Taking the ‘Mis’- out of the Misdiagnosis of CIDP

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Disclosures

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Overview

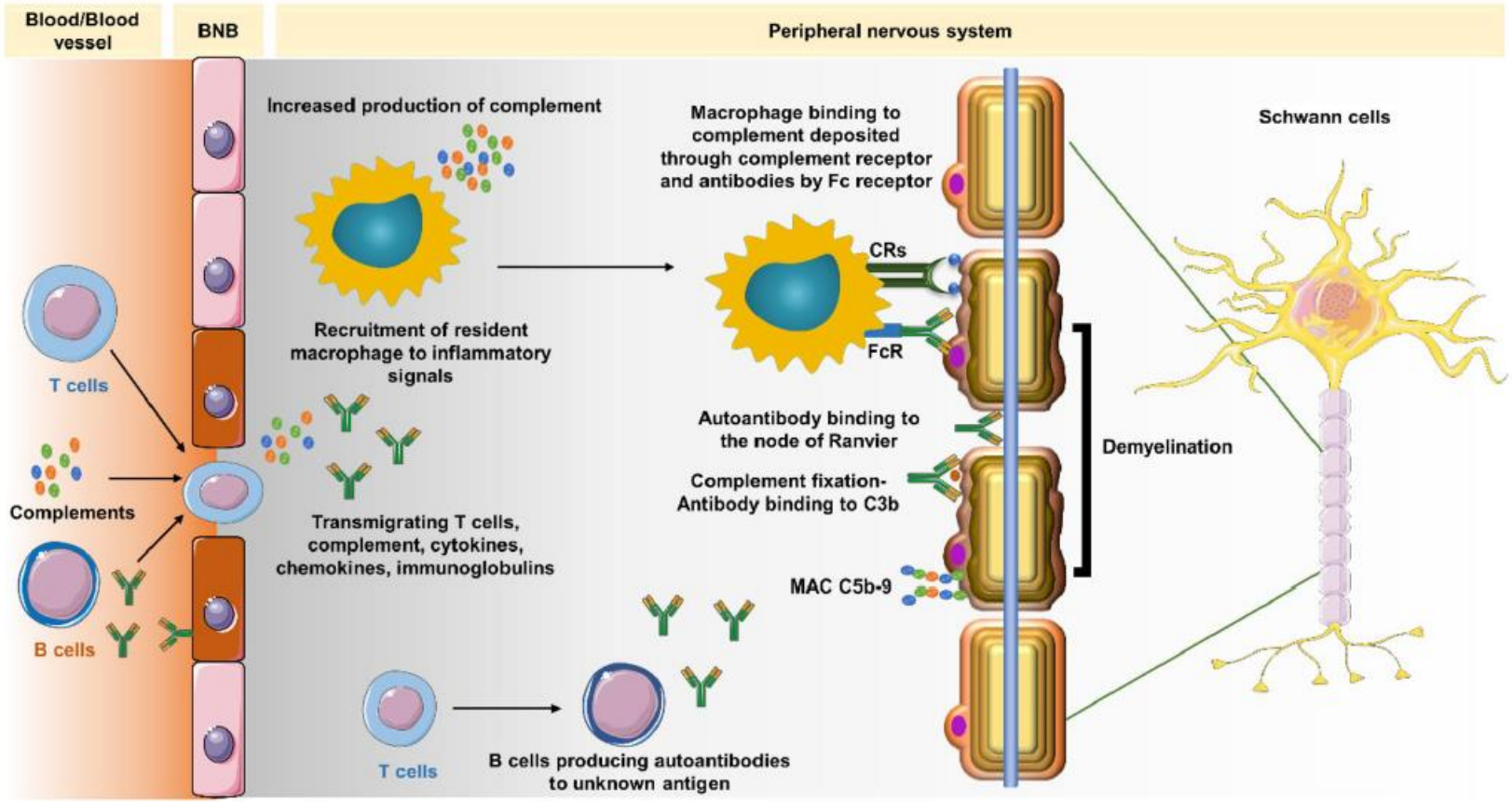
- Epidemiology, Definitions, Clinical Burden, and Rate of Misdiagnosis
- Overview of updated EAN/PNS diagnostic criteria
- Key history and neurological examination elements raising suspicion
- Recommended electrodiagnostic testing
- Differential diagnoses of CIDP variants based on electrodiagnostic and supportive criteria
- Common diagnostic pitfalls and strategies for avoidance

CIDP Epidemiology

- Incidence: 0.2 to 1.6 per 100,000/year
- Prevalence: 0.8 to 8.9 per 100,000/year
- Median age of onset: 40-60 years
- Men : women = 2:1

RS Laughlin et al. Neurology 2009

Pathophysiology of CIDP



Querol L. et al. The Role of Complement System in CIDP. Neurotherapeutics. 2022.

“Typical” CIDP

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

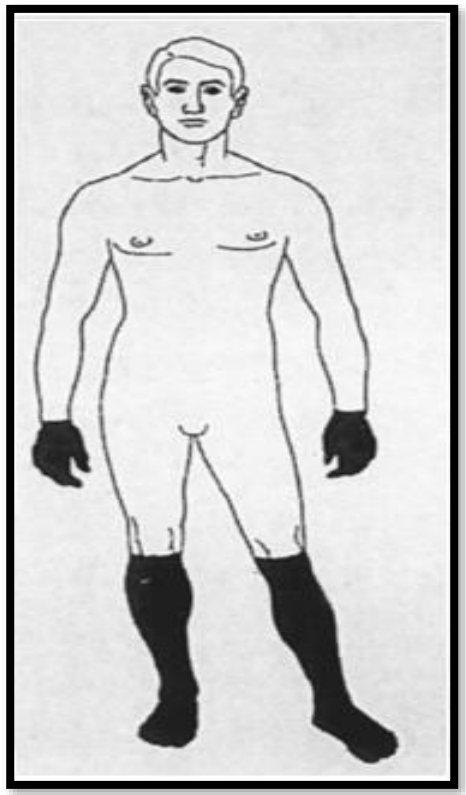
- Electrophysiologic features:
  - Evidence of peripheral nerve demyelination

- Supportive data:
  - CSF: Albuminocytologic dissociation
  - MRI/Ultrasound: Nerve root enlargement or enhancement, focal cross sectional area enlargement
  - Histology: Segmental demyelination or inflammation
  - Clinical improvement with immunomodulating agents

- Exclusionary: No hereditary neuropathy, malignancy, MAG, MMN, or other explanation

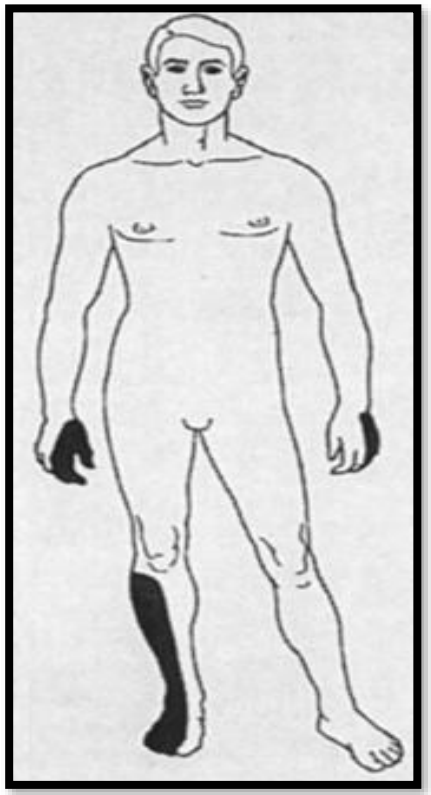
CIDP Variants

Still considered CIDP but with different features



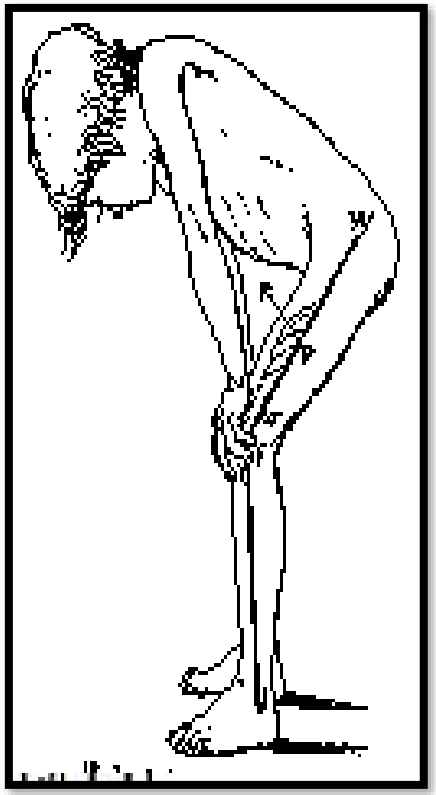
Distal [1]

Distal acquired demyelinating symmetric or DADS

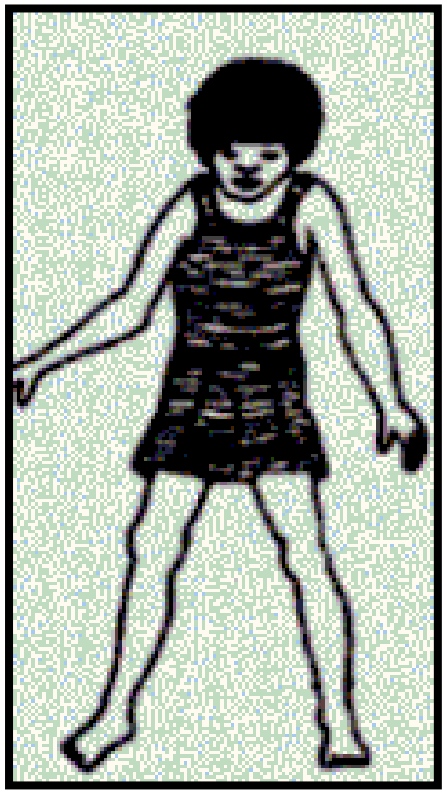


Multifocal [2]

Lewis-Sumner or MADSAM



Pure motor [3]



Pure sensory [4]

Chronic immune sensory polyradiculopathy

1. Katz JS et al. Neurology 2000:54;615–620. 2. Lewis RA et al. Neurology 1982:32;958–964.
3. Nobile-Orazio E. J Peripher Nerv Syst. 2014 Mar;19(1):2-13. 4. Sinnreich M et al. Neurology 2004: 63:1662–1669.

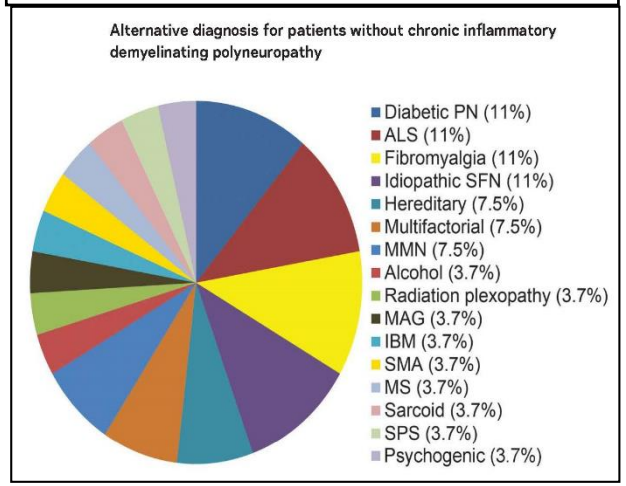
CIDP Clinical Burden

- Treatments can be cumbersome, and 2/3 of patients require treatment lifelong
  - Length of IVIG infusions
  - Requirements for infusion center use only in certain cases
  - Side effects of treatments
- Delays in diagnosis: both underdiagnosis and overdiagnosis
- Reduced independence
- Prolonged treatments without attempts to taper, as 1/3 of patients do eventually go into medication-free remission
- Undertreatment and overtreatment
- Long wait time to see neurology and neuromuscular specialists

Querol et al, 2021; Van Schaik et al, 2010

CIDP misdiagnosis is common

CIDP diagnostic pitfalls and perception of treatment benefit[1]



Almost half **(47%)** did not have CIDP (n=58)

Review process for IVIg treatment: Lessons from the Insight study[2]

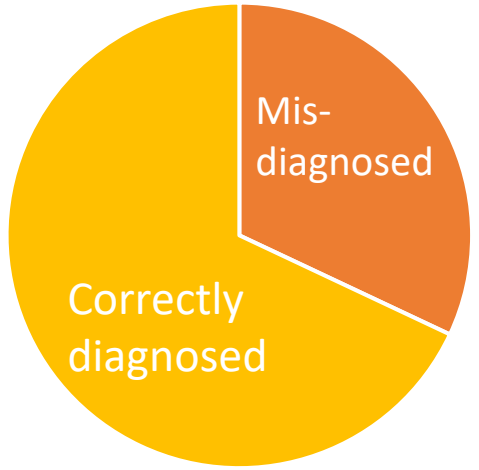
Table 3 Initial expert reviewer's assessments

Clinical condition	Assessment	No. of cases	Percentage of total cases
Immune neuropathy present	Yes	80	32.2
	No	115	46.4
	Unable to determine	53	21.4
Appropriate candidate for therapy	Yes	80	32.2
	No	119	48
	Unable to determine	49	19.8
Positive response to IVIg predicted	Yes	37	14.9
	No	149	60.1
	Unable to determine	62	25
Evidence for demyelination	None	82	33
	Some—does not meet EFNS criteria	42	16.9
	Meets EFNS criteria	26	10.4
	Uninterpretable	20	8
	No NCV submitted	78	31.4

Abbreviations: IVIg = IV immunoglobulin; EFNS = European Federation of Neurological Societies.

68% did not have CIDP or other immune neuropathy

Misdiagnosis and Diagnostic Pitfalls of CIDP in the Netherlands[3]



About a third **(32%)** were misdiagnosed as CIDP

In multiple independent studies, between 1/3 and 2/3 of patients that carry a diagnosis of CIDP have been found to not have that condition

1. Allen JA and Lewis RA. Neurology. 2015.
2. Levine, Katz, Barohn et al. Neurology Clinical Practic. 2018
3. Broers M et al. European Journal of Neurology. 2021

CIDP delayed or missed diagnosis is also common

- ICE trial: 40.8 months between symptom onset and diagnosis[1]
- Mayo: 10 months (range 2-64) symptom duration before presentation[2]
- Allen and Lewis: 11.4 months between symptom onset and diagnosis[3]

For both *mis* diagnosis and *missed* diagnosis, the variants are especially challenging

1. Hughes RA et al. Lancet Neurol 2008. 2. Laughlin RS et al. *Neurology* 2009. 3. Allen JA and Lewis R A. Neurology 2015

CIDP: Results of Misdiagnosis

- Diagnostic delay:
  - Clinical consequences
    - Increased disability
    - Worse long-term outcomes
    - Irreversible nerve damage

- Psychosocial and economic impact
  - Economic burden
  - Delays can lead to frustration, anxiety, depression
  - Undiagnosed patients often experience daily pain, fatigue, and impairments

The EAN/PNS criteria are more specific but less sensitive than the EFNS/PNS criteria. With the EAN/PNS criteria, more extended nerve conduction studies (4 motor nerves at least) are recommended to obtain an acceptable sensitivity while maintaining a high specificity.

EAN/PNS specificity with definite CIDP 98% vs 84%with EFNS/PNS criteria

EAN/PNS sensitivity with definite CIDP 75% vs 84% with EFNS/PNS

Doneddu PE. Comparison of the diagnostic accuracy of the 2021 EAN/PNS and 2010 EFNS/PNS diagnostic criteria for chronic inflammatory demyelinating polyradiculoneuropathy. J Neurol Neurosurg Psychiatry. 2022 Dec;93(12):1239-1246.

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RESEARCH REPORT

WILEY

European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: Report of a joint Task Force—Second revision

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Abstract

To revise the 2010 consensus guideline on chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). Seventeen disease experts, a patient representative, and two Cochrane methodologists constructed 12 Population/Intervention/Comparison/

EAN/PNS CIDP diagnostic criteria (2021)

CIDP

- Clinical criteria + Strongly supportive electrodiagnostic criteria

Possible CIDP

- Clinical criteria + Weakly electrodiagnostic criteria + 2 supportive criteria

Supportive criteria

CSF, ultrasound and MRI, response to treatment or nerve biopsy

Van den Bergh PYK, et al. *Eur J Neurol*. 2021;28(11):3556–3583.

Electrodiagnostic criteria: Key features

MOTOR ABNORMALITIES	
Motor distal latency prolongation	Absence of F-waves
Motor conduction block*	Distal CMAP prolongation
Conduction slowing	F-wave latency prolongation
Temporal dispersion	

SENSORY ABNORMALITIES
Prolonged distal latency
Reduced SNAP amplitude
Slowed conduction velocity

Van den Bergh PYK et al. *J Peripher Nerv Syst*. 2021;26(3):242-268.

Electrodiagnostic testing

TABLE 2 Motor nerve conduction criteria

(1) Strongly supportive of demyelination:

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 ≥20% above ULN in two nerves (≥50% if amplitude of distal negative peak CMAP <80% of LLN), 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[a] in ≥1 other nerve, or

(e) Motor conduction block: ≥30% reduction of the proximal relative to distal negative peak CMAP amplitude, excluding the tibial nerve, and distal negative peak CMAP amplitude ≥20% of LLN in two nerves; or in one nerve + ≥1 other demyelinating parameter[a] except absence of F-waves in ≥1 other nerve, or

(f) Abnormal temporal dispersion: >30% duration increase between the proximal and distal negative peak CMAP (at least 100% in the tibial nerve) 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) prolongation in ≥1 nerve[b] + ≥1 other demyelinating parameter[a] in ≥1 other nerve

- (LFF 2 Hz) median > 8.4 ms, ulnar > 9.6 ms, peroneal > 8.8 ms, tibial > 9.2 ms
- (LFF 5 Hz) median > 8.0 ms, ulnar > 8.6 ms, peroneal > 8.5 ms, tibial > 8.3 ms
- (LFF 10 Hz) median > 7.8 ms, ulnar > 8.5 ms, peroneal > 8.3 ms, tibial > 8.2 ms
- (LFF 20 Hz) median > 7.4 ms, ulnar > 7.8 ms, peroneal > 8.1 ms, tibial > 8.0 ms

(2) Weakly supportive of demyelination

As in (1) but in only one nerve.

EAN/PNS Guidelines 2021

Sensory NCS

TABLE 3 Sensory nerve conduction criteria

(1) CIDP

- Sensory conduction abnormalities (prolonged distal latency, or reduced SNAP amplitude, or slowed conduction velocity outside of normal limits) in two nerves.

(2) Possible CIDP

- As in (1).
- Sensory CIDP with normal motor nerve conduction studies needs to fulfil a. or b.
  a. sensory nerve conduction velocity <80% of LLN (for SNAP amplitude >80% of LLN) or <70% of LLN (for SNAP amplitude <80% of LLN) [85] in at least two nerves (median, ulnar, radial, sural nerve), or
  b. sural sparing pattern (abnormal median or radial sensory nerve action potential [SNAP amplitude] with normal sural nerve SNAP amplitude) (excluding carpal tunnel syndrome) [88–90].

Note 1. Skin temperature should be maintained to at least 33°C at the palm and 30°C at the external malleolus. 1. Since these criteria do not permit to identify normal reference values compatible with sensory nerve demyelination, sensory CIDP cannot be more than a possible diagnosis as based on clinical and electrophysiological criteria.

Note 2. Decline in sural nerve action potential amplitude occurs with age and use of age-dependent reference values after age 60 is advised [91].

Abbreviations: CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; LLN, lower limit of normal; SNAP, sensory nerve action potential. [Correction added on 18 December 2021 after first online publication: The term 'but in only one nerve' has been removed under the subheading 'Possible CIDP' in Table 3 in this version.]

EAN/PNS 2021 Guidelines

What Electrodiagnostic Errors Contribute to Misdiagnosis?

Mistakes more often with data interpretation than data quality

Three patterns commonly mistaken as CIDP:

1. **Length-dependent axonal neuropathies**
   - With mild or moderate CV slowing
2. **Motor neuron disease**
   - With mild CV slowing
3. **Single or multiple neuropathies at compressible sites**
   - With focal slowing across those sites

Allen JA, et al. *Muscle Nerve*. 2018;57(4):542-549.

Imaging criteria

Ultrasound criteria

*Cross-sectional area median nerve >10 mm^2 at forearm, >13 mm^2upper arm, >9 mm^2 interscalene (trunks) or >12 mm^2 for nerve roots

CIDP may be more likely if there is enlargement of at least two sites in proximal median nerve and/or the brachial plexus

MRI Criteria

- Enlargement and/or increased signal intensity of nerve root(s) on T2 weighted MRI sequences or contrast enhancement

EAN/PNS 2021 Guidelines

CSF albuminocytological dissociation

- Caution with mild or moderate CSF protein elevation especially in the presence of diabetes
- Recommend against using isolated CSF protein elevation for diagnosis of CIDP
- More research needs to be done to fully establish cut off values

Higher normal CSF reference values may improve specificity:

- Age ≤ 50 years: < 50 mg/dL
- Age > 50 years: < 60 mg/dL

Allen JA and Lewis RL. CIDP diagnostic pitfalls and perception of treatment benefit. Neurology 2015.
Breiner A, Bourque, P, Allen JA. Updated CSF total protein reference values improves CIDP diagnosis. Muscle and Nerve. August 2019.
Liberatore L et al. Relevance of diagnostic investigations in CIDP. 2020.

Nerve biopsy

- Rarely needed

Features:

- Thinly myelinated axons and small onion bulbs
- Thinly myelinated or demyelinated internodes in teased fibers
- Perivascular macrophage clusters
- Supportive features of demyelinating on electron microscopy

Differential diagnosis of CIDP

RED FLAGS THAT SUGGEST ANOTHER DIAGNOSIS					
	TYPICAL CIDP	**DISTAL CIDP**	**MULTIFOCAL/FOCAL CIDP**	**MOTOR CIDP**	**SENSORY CIDP**
CLINICAL	Subacute, low frequency tremor, marked ataxia, distal predominance → autoimmune nodopathy phenotype?	Family history → CMT, ATTRv? Autonomic features, pain → ATTRv neuropathy, diabetic neuropathy?	Pain → diabetic radiculo-plexopathy, neuralgic amyotrophy? Normal sensation → multifocal motor neuropathy? Focal: only 1 nerve in 1 limb → nerve entrapment/tumour? Family history → HNPP?	Dyspnea, dysarthria, dysphagia → motor neuron disease, myasthenia? Family history → hereditary motor neuropathies (fALS, dHMN, SMA)? Prominent asymmetry at onset → multifocal motor neuropathy?	idiopathic sensory axonal neuropathy? Family history → hereditary sensory neuropathy?
LABORATORY	Fasting blood glucose or HbA1c elevated → diabetic neuropathy? IgA or IgG monoclonal gammopathy → multiple myeloma, AL amyloidosis, POEMS syndrome?	IgM monoclonal gammopathy → anti-MAG neuropathy?	ANA/ANCA + → vasculitis neuropathy?	Elevated serum CK level → inflammatory myopathy?	Fasting blood glucose or HbA1c elevated → diabetic neuropathy? Low vitamin B12 level, chemotherapy → sensory neuronopathy? IgM monoclonal gammopathy → anti-MAG neuropathy? Normal motor and sensory conduction → chronic immune sensory polyradiculopathy (CISP)?

EAN/PNS 2021 Guidelines

Alternate diagnoses to consider

	Red flags	Alternative diagnosis
Distal CIDP	Family history	CMT
	Autonomic involvement, Pain	hTTR amyloidosis, diabetes
	Ataxia, tremor, No response to IVIG	Autoimmune nodopathy
	No definite demyelination on NCS	Axonal causes of neuropathy
	IgA or IgG monoclonal protein	POEMS or AL amyloid
	IgM or MAG antibody	Anti-MAG neuropathy

	Red flags	Alternative diagnosis
Sensory CIDP	No definite demyelinating features	Axonal causes of neuropathy (diabetes, B12, thyroid, toxic medications, many others)
	Family history	Hereditary sensory neuropathy
	Normal NCS but clinical features of sensory CIDP	CISP

Van den Bergh PYK, et al. *Eur J Neurol*. 2021;28(11):3556–3583.

Alternate diagnoses to consider

	Red flags	Alternative diagnosis
Multifocal CIDP	Pain	Vasculitis, diabetic amyotrophy. Parsonage-Turner syndrome
	Normal sensation	MMN
	Family history	HNPP
	Positive ANA/ANCA	vasculitis
	Only 1 nerve or limb affected	Entrapment, trauma, tumor

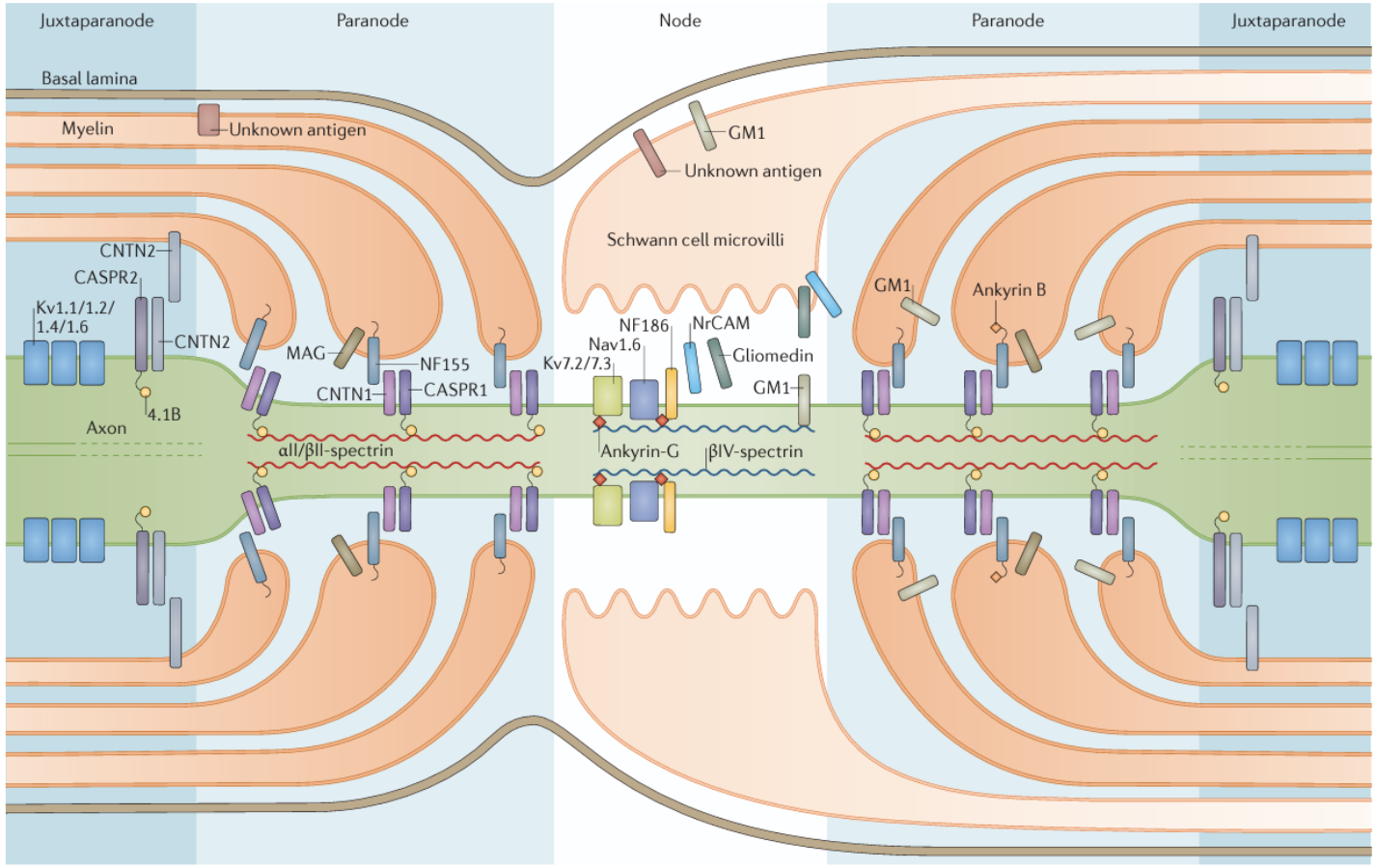
	Red flags	Alternative diagnosis
Motor CIDP	Bulbar involvement	MND, myasthenia
	Family history	Hereditary motor neuropathy
	Asymmetric	MMN
	Elevated CK	Inflammatory myopathy

Van den Bergh PYK, et al. *Eur J Neurol*. 2021;28(11):3556–3583.

Consider Further Investigation of Variants

- **Distal CIDP**: anti-MAG antibodies when IgM monoclonal gammopathy is present
- **Lewis-Sumner syndrome and focal CIDP**: ESR, ANA, ANCA, anti-GM1 antibodies
- **Motor CIDP**: CK, NMJ testing with antibodies and electrodiagnostic testing, muscle biopsy
- **Sensory CIDP**: IgM paraproteinemic neuropathy with anti-MAG antibodies, antiganglioside antibodies, B12, B6 levels, paraneoplastic antibody screen, SSEPs if NCS are normal.

Nodopathies and paranodopathies



Nodopathies and paranodopathies

- Clinical phenotype specifics: tremor, younger age, high CSF protein, nephrotic syndrome
- Anti-Neurofascin 155 and anti-contactin antibodies
- Cell based assay is better for detection and limits false positives
- Generally, IgG4 mediated and responds as other IgG 4 mediated diseases do to B-cell depletion treatment

Common pitfalls when considering supportive data

- Attributing mild or moderate “demyelinating” changes on NCS to CIDP
  - Especially when amplitudes are low
  - Especially in the presence of diabetes
- Placing an overstated importance on CSF protein elevations
  - Especially if age >60
  - Especially in the presence of diabetes or spondylosis
- Overcalling MRI or ultrasound
  - Especially if not experienced in nerve imaging
- Using as “improvement after immunotherapy” as diagnostic test
  - Especially if only subjective changes
  - Objective changes in strength or disability outcomes are more reliable

Van den Bergh PY et al. European Academy of Neurological Societies/Peripheral Nerve Society guideline on management of CIDP - second revision. J Peripher Nerve Syst 2021;26(3):242–268.

Metrics to assess response to treatment

Table 6. Frequently used definitions of minimal clinically important difference (MCID) in CIDP.

Scale	MCID	Remarks
(adjusted) INCAT	1 point	Not a linear scale Less responsive in some patients May not capture all activities important to all patients
I-RODS	Individual SE (differs on the scale) on centile score or 4 points on the centile score	Calculation of MCID using individual standard errors (MCID ≥ ± 1.96 SE) requires an automated tool for calculation 4 points on raw score requires additional research to assess relevance Raw score (0–48) is easy to collect but less is known about the MCID May not capture all activities important to all patients
Grip strength, Martin vigorimeter	8 kPa 14 kPa	Repeated measurements are needed for consistency Not practical for patients with very weak grip
Grip strength, Jamar dynamometer	10% change (kg or lb)	Requires values averaged over at least 3 consecutive days Not practical for patients with very weak grip
MRC sum score	2–4 points	Usually a total score of 60 points (6 paired muscle groups) Poor interrater reliability Relatively unresponsive, especially to capture deterioration

CIDP, chronic inflammatory demyelinating polyradiculoneuropathy; INCAT, Inflammatory Neuropathy Cause and Treatment; I-RODS, Inflammatory Rasch-Built Overall Disability Scale; MRC, Medical Research Council; SE, standard error.

Allen JA et al. Outcome measures and biomarkers in CIDP. 2021

Inflammatory Neuropathy Cause and Treatment (INCAT) Disability Score

Score	Arm Disability	Score	Leg Disability
0	No upper limb problems	0	Walking not affected
1	Symptoms, in 1 arm or both arms, not affecting ability to perform any of the following functions: doing all zippers and buttons, washing or brushing hair, using knife and fork together, handling small coins	1	Walking affected, but walks independently outdoors
2	Symptoms, in 1 arm or both arms, affecting but not preventing any of functions listed above	2	Usually uses unilateral support (stick, single crutch, 1 arm) to walk outdoors
3	Symptoms, in 1 arm or both arms, preventing 1 or 2 of functions listed above	3	Usually uses bilateral support (sticks, crutches, frame, 2 arms) to walk outdoors
4	Symptoms, in 1 arm or both arms, preventing 3 or all of functions listed above, but some purposeful movements still possible	4	Usually uses wheelchair to travel outdoors, but able to stand and walk few steps
5	Inability to use either arm for any purposeful movement	5	Restricted to wheelchair, unable to stand and walk a few steps with help

Hughes R, et al. *Ann Neurol.* 2001;50(2):195–201.

I-RODS

	Not possible (0)	Possible but difficult (1)	Possible no difficulty (2)
Read a book?			
Eat?			
Brush teeth?			
Wash upper body?			
Sit on toilet?			
Make sandwich?			
Dress upper body?			
Wash lower body?			
Move chair?			
Turn key in lock?			
Go to doctor?			
Take shower?			
Do dishes?			
Do shopping?			
Catch object (ball)?			
Bend & pick up object?			
Walk one flight stairs?			
Travel by public transportation?			
Walk and avoid obstacles?			
Walk < 1 km?			
Carry & put down heavy object?			
Dance?			
Stand for hours?			
Run?			

SI Van Nes et al. Neurology. 2011.

Strength impairment: Grip strength

Martin Vigorimeter[1]

Jamar Dynamometer[1]

- Grip strength is a sensitive tool for assessing clinically relevant changes in patients with CIDP
- It is a reliable measure of global neurologic status in CIDP, not limited to upper limb or exclusively motor function
- It is not a time-consuming procedure
- Easy to perform, immediately available results, and can be conducted by patients at home

1. Reprinted from J Hand Ther, vol . 23, Irwin CB and Sesto ME. Reliability and validity of the multiaxis profile dynamometer with younger and older participants. pp. 281–288. Copyright (2010), with permission from Elsevier. 2. Vanhoutte EK *et al.* Eur J Neurol. 2013;20(5):748–755. 3. Draak TH *et al.* Neurology 14;83(23):2124–2132. 4. Rajabally YA, Narasimhan M. J Neurol Sci. 2013;325(1–2):36–38.

Gait impairment

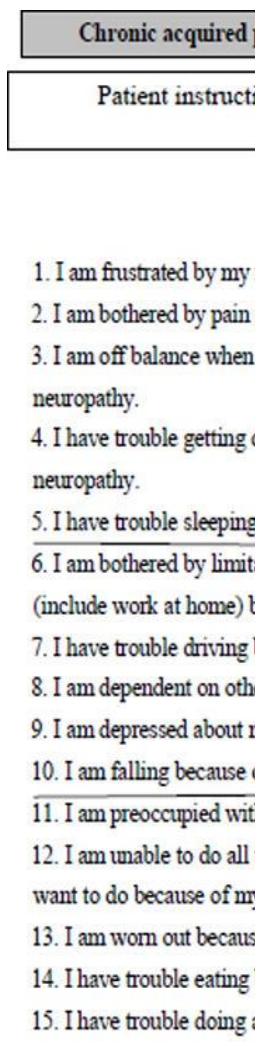
Assessment of Gait is an unmet need in CIDP

Test	Description	Pro	Con
Timed Up and Go (TUG)	Time to stand up from a standard arm chair, walk 3 meters, turn, walk back to the chair, sit down	Quick; No special equipment; Assess multiple lower leg functions including standing, walking & turning	Unknown validity and sensitivity to change in CIDP
10 Meter Walk test	Time to walk 10 meters	Quick; No special equipment	Unknown validity and sensitivity to change in CIDP
6 minute walk test	Measures the distance that can be quickly walked on a flat hard surface in a period of 6 minutes	Better able to assess fatigable gait impairment than TUG or 10 meter walk; No special equipment	Unknown validity and sensitivity to change in CIDP; Less practical during routine clinical care
Wearable sensors	Sensors placed on various parts of the patient's body	Able to measure various characteristics of gait	Unknown validity and sensitivity to change in CIDP

1. Mathias S, Nayak US, Isaacs B. Balance in elderly patients: the "get-up and go" test. Archives of physical medicine and rehabilitation. 1986;67(6):387-9.
2. Erdmann PG, van Meeteren NL, Kalmijn S, Wokke JH, Helders PJ, van den Berg LH. Functional health status of patients with chronic inflammatory neuropathies. Journal of the peripheral nervous system : JPNS. 2005;10(2):181-9.
3. Montes J, McDermott MP, Martens WB, Dunaway S, Glanzman AM, Riley S, et al. Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy. Neurology. 2010;74(10):833-8.

Quality of life

- Many QoL questionnaires available
- Few developed for inflammatory neuropathy
- EuroQoL 5D
  - Applicable for multiple conditions
  - Assess across 5 dimensions
  - QoL measure in Path trial
- EuroQoL VAS
  - Quantitative measure of health as judged by individual respondents
  - Self-rated health on a 20 cm scale
- **CAP-PRI**
  - **Developed for chronic, immune-mediated polyneuropathy**
  - **Quick and easy to perform**
  - **Address multiple life domains**
- In-QoL
  - Developed for inflammatory neuropathy
  - Fulfills Rasch model requirements
  - Correlates strongly self-assessment of their own quality of health (EQ VAS)



Chronic acquired

Patient instructi

1. I am frustrated by my
2. I am bothered by pain
3. I am off balance when
neuropathy.
4. I have trouble getting
neuropathy.
5. I have trouble sleeping
6. I am bothered by limit
(include work at home)
7. I have trouble driving
8. I am dependent on oth
9. I am depressed about
10. I am falling because
11. I am preoccupied wit
12. I am unable to do all
want to do because of m
13. I am worn out becaus
14. I have trouble eating
15. I have trouble doing

Neuromuscular

RESEARCH PAPER

Quality of life in inflammatory neuropathies: the IN-QoL

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ABSTRACT

Background No consensus exists which quality of life (QoL) measure should be used in patients with inflammatory neuropathies. Moreover, most QoL measures are ordinal-based scales with their known deficiencies.

Objectives To establish a new disease-specific interval-based QoL questionnaire in inflammatory neuropathies (IN-QoL) using the Rasch model and evaluate its scientific properties (validity, reliability and responsiveness).

Methods 264 patients with inflammatory neuropathies completed six commonly used QoL questionnaires. The obtained data were stacked and subjected to Rasch analysis. Responsiveness was determined by using the concept of minimum clinically important differences related to varying individually obtained SEs (responsiveness definition: MCID-SE≥1.96 after 1-year follow-up compared with baseline).

Results The IN-QoL fulfilled all Rasch's model requirements with high internal reliability values (patient separation index of 0.94), except being multidimensional. Additional factor analysis resulted in two (functional and mental) subsets that were unidimensional on their own. The IN-QoL showed good correlation with the EuroQol-health quality visual analogue scale (EQ-VAS) (Spearman's rho 0.72). It demonstrated acceptable responsiveness in patients with Guillain-Barré syndrome (GBS) and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), as did the EQ-VAS. In patients with monoclonal gammopathy-related neuropathy and multifocal motor neuropathy, hardly any changes were seen over time.

Conclusion The IN-QoL questionnaire fulfils modern clinimetric requirements and correlates strongly with a patient's self-assessment of their own quality of health, while also showing responsiveness in patients with GBS and CIDP. We propose using the IN-QoL and the EQ-VAS for assessing the QoL of patients with inflammatory neuropathies in future studies.

Check for updates

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INTRODUCTION

Quality of life (QoL) is a highly valued outcome measurement in any chronic illness in modern medicine. Over time, a multitude of questionnaires have been developed aiming to capture patient's QoL.[1–3] These questionnaires are created for example through patient focused groups, experts' opinion or by combining different pre-existing questionnaires. Several of these questionnaires have fulfilled the basic clinimetric requirements like being valid, reliable and responsive.[4–6] However, most, if not all, QoL instruments have limitations such as summing up ordinal data with their known deficiencies.[9–12] Furthermore, they are often used outside the field for which they were initially developed, assuming that QoL could be captured in the same way across all fields of medicine, thus not respecting potential disease-specific aspects. Only few scales are designed specifically for peripheral neuropathies, but both are based on ordinal sum scores.[7 13] To date, no consensus exists regarding which QoL measure should be used in patients with inflammatory neuropathies. Based on these observations, we aimed to create an interval-based QoL questionnaire specifically for inflammatory neuropathies (IN-QoL) from a comprehensive set of items, originating from six commonly used QoL questionnaires, aiming for the metric to be unidimensional, free from item bias, without disordered thresholds or local dependency, and fulfilling all Rasch model requirements. In addition, we examined the scientific soundness (validity, reliability and responsiveness) of the IN-QoL. In particular, we correlated the IN-QoL findings with patients' own ability to address their health quality using the EuroQol-health quality visual analogue scale (EQ-VAS).[3] We postulated that there would be a strong correlation between the outcome of the new questionnaire and patient's self-assessed quality of health.

METHODS

Patients

This study is part of the Peripheral Neuropathy Outcome Measures Standardisation (PeriNomS) Study (duration: 7 years; database closed 31 December 2012), an international collaborative effort of 26 neuromuscular centres with special interest in inflammatory neuropathies, located in nine countries (USA, Canada, Spain, Brazil, Italy, France, Belgium, the Netherlands and UK). A total of 264 patients with Guillain-Barre syndrome (GBS), chronic inflammatory demyelinating polyradiculopathy (CIDP), IgM monoclonal gammopathy-related polyneuropathy (MGUSP) and multifocal motor neuropathy (MMN) were included in the study. These patients completed the WHO quality of life scale (WHOQoL BREF),[4] Sickness Impact Profile,[2] EuroQoL scale,[3] Nottingham Health Profile,[4] short form 36-item health survey (SF-36)[5 6 8] and Vickrey Peripheral Neuropathy Quality-of-Life Instrument-97.[7] The questionnaires were made available using the validated native

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QoL assessment with CAP-PRI

Chronic Acquired Polyneuropathy – Patient Reported Index CAP-PRI				
		Not at all (0)	**A little bit (1)**	**A lot (2)**
1	I am frustrated by my neuropathy.			
2	I am bothered by pain from neuropathy			
3	I am off balance when walking because of my neuropathy.			
4	I have trouble getting dressed because of my neuropathy.			
5	I have trouble sleeping because of my neuropathy.			
6	I am bothered by limitations in performing my work (include work at home) because of my neuropathy.			
7	I have trouble driving because of my neuropathy.			
8	I am dependent on others because of my neuropathy.			
9	I am depressed about my neuropathy.			
10	I am falling because of my neuropathy.			
11	I am preoccupied with my neuropathy.			
12	I am unable to do all the leisure activities that I want to do because of my neuropathy.			
13	I am worn out because of my neuropathy.			
14	I have trouble eating because of my neuropathy.			
15	I have trouble doing activities around the house.			
	Total per column			

Common Pitfalls and Strategy

- Strategy: Clinical phenotype + Electrodiagnostic testing
- Exclude mimics
- Obtain diagnostic supportive testing when necessary
- Be vigilant

Case #1

- 41 year old man
- Symptoms:
  - Cramps since his late 20's
  - Paresthesia in hands & feet
  - Weakness in hands > feet
  - Minimizes motor & sensory deficits, but the cramps drive him crazy
- Exam:
  - Sensory: Mildly reduced vibration in toes
  - Motor: 4/5 or less at and distal to wrist and ankle
  - Reflex: Diffusely hypoactive or absent
- NCS:
  - Sensory: Small but present in upper and lower limbs
  - Motor: Normal median & ulnar amplitude with CV in low 30's. Peroneal & tibial amplitude small with CV in upper 20's. Possible CB in 1 nerve (ulnar)
- CSF protein 49

→ Atypical for CIDP

→ Atypical for CIDP, no proximal weakness

→ Unequivocal demyelinating neuropathy

→ Probably normal

Case #2

- 62 year old woman
- Symptoms:
  - 5-6 years of declining gait, now needs walker
  - Paresthesia & numbness in hands & feet
  - Weakness below elbows & knees
  - Mild tremor and ataxia
- Exam:
  - Sensory: Reduced pin & vibration below wrists and mid leg
  - Motor: 4/5 distal upper limbs, 4/5 proximal and 3/5 distal lower limbs
  - Reflex: Diffusely hypoactive or absent
- NCS:
  - Sensory: Absent in upper & lower limbs
  - Motor: Median & ulnar amplitude about 3 mV with CV in low 20's. Peroneal & tibial motor absent
- CSF protein 64

→ Typical for CIDP, although clinical course longer than most

→ Typical for CIDP

→ Unequivocal demyelinating neuropathy

→ Mildly elevated

Case #1

- 41 year old man
- Symptoms:

Atypical for CIDP

- Exam:

Atypical for CIDP, no proximal weakness

- NCS:

Unequivocal demyelinating neuropathy

- CSF

Probably normal

Questions:

1. Do you have enough to start treatment or is more work up needed?
2. If you think more work up is needed, what makes the most sense to check next?
3. If you start treatment, how is the response to treatment going to inform the conclusions you drew about the diagnosis?

Case #2

- 62 year old woman
- Symptoms:

Typical for CIDP, although clinical course longer than most

- Exam:

Typical for CIDP

- NCS:

Unequivocal demyelinating neuropathy

- CSF

Mildly elevated

Case #1

- 41 year old man with an unequivocally demyelinating polyneuropathy but atypical clinical features

Treat or more work up?

Genetic testing for 70+ genes showed no mutations

Treatment started. Is it helpful?

	5/24	7/24	8/24	11/24	3/25	7/25
I-RODS	43	41	IVIG started	47	48	48
Grip right, kg	19	12		44	Virtual	43
Grip left, kg	18	10		42	Virtual	40

Treatment response interpretation?

- Diagnostically supportive: Distal CIDP variant
- Justifies risk of long- term treatment

Case #2

- 62 year old woman with an unequivocally demyelinating polyneuropathy and mostly typical features

Treat or more work up?

Treatment started.

	3/24	4/24	6/24	8/24	8/24	11/24	1/25
I-RODS	20	IVIG started	18	17	CS started	17	17
Grip right, kg	9		8	10		10	8
Grip left, kg	8		8	8		6	8

Treatment response interpretation?

- Despite subjective positive experience no objective support for treatment benefit

Treat or more work up?

Genetic testing revealed pathogenic PMP22 duplication, diagnostic of CMT1A

Key Points

- Recognizing characteristic clinical and electrophysiologic features is key for early and accurate diagnosis
  - Diagnostic criteria can help!
- Supportive CIDP findings are not diagnostic of CIDP in isolation
  - Beware of mild or moderately elevated CSF protein
  - Beware of “subjective” responses to treatment
- Supportive data is not needed if:
  - Clinical and electrophysiologic findings are clear
  - No “red flags” for alternative diagnosis
- Supportive data can be helpful if:
  - Electrophysiologic findings are only weakly supportive of CIDP
  - If there are mimics that need to be excluded
- Failure to identify “red flags” and to consider diagnostic alternatives may lead to misdiagnosis
  - The variants can be especially tricky