- or MAG-related polyneuropathy
  - Chronic idiopathic axonal polyneuropathy

- Most patients respond to treatment (at least to some extent).

- CIDP may recover, so try reduce or stop therapy regularly.

- Discriminate between:
  - active CIDP requiring treatment
  - inactive CIDP with residual damage
Multifocal Motor Neuropathy (MMN)
MMN

- **Clinical features:**
  - Slow onset
  - Asymmetrical (stepwise involvement specific motor nerves)
  - Weakness in legs more than arms
  - Rarely sensory symptoms (at later stages)

- **Diagnosis:**
  - Neurological exam
  - Blood tests (antibodies to GM1)
  - Spinal tap
  - Nerve electrophysiology

- **Treatments:**
  - Immunoglobulins (IVIg)
Disease mechanism of MMN

Vlam et al. 2013
Typical clinical course of GBS, CIDP and MMN

- **GBS**
- **MMN**
- **CIDP**
# Differences between GBS, CIDP and MMN

<table>
<thead>
<tr>
<th></th>
<th>GBS</th>
<th>CIDP</th>
<th>MMN</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Onset</strong></td>
<td>sudden</td>
<td>slow</td>
<td>slow</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td>symmetric</td>
<td>symmetric</td>
<td>asymmetric</td>
</tr>
<tr>
<td><strong>Weakness</strong></td>
<td>legs + arms</td>
<td>legs &gt; arms</td>
<td>arms &gt; legs</td>
</tr>
<tr>
<td><strong>Sensory deficits</strong></td>
<td>usually</td>
<td>usually</td>
<td>rare</td>
</tr>
<tr>
<td><strong>Effective therapy</strong></td>
<td>IVIg, PF</td>
<td>IVIg, steroids, PF</td>
<td>IVIg</td>
</tr>
<tr>
<td><strong>Course</strong></td>
<td>single episode (95%)</td>
<td>relapsing-remitting, chronic</td>
<td>persistent</td>
</tr>
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</table>
Gaps in current knowledge

- No risk factors known, so all persons may develop these neuropathies.

- Not known in many patients which targets attacked by immune system (especially in AIDP en CIDP).

- No 100% accurate diagnostic tests, so still complex diagnoses.

- Treatable diseases, but only when diagnosed early.

- Highly variable response to treatments between patients.

- Little known about long-term effects and how to treat these.
International GBS Outcome Study
International GBS Outcome Study (IGOS)

• Study objectives
  ▪ Find infections and genes that cause GBS
  ▪ Find factors that determine clinical course and outcome in individual patients
  ▪ Develop better treatments for individual patients

• Patients
  ▪ All patients with GBS (and variants) in acute phase (first 2 weeks)
  ▪ More than 1000 patients will participate

• Design
  ▪ Prospective study with follow-up of each patients of 1-3 years
  ▪ Collection of clinical data and blood samples
  ▪ 3 new treatments tested
    ▪ International Second IVIg Dose (I-SID) study
Inflammatory Neuropathy Consortium (INC)

INC meeting in June 2012 in Rotterdam
IGOS: a worldwide study

- 18 participating countries
- 142 participating centers

Inclusion of patients

In process of IRB approval

- Inclusion of patients
- In process of IRB approval
Number of patients participating in IGOS
update October 28th, 2014

715 patients
Number of inclusions per country
update October 28th, 2014
What will IGOS deliver?

- Largest data and biobank ever collected for GBS research.
- Better understanding of the risk factors for developing GBS.
- Prediction of disease course and handicap in individual patients.
- First clues how to adjust treatment in individual patients.
- International collaboration between clinicians and experts.
- Training of young researchers and clinicians.
- Network for similar studies in CIDP, MMN and other neuropathies.
What could you do to support IGOS?

• Continue to participate as a patient in the research project.

• Financial support via GBS-CIDP Foundation International.
Thanks to:

- All patients and relatives involved in research projects
- Research team in Rotterdam
- IGOS Consortium
- Financial support:

GBS•CIDP
Foundation International

Erasmus MC
Universiteit Medisch Centrum Rotterdam

GRIFOLS

CSL Behring
If you can dream it, you can do it.

Walt Disney