PolyNeuro exchange

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

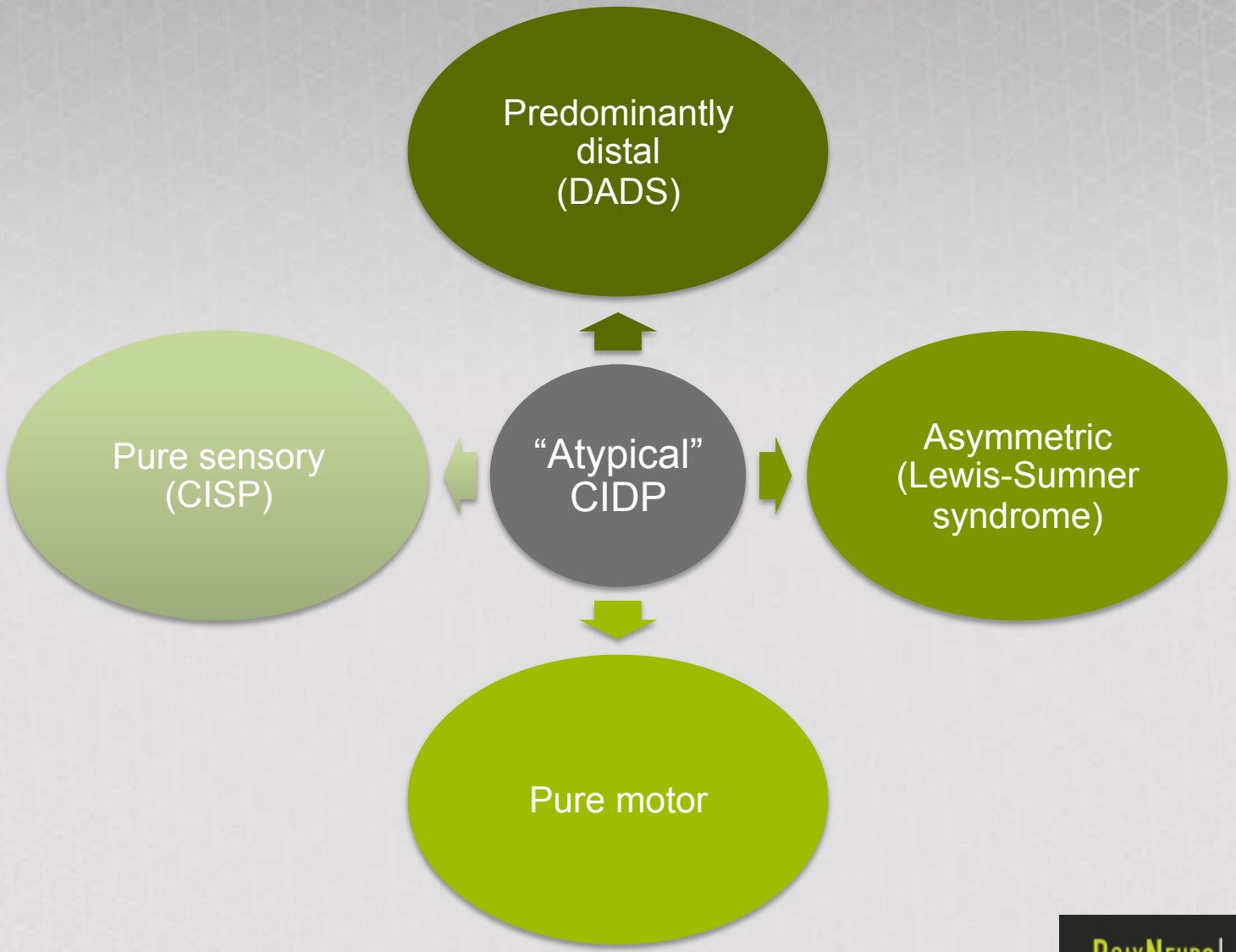
- Cerebrospinal fluid (CSF): albuminocytologic dissociation
- Magnetic resonance imaging (MRI): nerve root enlargement or enhancement
- Histology: segmental demyelination or inflammation
- Clinical improvement with immunomodulating agents

Exclusionary

- None

1. Joint Task Force of EFNS and the PNS. J Peripher Nerv Syst. 2010;15(3):185–195.

Not all patients have “typical” CIDP[1]



DADS: distal acquired demyelinating symmetric, CISP: chronic immune sensory polyradiculopathy

1. Joint Task Force of EFNS and the PNS. J Peripher Nerv Syst. 2010;15(3):185–195.

CIDP: Other stuff happens…

Symptom	Frequency	Comment
Fatigue[1]	Up to 65%	Can be hard to differentiate from weakness
Pain[1]	Up to 39%	Can be moderate to severe
Tremor[2]	Up to 58%	
Autonomic dysfunction[3,4]	Approximately 17–25%	Usually mild
Cranial nerve dysfunction[5,6]	Approximately 5–17%	Facial nerve most common
Respiratory failure[7]	Rare	

1. Rajabally YA *et al*. Neurodegener Dis Manag. 2015;5(3):257–268.
2. Saifee TA *et al*. J Neurol Neurosurg Psychiatry. 2013;84(11):1282–1287.
3. Figueroa JJ *et al*. Neurology. 2012;78(10):702–708.
4. Sakakibara R *et al*. Neurology. 1998;50(4):1179–1182.
5. Busby M, Donaghy M. J Neurol. 2003;250(6):714–724.
6. Rotta RT *et al*. J Neurol Sci. 2000;173(2):129–139.
7. Dimachkie MM, Barohn RJ. Curr Treat Options Neurol. 2013;15(3):350–366.

Diagnostic confusion[1,2]

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

No reliable CIDP biologic markers

1. Joint Task Force of EFNS and the PNS. J Peripher Nerv Syst. 2010;15(3):185–195.
2. Brannagan TH 3rd. J Peripher Nerv Syst. 2011;16(Suppl 1):3–13.

CIDP criteria sensitivity and specificity

European Journal of Neurology 2010, 17: 356–363 doi:10.1111/j.1468-1331.2009.02930.x

EFNS TASK FORCE/CME ARTICLE

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

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Keywords:
chronic inflammatory demyelinating polyradiculoneuropathy, definition, diagnosis, guidelines, treatment

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Background: Consensus guidelines on the definition, investigation, and treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) have been previously published in *European Journal of Neurology* and *Journal of the Peripheral Nervous System*.

Objectives: To revise these guidelines.

Methods: Disease experts, including a representative of patients, considered references retrieved from MEDLINE and Cochrane Systematic Reviews published between August 2004 and July 2009 and prepared statements that were agreed in an iterative fashion.

Recommendations: The Task Force agreed on Good Practice Points to define clinical and electrophysiological diagnostic criteria for CIDP with or without concomitant diseases and investigations to be considered. The principal treatment recommendations were: (i) intravenous immunoglobulin (IVIg) (Recommendation Level A) or corticosteroids (Recommendation Level C) should be considered in sensory and motor CIDP; (ii) IVIg should be considered as the initial treatment in pure motor CIDP (Good Practice Point); (iii) if IVIg and corticosteroids are ineffective, plasma exchange (PE) should be considered (Recommendation Level A); (iv) if the response is inadequate or the maintenance doses of the initial treatment are high, combination treatments or adding an immunosuppressant or immunomodulatory drug should be considered (Good Practice Point); (v) symptomatic treatment and multidisciplinary management should be considered (Good Practice Point).

- The sensitivity and specificity of the EFNS/PNS criteria was calculated including clinical, laboratory, and electrodiagnostic components. The results were as follows:[1]
  - Sensitivity: 73–91%
  - Specificity: 66–88%

EFNS/PNS: European Federation of Neurological Societies/Peripheral Nerve Society

1. Breiner A, Brannagan TH 3rd. Muscle Nerve. 2014;50(1):40–46.

Is CIDP under diagnosis a problem?

CIDP disability

- Disability is common
  - 94 patients over mean 8.9 years[1]
    - 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 CIDP[2]
    - Mean Rankin at diagnosis 2.9
- Predictors of disability and poorer long-term prognosis[3,4,5]
  - Older age of onset
  - 4-limb weakness at onset
  - Progressive course
  - Prominent axonal loss on nerve biopsy or electrophysiology

Modified Rankin Score[6]	
Score	**Description**
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

1. Lunn MP *et al*. J Neurol Neurosurg Psychiatry. 1999;66(5):677–680.
2. Cocito D *et al*. Eur J Neurol. 2010;17(2):289–294.
3. Bouchard C *et al*. Neurology. 1999;52(3):498–503.
4. Simmons Z *et al*. Brain. 1995;118(Pt 2):359–368.
5. Sghirlanzoni A *et al*. Neurol Sci. 2000;21(1):31–37.
6. Modified Rankin Score (MRS). Available at: http://www.strokecenter.org/wp-content/uploads/2011/08/modified_rankin.pdf. Accessed Mar 2016.

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]

1. Dyck PJ *et al*. Ann Neurol. 1981;10(3):222–226.
2. Dimachkie MM, Barohn RJ. Curr Treat Options Neurol. 2013;15(3):350–366.
3. Barohn RJ, Saperstein DS. Semin Neurol. 1998;18(1):49–61.
4. Hughes RA *et al*. Lancet Neurol. 2008; 7(2):136–144.
5. Laughlin RS *et al*. Neurology. 2009;73(1):39–45.
6. Allen JA and Lewis RA. Neurology. 2015;85(6):498–504.

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

1. Cocito D et al. Eur J Neurol. 2010;17(2):289–294.
2. Allen JA and Lewis RA. Neurology. 2015;85(6):498–504.
3. Bouchard C *et al*. Neurology. 1999;52(3):498–503.

Under diagnosis of the "atypical" CIDP patient

Features distinguishing "atypical" CIDP from length dependent axonal neuropathy		
Sensory[1,2]	Clinical: Sensory ataxia, generalized areflexia, cranial nerve involvement, rapid upper limb involvement, age at onset ≤55 yrs	Might be 5–15% CIDP[3,4] Commonly referred to as CISP[2]
	NCS: normal or small sensory responses SSEP prolongations MRI root enhancement/enlargement CSF protein elevations	
Motor[4,5]	Clinical: Proximal and distal weakness with spared sensation	Probably <6% of CIDP[4] Not well described[4,5]
	NCS: Generalized demyelinating features in motor nerves MRI nerve root enhancement/enlargement CSF protein elevations	
Distal[6]	Clinical: Sensory ataxia, distal large fiber sensory loss, relatively spared strength	Commonly referred to as DADS[6]
	NCS: slowed motor CV and markedly prolonged motor distal latencies CSF protein elevations IgM gammopathy in 2/3rds (and MAG in 2/3rds of those)	

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

1. Ayrignac X. Muscle Nerve. 2013;48(5):727–732.
2. Sinnreich M *et al*. Neurology. 2004;63(9):1662–1669.
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4. Busby M, Donaghy M. J Neurol. 2003;250(6):714–724.
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6. Katz JS *et al*. Neurology. 2000;54(3):615–620.

Summary: CIDP under diagnosis challenges

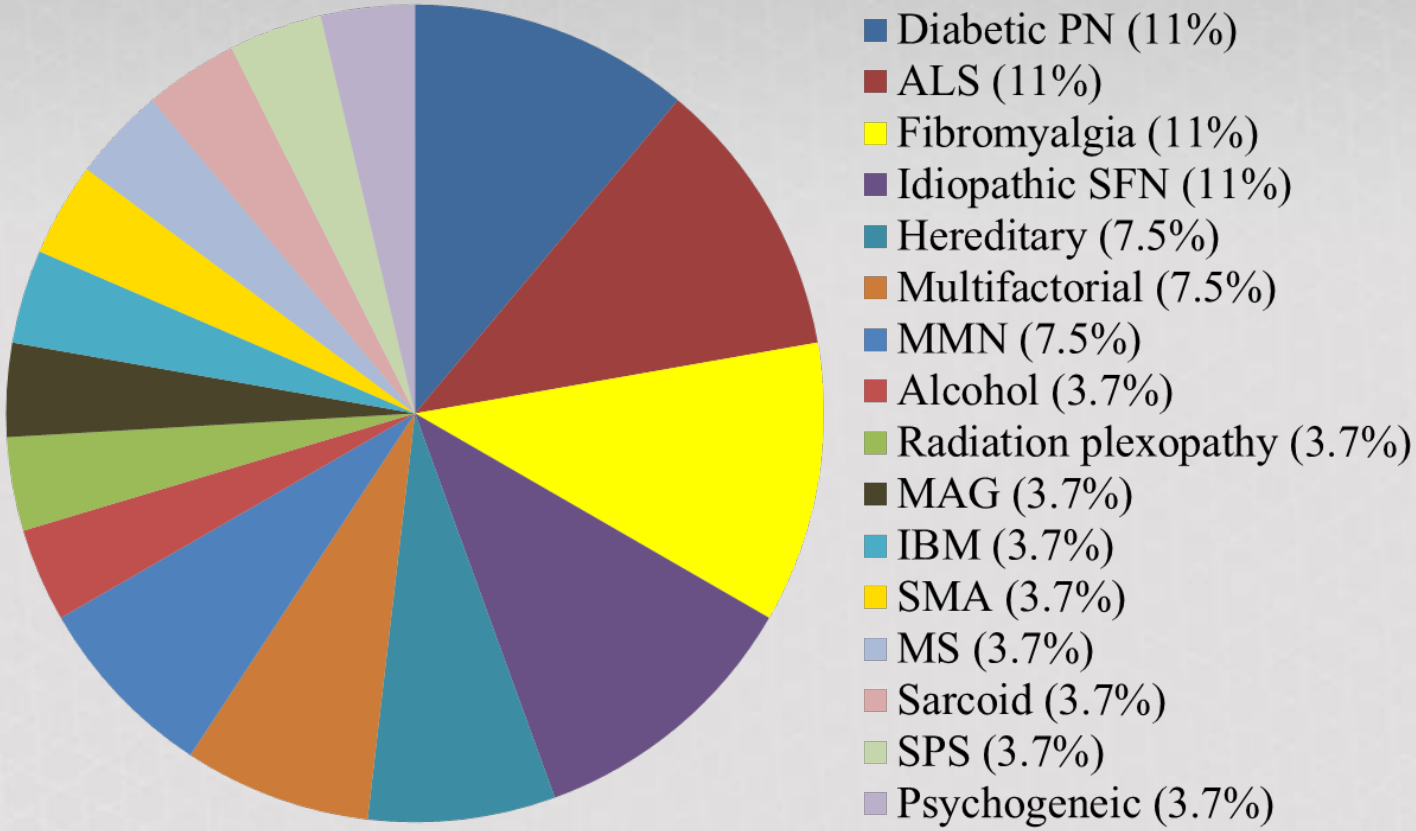
- Diagnosis
  - Under diagnosis of CIDP is a problem
  - Diagnosis is often delayed by a year or more
  - Patients with “atypical” features are probably more at risk for failed diagnosis
  - Delayed diagnosis results in missed opportunity to treat

- Treatment
  - Delayed treatment may result in axonal degeneration
  - Axonal degeneration leads to more disability

Is CIDP over diagnosis a problem?

Alternative diagnosis for patients without CIDP[1]

- Almost half (47%) of consecutive CIDP referrals (n=58) had an alternative diagnosis



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.

1. Allen JA and Lewis RA. Neurology. 2015;85(6):498–504.

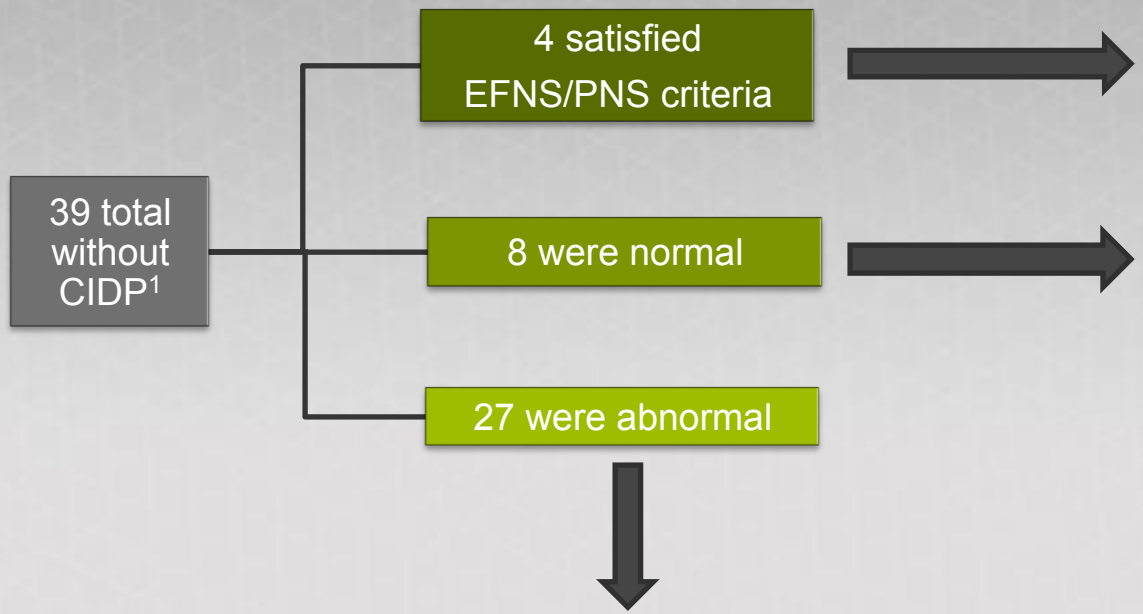
Clinical errors[1]

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

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

1. Allen JA and Lewis RA. Neurology. 2015;85(6):498–504.

Electrodiagnostic errors



Re-classified diagnosis	Number
MMN	2
MAG-associated neuropathy	1
Hereditary neuropathy	1

Re-classified diagnosis	Number
Small fiber neuropathy	3
Fibromyalgia	1
Stiff-person syndrome	1
Remote GBS	1
Multifactorial	1
Unknown	1

Four patterns[2]

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

1. Allen JA and Lewis RA. Manuscript in preparation.
2. Allen JA and Lewis RA. Neurology. 2015;85(6):498–504.

Data interpretation errors[1]

- Overstated importance on mild or moderate CSF protein elevations

	CIDP (n=31)	Not CIDP (n=27)	P-value
CSF cytoalbuminologic dissociation	90.3% (n=31)	50.0% (n=20)	0.02
CSF protein mg/dl, mean (SD, range)	156.3 (130.5, 33–550)	61.4 (30.7, 18–128)	<0.01

1. Allen JA and Lewis RA. Neurology. 2015;85(6):498–504.

Interpreting the treatment response[1]

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

Response to any immunotherapy	CIDP	Not-CIDP	P-value
Subjective improvement, probable or definite (%)	89.6% (n=29)	85.7% (n=21)	0.69
Strength/sensation improvement, definite (%)	68.9%	19.0%	<0.01

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

1. Allen JA and Lewis RA. Neurology. 2015;85(6):498–504.

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

CIDP diagnosis: We can do better

1. There is no single diagnostic test for CIDP

→

- Utilizing existing diagnostic criteria can improve diagnosis

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

→

- Recognize atypical features
- Push the work up when uncertain

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

→

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