Improving CIDP diagnosis: The challenges of under and over diagnosis
Chronic inflammatory demyelinating polyneuropathy (CIDP)¹

Clinical features
- Relatively symmetric proximal and distal weakness and numbness
- Hyporeflexia or areflexia
- Evolving over >2 months in a progressive or relapsing pattern

Electrophysiologic features
- Evidence of peripheral nerve demyelination

Supporting data
- Cerebrospinal fluid (CSF): albuminocytologic dissociation
- Magnetic resonance imaging (MRI): nerve root enlargement or enhancement
- Histology: segmental demyelination or inflammation
- Clinical improvement with immunomodulating agents

Exclusionary
- None

Not all patients have “typical” CIDP\(^1\)


DADS: distal acquired demyelinating symmetric, CISP: chronic immune sensory polyradiculopathy
## CIDP: Other stuff happens...

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fatigue(^1)</td>
<td>Up to 65%</td>
<td>Can be hard to differentiate from weakness</td>
</tr>
<tr>
<td>Pain(^1)</td>
<td>Up to 39%</td>
<td>Can be moderate to severe</td>
</tr>
<tr>
<td>Tremor(^2)</td>
<td>Up to 58%</td>
<td></td>
</tr>
<tr>
<td>Autonomic dysfunction(^3,4)</td>
<td>Approximately 17–25%</td>
<td>Usually mild</td>
</tr>
<tr>
<td>Cranial nerve dysfunction(^5,6)</td>
<td>Approximately 5–17%</td>
<td>Facial nerve most common</td>
</tr>
<tr>
<td>Respiratory failure(^7)</td>
<td>Rare</td>
<td></td>
</tr>
</tbody>
</table>

---

Diagnostic confusion\textsuperscript{1,2}

- **Symptoms and Signs**
  - Electrophysiologic changes
    - CSF
    - MRI
    - Nerve biopsy
  - Response to treatment
  - Exclusionary factors

No reliable CIDP biologic markers

The sensitivity and specificity of the EFNS/PNS criteria was calculated including clinical, laboratory, and electrodiagnostic components. The results were as follows:

- **Sensitivity:** 73–91%
- **Specificity:** 66–88%

Is CIDP under diagnosis a problem?
CIDP disability

• Disability is common
  – 94 patients over mean 8.9 years¹
    • Rankin 4 or 5 (unable to lead an independent existence) at some stage during illness in 54%
    • Rankin 4 or 5 at prevalence date 13%
  – 267 patients with CIDP²
    • Mean Rankin at diagnosis 2.9
• Predictors of disability and poorer long-term prognosis³,⁴,⁵
  – Older age of onset
  – 4-limb weakness at onset
  – Progressive course
  – Prominent axonal loss on nerve biopsy or electrophysiology

<table>
<thead>
<tr>
<th>Modified Rankin Score⁶</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>

Opportunities for early diagnosis

- Failed opportunities to diagnose
  - CIDP might represent up to approximately 21% of initially undiagnosed neuropathies\(^1,2\)
  - Might account for up to 10% of all patients referred to neuromuscular clinics\(^3\)

- Delayed diagnosis is common
  - ICE trial: 38.4 months between symptom onset and diagnosis\(^4\)
  - Mayo: 10 months (range 2–64) symptom duration before presentation\(^5\)
  - Allen and Lewis: 11.4 months between symptom onset and diagnosis\(^6\)

References:
Consequences of under or delayed diagnosis

• CIDP is treatable\(^1\)
  – 56%–78% of patients respond to first-line treatment (IVIG, corticosteroids, plasma exchange)
  – Approximately 50% of non-responders benefit from switching between first-line therapies
  – Overall, approximately 80% of patients respond to one of the first-line therapies

• When diagnosis is delayed, treatment is delayed\(^2,3\)
  – Axon loss accumulates
  – Disability accumulates
  – Missed opportunity to prevent irreversible deficits

---

Under diagnosis of the “atypical” CIDP patient

<table>
<thead>
<tr>
<th>Features distinguishing “atypical” CIDP from length dependent axonal neuropathy</th>
<th>Sensory(^{1,2})</th>
<th>Motor(^{4,5})</th>
<th>Distal(^{6})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical:</strong></td>
<td>Sensory ataxia, generalized areflexia, cranial nerve involvement, rapid upper limb involvement, age at onset ≤55 yrs</td>
<td>Proximal and distal weakness with spared sensation</td>
<td>Sensory ataxia, distal large fiber sensory loss, relatively spared strength</td>
</tr>
<tr>
<td>NCS:</td>
<td>Normal or small sensory responses</td>
<td>Generalized demyelinating features in motor nerves</td>
<td>Slowed motor CV and markedly prolonged motor distal latencies</td>
</tr>
<tr>
<td>SSEP:</td>
<td>Prolongations</td>
<td>MRI nerve root enhancement/enlargement</td>
<td>CSF protein elevations</td>
</tr>
<tr>
<td>MRI:</td>
<td>Root enhancement/enlargement</td>
<td>CSF protein elevations</td>
<td>IgM gammopathy in 2/3rds (and MAG in 2/3rds of those)</td>
</tr>
<tr>
<td>CSF:</td>
<td>Protein elevations</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Might be 5\(\%\)–15% CIDP\(^{3,4}\)
Commonly referred to as CISP\(^2\)
Probably <6% of CIDP\(^4\)
Not well described\(^{4,5}\)
Commonly referred to as DADS\(^6\)

NCS: nerve conduction studies; SSEP: somatosensory evoked potential; CV: conduction velocity; MAG: myelin-associated glycoprotein

Summary: CIDP **under** diagnosis challenges

- **Diagnosis**
  - *Under* diagnosis of CIDP is a problem
  - Diagnosis is often delayed by a year or more
  - Patients with “atypical” features are probably more at risk for failed diagnosis
  - Delayed diagnosis results in missed opportunity to treat

- **Treatment**
  - Delayed treatment may result in axonal degeneration
  - Axonal degeneration leads to more disability
Is CIDP over diagnosis a problem?
Almost half (47%) of consecutive CIDP referrals (n=58) had an alternative diagnosis.

- Diabetic PN (11%)
- ALS (11%)
- Fibromyalgia (11%)
- Idiopathic SFN (11%)
- Hereditary (7.5%)
- Multifactorial (7.5%)
- MMN (7.5%)
- Alcohol (3.7%)
- Radiation plexopathy (3.7%)
- MAG (3.7%)
- IBM (3.7%)
- SMA (3.7%)
- MS (3.7%)
- Sarcoid (3.7%)
- SPS (3.7%)
- Psychogenic (3.7%)

ALS: amyotrophic lateral sclerosis; IBM: inclusion body myositis; MAG: myelin-associated glycoprotein; MMN: multifocal motor neuropathy; MS: multiple sclerosis; PN: polyneuropathy; SFN: small fiber neuropathy; SMA: spinal muscular atrophy; SPS: stiff person syndrome.

Clinical errors¹

- Liberal interpretation of “atypical” symptoms
- Failure to focus on symptoms and signs distinct to CIDP

<table>
<thead>
<tr>
<th></th>
<th>CIDP (n=31)</th>
<th>Not-CIDP (n=27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptom duration, months (SD, range)</td>
<td>72.3 (75.5, 6–252)</td>
<td>99.4 (72.6, 6–240)</td>
<td>0.16</td>
</tr>
<tr>
<td>Time since diagnosis, months (SD, range)</td>
<td>60.9 (70.2, 4–216)</td>
<td>36.0 (34.8, 6–120)</td>
<td>0.10</td>
</tr>
<tr>
<td>EFNS/PNS clinical criteria, any</td>
<td>100%</td>
<td>44%</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>EFNS/PNS clinical criteria, typical</td>
<td>80.6%</td>
<td>0%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Electrodiagnostic errors

39 total without CIDP¹

- 4 satisfied EFNS/PNS criteria
- 8 were normal
- 27 were abnormal

Four patterns²

1. Length-dependent axonal neuropathies
   • With mild or moderate CV slowing
2. Peroneal-EDB as the focal diagnostic abnormality
   • Often with mild to moderate CV slowing
3. Motor neuron disease
   • With mild CV slowing
4. Neuropathies limited to compressible sites
   • With focal slowing across those sites

Mild to moderate “demyelinating” features often observed within the primary pattern

<table>
<thead>
<tr>
<th>Re-classified diagnosis</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMN</td>
<td>2</td>
</tr>
<tr>
<td>MAG-associated neuropathy</td>
<td>1</td>
</tr>
<tr>
<td>Hereditary neuropathy</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Re-classified diagnosis</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small fiber neuropathy</td>
<td>3</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>1</td>
</tr>
<tr>
<td>Stiff-person syndrome</td>
<td>1</td>
</tr>
<tr>
<td>Remote GBS</td>
<td>1</td>
</tr>
<tr>
<td>Multifactorial</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
</tbody>
</table>

¹ Allen JA and Lewis RA. Manuscript in preparation.
Data interpretation errors

- Overstated importance on mild or moderate CSF protein elevations

<table>
<thead>
<tr>
<th></th>
<th>CIDP (n=31)</th>
<th>Not CIDP (n=27)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF cytoalbuminologic dissociation</td>
<td>90.3% (n=31)</td>
<td>50.0% (n=20)</td>
<td>0.02</td>
</tr>
<tr>
<td>CSF protein mg/dl, mean (SD, range)</td>
<td>156.3 (130.5, 33–550)</td>
<td>61.4 (30.7, 18–128)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

Interpreting the treatment response

- Most patients feel better when given IVIG or corticosteroids
- Treatment response rarely defined by objective efficacy measures

<table>
<thead>
<tr>
<th>Response to any immunotherapy</th>
<th>CIDP</th>
<th>Not-CIDP</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjective improvement, probable or definite (%)</td>
<td>89.6% (n=29)</td>
<td>85.7% (n=21)</td>
<td>0.69</td>
</tr>
<tr>
<td>Strength/sensation improvement, definite (%)</td>
<td>68.9%</td>
<td>19.0%</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment duration</th>
<th>CIDP</th>
<th>Not-CIDP</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIG duration, months (average, range)</td>
<td>41.5 (3–144)</td>
<td>18.6 (3–60)</td>
<td>0.04</td>
</tr>
<tr>
<td>IVIG frequency, weeks (average, range)</td>
<td>3.1 (1–6)</td>
<td>3.62 (1–8)</td>
<td>0.18</td>
</tr>
<tr>
<td>IVIG dose per month, g/kg (average, range)</td>
<td>1.16 (0.3–2)</td>
<td>1.15 (0.2–4)</td>
<td>0.93</td>
</tr>
<tr>
<td>Corticosteroid duration, months (average, range)</td>
<td>22.4 (3–132)</td>
<td>16.2 (3–48)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Summary: CIDP over diagnosis challenges

• Diagnosis
  – Over diagnosis of CIDP is a problem
    • Exposes individuals and society to medical adverse events and financial challenges
  – Patients with “atypical” features are at higher risk for over diagnosis
    • Absent clinical features of CISP
    • Absent electrodiagnostic support
    • Absent CSF, MRI, SSEP, or nerve biopsy support

• Treatment
  – Most patients without CIDP feel better after treatment
    • Can lead to long-term immunotherapy with perpetuation of wrong diagnosis
    • Does not necessarily mean the neuropathy is improved
  – Objective indicators of improvement might help
    • Define the treatment response
    • Especially useful during treatment trials of unconfirmed disease
1. There is no single diagnostic test for CIDP

2. CIDP under diagnosis:
   - Is common
   - May lead to irreversible disability
   - Increases with atypical variants

3. CIDP over diagnosis:
   - Is common
   - Exposes patients to unnecessary risks and cost
   - Increases with atypical features

• Utilizing existing diagnostic criteria can improve diagnosis

• Recognize atypical features
• Push the work up when uncertain

• Recognize potential areas of diagnostic vulnerability
• Use objective measures of treatment response to guide treatment decisions