The clinical spectrum of chronic inflammatory neuropathies

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Disclosures

Consultancies for

- Baxter
- CSL Behring
- Grifols
- LFB
- Novartis

Member of

- Editorial Board Cochrane Neuromuscular Disease Group

Learning Objectives

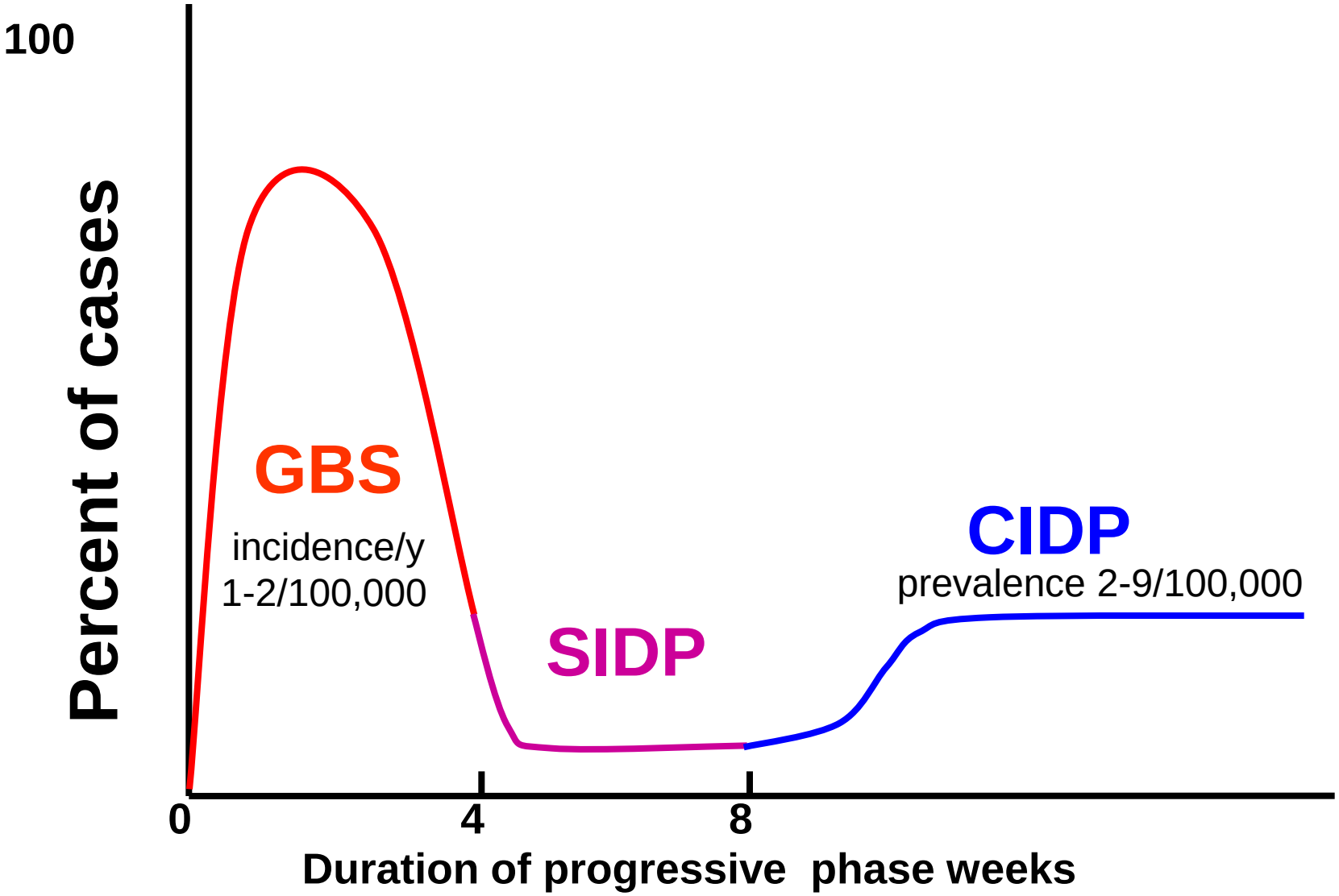
To be able to

- Recognise the spectrum from GBS to CIDP
- Distinguish CIDP subtypes
- Recognise their important differential diagnoses
- Plan their investigation

Key messages

- Recurrent GBS: if >2 relapses; >9 weeks from onset CIDP more likely
- CIDP has a wide spectrum:
  - symmetrical vs asymmetrical
  - mixed vs motor vs sensory
- Paraprotein may indicate special pathology
  - anti-MAG, POEMS, CANOMAD
- Red flags: distal, pain, autonomic, pure motor

Spectrum GBS to CIDP



Subacute inflammatory demyelinating polyradiculoneuropathy

- Nadir 4 – 8 weeks
- Frequent preceding infection
- Demyelinating neurophysiology
- No other cause
- CSF protein raised in 19/21
- Macrophage associated demyelination
- Complete recovery in 18/23 with no Rx or steroids

Hughes R et al. Arch Neurol 1992 49 612-16 7 cases
Oh SJ et al. Neurology 2003 61 1507-12 16 cases

Acute onset CIDP

Differentiating recurrent GBS from acute onset CIDP

Ruts 2010 Neurology 74 1680

	GBS-TRF (n = 16)	A-CIDP (n = 8)	p Value
Course			
Days to reach nadir, median (95% CI)[a]	8.5 (6–11)	16.5 (5–22)	0.03
Days to reach first TRF/exacerbation, median (95% CI)[a]	18 (15–27)	51 (31–63)	0.00
Number			
>2 TRFs/exacerbations, n (%)[f]	0	4 (50)	0.01
Severity			
GBS disability score ≤2 at nadir, n (%)	0	5 (63)	0.00
MRC sumscore at nadir, median (95% CI)	42 (26–48)	49 (46–54)	0.01
GBS disability score ≤2 at first TRF/exacerbation, n (%)	0	4 (50)	0.01
MRC sumscore at first TRF/exacerbation, median (95% CI)	31 (10–40)[c]	50 (45–52)[g]	0.00
Ventilatory support after onset of disease, n (%)	7 (44)	0 (0)	0.05

CIDP definition

European Journal of Neurology 2010, **17:** 356–363

EFNS TASK FORCE/CME ARTICLE

	Viala et al 2010 JPNS 15 50	Kuwabara 2014
• **Typical**	51%	60%
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		
• **Atypical**		
– Distal (DADS)		8%
– Pure motor	10%	0%
– Pure sensory	35%	1%
– Multifocal (Lewis-Sumner syndrome)	15%	34%
– Focal		
– CNS involvement		

EFNS PNS CIDP definition

2. Exclusion criteria

1. *Borrelia burgdorferi* infection
2. Diphtheria, drug or toxin exposure
3. Hereditary demyelinating neuropathy
4. Prominent sphincter disturbance
5. MMN
6. IgM monoclonal gammopathy with MAG antibodies
7. Other causes including POEMS syndrome, osteosclerotic myeloma, diabetic and non-diabetic lumbosacral radiculoplexus neuropathy, PNS lymphoma and amyloidosis

EFNS PNS electrodiagnosis 1
The rules

To apply these criteria, the median, ulnar (stimulated below the elbow), peroneal (stimulated below the fibular head), and tibial nerves on one side are tested. If criteria are not fulfilled, the same nerves tested on the other side, and/or the ulnar and median nerves are stimulated bilaterally at the axilla and at Erb's point.

Motor conduction block is not considered in the ulnar nerve across the elbow and at least 50% amplitude reduction between Erb's point and the wrist is required for probable conduction block.

Temperatures maintained to at least 33◦C at the palm and 30◦C at the external malleolus

EFNS PNS electrodiagnosis 2

1. Definite: at least one of the following

(a) Motor distal latency prolongation ≥50% above ULN in two nerves (excluding median neuropathy at the wrist from carpal tunnel syndrome), or

(b) Reduction of motor conduction velocity ≥30% below LLN in two nerves, or

(c) Prolongation of F-wave latency ≥30% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP <80% of LLN values), or

(d) Absence of F-waves in two nerves if these nerves have distal negative peak CMAP amplitudes ≥20% of LLN + ≥1 other demyelinating parameter in ≥1 other nerve, or

EFNS PNS electrodiagnosis 3

(e) Partial motor conduction block: ≥50% amplitude reduction of the proximal negative peak CMAP relative to distal, if distal negative peak CMAP ≥ 20% of LLN, in two nerves, or in one nerve + ≥1 other demyelinating parameter in ≥1 other nerve, or

(f) Abnormal temporal dispersion (>30% duration increase between the proximal and distal negative peak CMAP) in ≥2 nerves, or

(g) Distal CMAP duration (interval between onset of the first negative peak and return to baseline of the last negative peak) increase in ≥1 nerve (median ≥ 6.6 ms, ulnar ≥ 6.7 ms, peroneal ≥ 7.6 ms, tibial ≥ 8.8 ms) + ≥1 other demyelinating parameter in ≥1 other nerve

EFNS PNS electrodiagnosis 4

2. Probable

≥30% ampl reduction of prox negative peak CMAP relative to distal, excl post tibial, if distal negative peak CMAP ≥ 20% of LLN, in two nerves,

or in one nerve + ≥1 other demyelinating parameter in ≥1 other nerve

3. Possible

As in 1 but in only one nerve

Supportive Criteria

1. **Elevated CSF protein** with leukocyte count <10/mm3

2. **MRI** showing **gadolinium enhancement** and/or **hypertrophy** of cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses

3. **Abnormal sensory electrophysiology in at least one nerve**:

a. Normal sural with abnormal median (excluding median neuropathy at the wrist from carpal tunnel syndrome) or radial SNAP amplitudes; or

b. Conduction velocity <80% of LLN (<70% if SNAP amplitude <80% of LLN); or

c. Delayed SEPs without CNS disease

4. Objective **clinical improvement following immunomodulatory** treatment

5. **Nerve biopsy** showing **demyelination and/or remyelination** by EM or teased fiber

Diagnostic categories

Definite CIDP

- **Clinical** criteria with **electrodiagnostic** criterion **1**; or
- **Probable** CIDP **+** at least **one supportive** criterion; or
- **Possible** CIDP **+** at least **two supportive** criteria

Probable CIDP

- **Clinical** criteria with **electrodiagnostic** criterion **2**; or
- **Possible** CIDP **+** at least **one supportive** criterion

Possible CIDP

- **Clinical** criteria with **electrodiagnostic** criterion **3**
- CIDP (**definite, probable, possible**) associated with **concomitant diseases**

Chronic immune sensory polyradiculopathy

Sinnreich et al 2004 Neurology 63 1662

- 66-year-old woman with 10 year history of progressive numbness up to hips and gait ataxia needing sticks
- normal strength hypo/areflexia absent vibration and position sense in lower limbs.
- Motor and sensory nerve conduction normal
- Tibial SSEPs delayed scalp responses with absent cervical and lumbar responses.
- CSF protein 1.03 g/l
- MRI hypertrophic nerve roots
- Thoracic dorsal root biopsy loss of large myelinated fibres endoneurial macrophages and onion bulbs
- Marked response to IVIg

Differential diagnosis

- Chronic idiopathic axonal neuropathy
- Diabetic lumbosacral radiculoplexus neuropathy
- Paraproteinaemic demyelinating neuropathy
- Multifocal motor neuropathy
- Lyme disease
- Vasculitic neuropathy
- Lymphoma
- Amyloid neuropathy
- Genetic neuropathies

Diagnosis changed in
5 of 40 in Dyck 1982 prednisone trial
7 of 41 in PREDICT 2010 steroid trial

Neligan, Reilly and Lunn 2014 CIDP: mimics and chameleons Practical Neurology 14 399 - 408

Genetic mimics

- GJB1 mutations CMT1X
- Transthyretin familial amyloid polyneuropathy
- CMT4C SH3TC2 mutations
- CMT4J FIG4 mutations
- HSAN1 SPTLC1
- CMT1A
- HNPP
- GDAP1
- MNGIE and other mitochondrial disorders

Neligan Reilly and Lunn 2014 Practical Neurology

Multifocal motor neuropathy

Diagnostic criteria

van Schaik et al. 2010 EFNS guideline

Core criteria (both must be present)

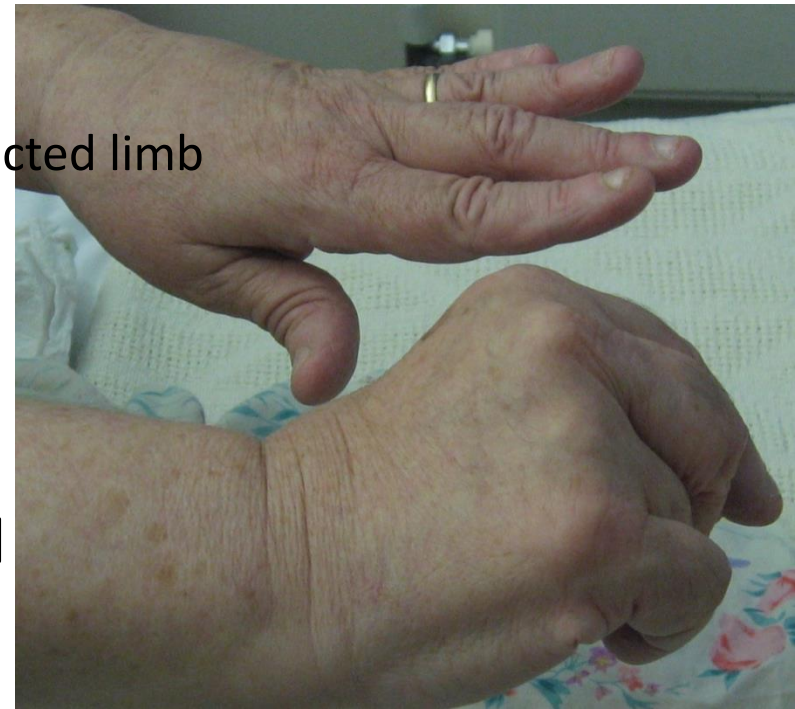
- Slowly progressive or stepwise progressive, asymmetric limb weakness (usually upper limb), or motor involvement of => 2 nerves, for > 1 month
- No objective sensory abnormality except minor VS in legs

Supportive clinical criteria

- Predominant upper limb involvement
- Decreased or absent tendon reflexes in affected limb
- Absence of cranial nerve involvement
- Cramps and fasciculations in affected limb

Neurophysiological criteria

[Antibodies to ganglioside GM1 in about 50%]

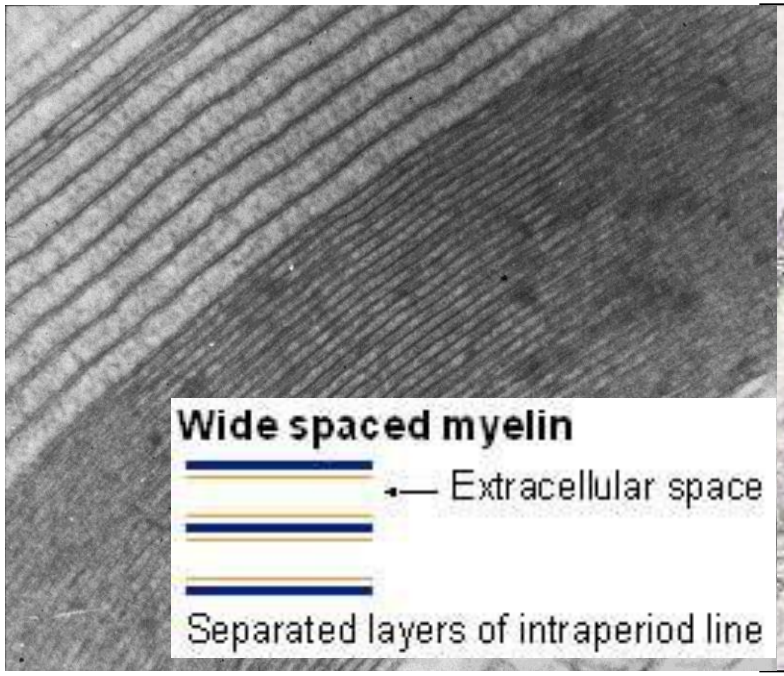


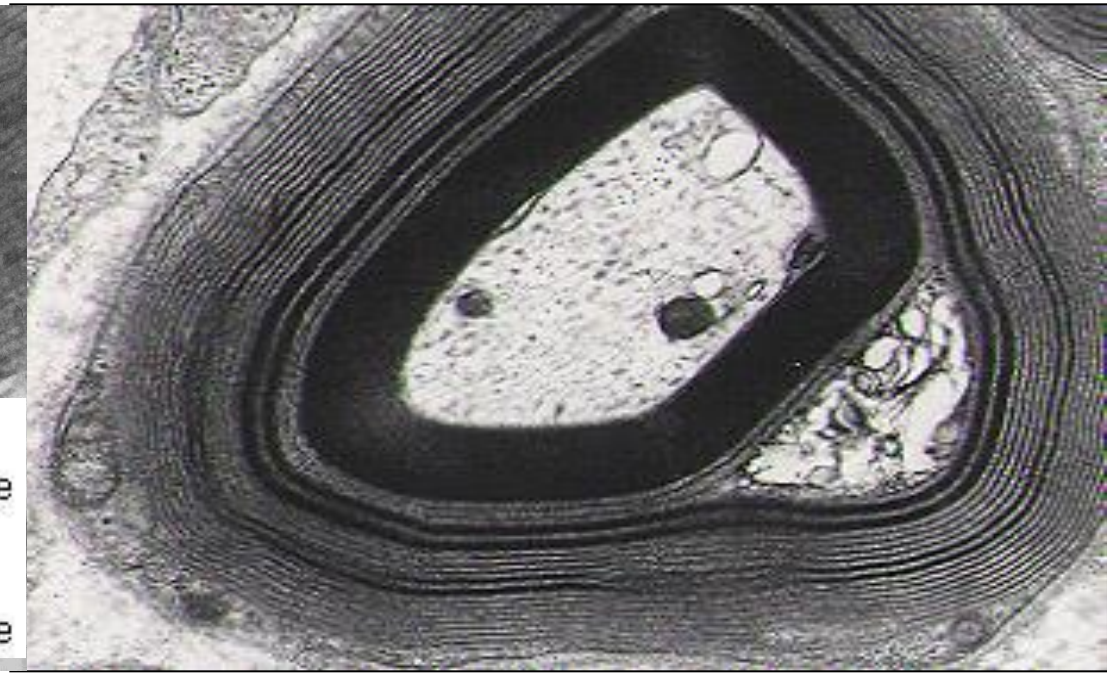
Paraprotein associated neuropathies

- CIDP with coincidental MGUS: IgG, IgA, (IgM)
- IgM paraprotein-associated demyelinating neuropathy with antibodies to myelin associated glycoprotein
- POEMS syndrome
- CANOMAD
- AL amyloid neuropathy

IgM paraproteinaemic demyelinating neuropathy and anti-myelin associated glycoprotein antibodies

Latov and others 1980 Plasma-cell dyscrasia and peripheral neuropathy with a monoclonal antibody to peripheral-nerve myelin NEJM 303 618





- Injection of anti-MAG IgM into chicks produces widely spaced myelin and demyelination Tatum and into nerves produces demyelination Willison

POEMS

Polyneuropathy - Organomegaly - Endocrinopathy - M Protein - Skin changes

Dispenzieri 2014 Am J Hem 89 2 214

Two mandatory major criteria

Polyneuropathy (typically demyelinating)

Monoclonal plasma cell-proliferative disorder (almost always λ)

and one of three major criteria

Castleman disease

Sclerotic bone lesions

VEGF elevation

Chronic ataxic neuropathy, ophthalmoplegia, IgM paraprotein, cold agglutinins and disialosyl antibodies (CANOMAD)

Ilyas et al 1985 Ann Neurol 18 655; Willison et al 1994 Neurology 44 2395
Willison et al 2001 Brain 124 1968

- Chronic sensory ataxia, ophthalmoplegia in 16/18, bulbar signs
- IgM paraprotein
- Cold agglutinins
- Antibodies to GDlb, GD3, GTlb and GQlb
- Response to IVIg (case reports)

Planning investigation

see differential diagnosis

Red flags

- Predominantly distal
- Pain
- Autonomic involvement
- Pure motor
- Diabetes
- Lack of treatment response

Investigations

- Neurophysiology
- Family history
- Glucose tolerance
- CSF
- Detection of M protein
- Bone imaging

- Nerve biopsy

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