Clinical Decision Making in Autoimmune Neuromuscular Disease:
Diagnosis, Treatment, and Management

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Topics of Today’s Discussion

- Clinical and laboratory diagnostic features used to distinguish among a series of treatable autoimmune neuromuscular diseases, including GBS, CIDP, MMN, and MG
- The role of expert opinion, consensus statements, and evidence-based medicine in clinical decision making in autoimmune neuromuscular disease
- Current issues and clinical trial data relating to the long-term prognosis and management of autoimmune neuromuscular diseases
Objectives

On completion of this activity, participants should be able to:

- Recognize the clinical presentations of chronic inflammatory demyelinating polyneuropathy (CIDP), multifocal motor neuropathy (MMN), Guillain-Barré syndrome (GBS), and myasthenia gravis (MG)
- Evaluate the diagnostic evidence of CIDP, MMN, GBS, and MG
- Outline appropriate therapy based on disease course, therapeutic mechanisms, and safety and efficacy data
- Determine the appropriate timing, dosage, and duration of specific therapies used in the treatment of autoimmune muscular disease based on available evidence and expert opinion
Case 1—25-year-old Man With Flaccid Paralysis

- 25-year-old Caucasian man with a history of diarrheal illness 4–5 weeks ago who initially noted mild paresthesia in his feet

- Clinical course over the next 7 days was marked by:
  - History: Subacute onset of lower-extremity weakness > upper extremities
  - Physical exam:
    - Mild bilateral facial weakness, swallowing intact; symmetrical 1/5 strength in the IP and 0/5 in AT muscles; deltoid 3/5 and grip 1/5
    - Loss of deep tendon reflexes (DTRs)
    - Sensory exam within normal limits (WNL)
  - Cerebral spinal fluid (CSF): protein 40 mg/dL, <6 monocytes

IP=Ileopsoas; AT=anterior tibial; CSF=cerebrospinal fluid
Case 1—Nerve Conduction Study Results

<table>
<thead>
<tr>
<th>Nerve</th>
<th>Amplitude</th>
<th>Distal Latency</th>
<th>Duration</th>
<th>Conduction Velocity</th>
<th>F-wave Latency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sural</td>
<td>15 μV</td>
<td>3.9 ms</td>
<td></td>
<td>55 m/s</td>
<td></td>
</tr>
<tr>
<td>Peroneal Motor</td>
<td>NR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Sensory</td>
<td>20 μV</td>
<td>3.0 ms</td>
<td></td>
<td>52 m/s</td>
<td></td>
</tr>
<tr>
<td>Median Motor</td>
<td>5.0 mV 2.2</td>
<td>2.7 ms</td>
<td>8.5 ms 8.7</td>
<td>50 m/s</td>
<td>32 ms</td>
</tr>
<tr>
<td>Ulnar Motor</td>
<td>5.5 mV 4.2 3.2</td>
<td>4.2 ms</td>
<td>9.0 ms 10.0 10.2</td>
<td>48 m/s 45</td>
<td>28 ms</td>
</tr>
</tbody>
</table>
## GBS—Immunotherapy: A Systematic Review


<table>
<thead>
<tr>
<th>Therapy</th>
<th>Number of Trials</th>
<th>Number of Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PE</td>
<td>5</td>
<td>585</td>
<td>Patients improved at 4 weeks vs placebo</td>
</tr>
<tr>
<td>IVIG</td>
<td>5</td>
<td>582</td>
<td>Results similar to PE</td>
</tr>
<tr>
<td>PE followed by IVIG</td>
<td>1</td>
<td>148</td>
<td>No additional benefit</td>
</tr>
<tr>
<td>IVIG in children (open-label)</td>
<td>3</td>
<td>91</td>
<td>IVIG hastens improvement</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>6</td>
<td>587</td>
<td>Less improvement compared to no treatment</td>
</tr>
</tbody>
</table>
GBS—Why do some patients experience incomplete recovery after the standard dose of IVIG?

- IVIG clearance may play a role, or the dose may be suboptimal for certain patients
- Patients with small increase in serum IgG at 2 weeks had worse outcome; a second IVIG may be beneficial
- A controlled study (IVIG-SD) is in progress

GBS—IVIG vs Plasma Exchange vs Combination

- 383 patients
- 3-arm study
  - IVIG group (5 infusions of 0.4 g/kg)
  - Plasma exchange group (5 exchanges of 50 mL/kg)
  - Plasma exchange followed by IVIG group
- Benefit of IVIG=plasma exchange at 4 weeks
- Combination therapy no better than either treatment

GBS—Long-Term Prognosis

- 6- to 7-year long-term follow-up studies
- 20%–40% will continue to have some motor weakness
- An even greater percentage may still have sensory impairment

GBS—Long-term Functional Status

- n=42 vs age and sex-matched control population from southwestern Norway
- Mean follow-up 6.4 yrs
- Scores worse for GBS group
  - Pain VAS ($p<0.05$)
  - Disability rating index ($p<0.001$)
  - SF-36: physical function and general health domains ($p\leq0.02$)
  - Fatigue severity scale (NS)
- No difference for shorter (<6 yrs) vs longer follow-up since onset
- Correlations
  - Higher age at GBS onset and disability rating
  - Higher Hughes disability at onset and fatigue severity
- Over time, the social and emotional distress seen in short-term studies recedes
  - Adaptation to deficits
  - Recalibration of expectations

Case 2—25-year-old Man With Tingling in His Feet

- Patient from Case 1
- Clinical course over the next 4 wks was marked by:
  - Progressive lower-extremity weakness and facial numbness
- Physical and laboratory findings included:
  - Bilateral facial weakness; symmetrical lower extremity weakness, loss of DTRs; decreased large fiber sensory loss
  - NCV: prolonged DL, F waves; temporal dispersion CMAP
  - CSF: 85mg % protein <10 monocytes
- Treated for AIDP; initial improvement in strength and less numbness, but weaker 1 month later
- Time course: chronic, progressive
- Diagnostic considerations: chronic neuropathy
Classic CIDP—Diagnostic Criteria

- No universally accepted diagnostic criteria\(^1\text{–}^5\)
- No biomarker\(^1\)

1. **Clinical**
   - Motor/sensory impairment
   - Disease duration/progression (≥8 weeks)
   - Hyporeflexia/areflexia

2. **Electrophysiology**
   - Evidence for demyelination

3. **CSF analysis**

4. **Nerve biopsy**

5. **Additional potentially supportive evidence**
   - MRI
   - Response to immunomodulatory treatment

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CSF=cerebrospinal fluid; MRI=magnetic resonance imaging.

CIDP—Electrodiagnostic Criteria

- **Goal:** criteria to distinguish primary demyelination in chronic neuropathies
- **Many criteria:** 60%–70% sensitive to primary demyelination

CIDP—Electrodiagnostic Criteria (cont)

• Practical concepts
  – Slower than expected for level of axonal loss: >25% (<75% of LLN; >125% of ULN)
  – Evidence of primary demyelination

Image courtesy of Mark B. Bromberg, MD, PhD.
Patients with a chronic polyneuropathy, progressive for at least 8 weeks, would be classified as having CIDP if:

- No serum paraprotein and
- No documented genetic abnormality

AND EITHER

At least 75% of motor nerves had recordable responses AND one of the following conditions is satisfied according to AAN criteria:

- Abnormal distal latency in >50% of nerves or
- Abnormal motor conduction velocity in >50% of nerves or
- Abnormal F-wave latency in >50% of nerves

OR

- Symmetrical onset of motor symptoms
- Symmetrical weakness of 4 limbs and
- Proximal weakness in > or = 1 limb

CIDP—Evidence-Based Treatments

- IVIG: 2 g/kg as induction therapy
- Plasma exchange: 5–6 treatments
- Prednisone: 60–100 mg per day, followed by taper

The ICE Trial—Study Design

The ICE Trial—Effect of IVIG on QoL Scores

Lower Probability of Relapse With Continued IVIG-C Maintenance Therapy

Hazard ratio = 0.19; 95% CI = 0.05–0.70


Cl = confidence interval.
Acute CIDP—Need to Distinguish From Fluctuating GBS

- 16% of CIDP patients have rapidly progressive course, reaching nadir within 8 weeks
- 8%–16% of GBS patients have one or more deteriorations after initial treatment (treatment-related fluctuation [TRF])
- Treatment decisions differ: a patient with GBS-TRF requires repeat IVIG or plasmapheresis (PEx), whereas a patient with acute CIDP requires long-term maintenance with immunotherapies, including steroids

Acute CIDP vs Fluctuating GBS—Criteria

- Patients thought to have GBS should be considered to have acute CIDP if:
  - They deteriorate again after 8 weeks from onset or have more than 3 TRFs
  - They have no CN involvement
  - They have no autonomic symptoms
  - NCV is more compatible with CIDP

CIDP—Long-term Prognosis

- n=38 seen at Chiba University Hospital 1990–2000
  - Evaluated at least q2 mo; NCS at least annually
  - Hughes Grade 0–6

- Follow-up 5 yrs after therapy initiation
  - 89% corticosteroids
  - 45% IVIG
  - 34% PE
  - 5% AZA, 5% CTX
  - 58% combined therapy

- Outcomes
  - 26% complete remission (Hughes 0 >2 yrs)
  - 61% partial remission (Hughes 1 or 2; all ambulatory)
  - 13% nonambulatory or relapsing course (Hughes Grade ≥3; 1 death)

CIDP—Long-term Prognosis (cont)

- Hughes improvement ≥1 within 2 mo of initiation
  - 70% corticosteroids
  - 82% IVIG
  - 58% PE

- Complete remission, treatment (n=10)
  - 9 on corticosteroids
  - 1 on IVIG

- Ongoing treatment
  - 39% dependent on immunotherapies

CIDP—Long-term Prognosis (cont)

- Prognostic factors predicting complete remission
  - Subacute onset (Rx within 6 mo)
  - Symmetric symptoms
  - No atrophy
  - Distal nerve NCS abnormalities
  - Initial corticosteroid response

- Poor prognostic factors
  - Insidious onset
  - Asymmetric symptoms
  - CB or TD in intermediate segments (forearm or lower leg)
  - Absence of sural sparing

MMN—Clinical Features

- Male > female, 3:1
- Pattern of nerve involvement
- Upper extremity > lower extremity
- Motor conduction block in clinically involved nerves with normal SCV over the same segments
- May have some degree of abnormal temporal dispersion
- GM1 antibodies in some patients (60%)
- Focal motor conduction block (40%–50%) in 2 or more nerves, excluding common sites of nerve entrapment
- Normal sensory conduction across area of block
MMN—Treatment

- **IVIG**
  - Randomized controlled trials: positive effect
  - Effect is temporary and follow-up infusions needed
  - Frequency of monthly IVIG is individualized and quite predictable in a given patient
  - IVIG is the only drug that helps MMN

- **Other immunomodulating drugs**
  - Corticosteroids: ineffective
  - Plasma exchange: not effective
  - Mycophenolate: not effective
  - Cyclophosphamide: inconsistent responses
  - Rituximab: variable response

MMN—Long-term IVIG Issues

- Increased conduction block and axonal degeneration in prior IVIG studies with follow-up to 8 yrs
- n=10 pts with conduction block
- Mean age at onset 46 ± 8 yrs
- IVIG 2g/kg q4 wks x 3 mos followed by maintenance infusions
  - If no functional decline, monthly dose decreased by 0.4 gm/kg
  - If functional decline, monthly dose increased by 0.4 gm/kg
  - Over time, IVIG dose “gradually adjusted,” so no functional decline between infusions
  - Average maintenance IVIG dose: 1.63 g/kg
- Follow-up mean 7.25 yrs (3.5–12)

MG—Diagnostic Criteria

- Characterized by fluctuating and fatiguing weakness of bulbar, ocular, and skeletal muscles
- Repetitive nerve stimulation confirms defects in neuromuscular junction typical of MG
- SFEMG
- AChR antibodies
- MuSK antibodies

MG—Differential Diagnosis

- Lambert Eaton syndrome (LEMS)—a presynaptic disorder on the NMJ associated with Ab to voltage-gated calcium channels (clinical overlap with MG)
  - Small resting CMAP (>10%) decreasing with low Hz stimulation
  - Facilitation with activation
  - Initial decrement at 20–50 Hz followed by facilitation more than 200% (small muscle of hand)

- Others
  - Myasthenic crisis
  - Botulism
  - Congenital myasthenic syndromes

MG—Treatment: EFNS Consensus Criteria

- Anticholinesterase agents (pyridostigmine) for symptomatic relief
- Oral prednisone
- Immunosuppressants for steroid-sparing effect (azathioprine, mycophenolate mofetil, cyclosporine, tacrolimus, rituximab)
- Plasma exchange or IVIG (both effective) for a crisis, before thymectomy, for severe exacerbations, or in patients with inadequate response to other agents
  - IVIG is more accessible
  - Plasma exchange may work faster
- Removal of thymoma
  - Effect of thymectomy is being reconsidered but remains an option

MG—Treatment and Outcomes

n=470, 19 tertiary centers

Outcomes (mean follow-up 8 yrs, minimum 1 yr)
- Remission 30%
- Ocular 35%
- Generalized 35% (only 4% with moderate to severe disability)
- MGFA 0-II increased from 78.7% to 96.7% ($p<0.01$)

IS=immunosuppressant; Anti-AchE=cholinesterase inhibitor; MGFA=Myasthenia Gravis Foundation of America.

MG—Treatment and Outcomes (cont)

Summary of Key Points

• We have reviewed four disorders of the neuromuscular system that cause weakness—GBS, CIDP, MMN, and MG

• Diagnosis of individual cases requires analysis of features of the history and physical as well as laboratory findings

• Electrophysiological testing and interpretation are pivotal to the diagnosis of disorders that in many cases have no known specific diagnostic test or biological marker
Summary of Key Points (cont)

- Although PEx and IVIG may work to hasten recovery in GBS, corticosteroids are ineffective in GBS.
- PEx and IVIG are the only evidence-based treatments for CIDP, although prednisone is frequently used.
- MMN has proven efficacy to IVIG but is not responsive to PEx, and may be exacerbated by corticosteroids.
Summary of Key Points (cont)

- Evidence-based treatments for MG include anticholinesterase agents; oral prednisone; immunosuppressants for steroid-sparing; and PEx or IVIG, particularly for acute exacerbations.

- Some long-term challenges in the treatment of neuromuscular disease include:
  - GBS: Physical disability (20%), emotional and general health, and QoL.
  - CIDP: Treatment dependency in up to half of patients and significant physical disability in 20%.
  - MMN: IVIG dependency in the majority; need to refine IVIG dosing in settings of ongoing motor decline and axonal loss.
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