CIDP

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Recognizing CIDP

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A Typical CIDP Case

This case is based on a hypothetical patient. This review is intended for illustrative purposes only. Individual treatment response may vary from patient to patient.

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68-Year-Old Man With Symmetric Progressive Weakness and Numbness

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History	Case notes
Presentation	• 2-year history of progressively worsening numbness and weakness • Jazz musician and early on, noticed difficulty playing the saxophone • Initially noted tingling affecting fingers and toes that spread to the whole hands and calves over 1 year • Over the past few months, has been dropping and having trouble manipulating objects and has difficulty rising from a low sofa and climbing stairs • Has stumbled several times while walking
Medical history	• Height: 6′ 1″; weight: 192 lb (87 kg) • Diagnosed with hypertension at age 61 – Blood pressure well controlled on lisinopril 20 mg QD
Social history	• Single • No longer plays music professionally

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Physical Findings

Examination	Case notes
Motor	• Normal tone and bulk • 4-/5 at toe movements • 4/5 at ankle dorsiflexion, inversion, eversion • 4-/5 at hip flexion • 4-/5 in hand intrinsic muscles • 4+/5 at deltoid
Sensory	• Vibration sense absent at toe; moderately reduced at ankles • Proprioception absent at toe; decreased at the fingers • Decreased light touch at distal palmar surface of the digits
Reflexes	• Areflexic
Function	• Difficulty walking; uses a cane while outdoors • Pseudo-athetoid movements in the hands with postural tremor

Electrophysiology Suggests Demyelination

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Nerve and site	Latency (ms)	Amplitude (mV)	Duration (ms)	CV (m/s)	F wave (ms)
R. peroneal – EDB (ankle)	5.8	1.2	8.1	—	77.6
R. peroneal – EDB (below knee)		0.4 (33%)	50.0	17	—
R. peroneal – EDB (above knee)		0.4	49.1	42	
L. peroneal – EDB (ankle)	7.3	0.38	7.5	—	57.4
L. peroneal – EDB (below knee)		0.11	22.1	10	—
L. peroneal – EDB (above knee)		0.19	19.4	27	—

Circled values are in demyelinating range.
Low amplitude or absent responses: R. tibial–FHB, bilateral sural, R. median sensory, R. ulnar sensory

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Electrophysiology Suggests Demyelination (cont.)

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Nerve and site	Latency (ms)	Amplitude (mV)	Duration (ms)	CV (m/s)	F wave (ms)
L. tibial – AH (ankle)	8.1	0.88	15.1	—	77.4
L. tibial – AH (knee)		0.82	15.5	26	—

Circled values are in demyelinating range.
Low amplitude or absent responses: R. tibial–FHB, bilateral sural, R. median sensory, R. ulnar sensory

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Electrophysiology Suggests Demyelination (cont.)

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Nerve and site	Latency (ms)	Amplitude (mV)	Duration (ms)	CV (m/s)	F wave (ms)
R. median – APB (wrist)	3.6	15.0	5.2	—	46.8
R. median – APB (elbow)		7.0 (47%)	8.5	40	—
R. ulnar – ADM (wrist)	2.4	10.6	5.0	—	43.8
R. ulnar – ADM (below elbow)	7.5	6.0 (57%)	7.7	41	—
R. ulnar – ADM (above elbow)		5.3	9.5	55	—

Circled values are in demyelinating range.

Low amplitude or absent responses: R. tibial–FHB, bilateral sural, R. median sensory, R. ulnar sensory

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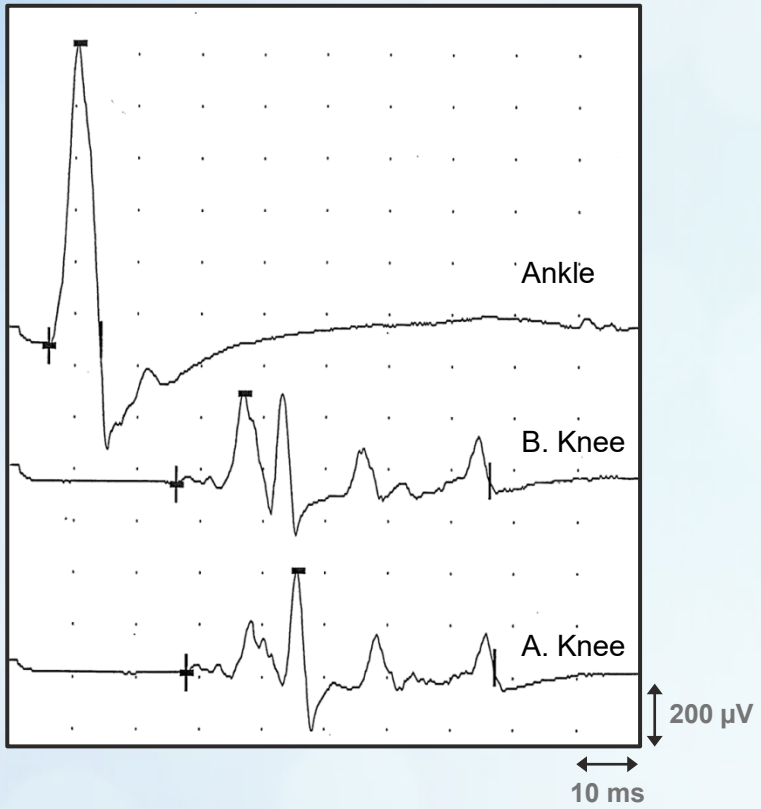
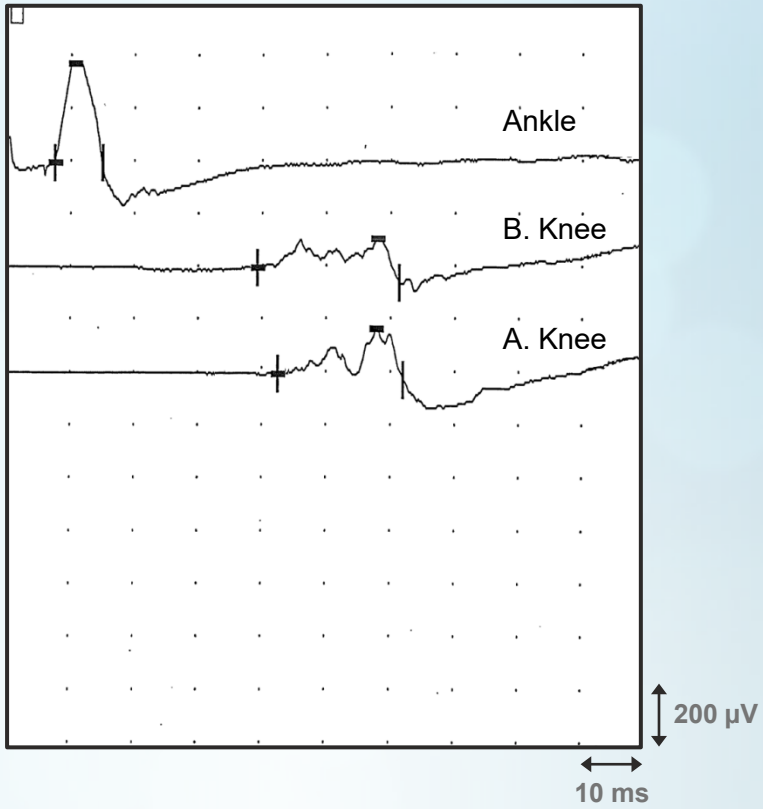
Temporal Dispersion of the Proximal CMAPs and Conduction Slowing Suggest Demyelination

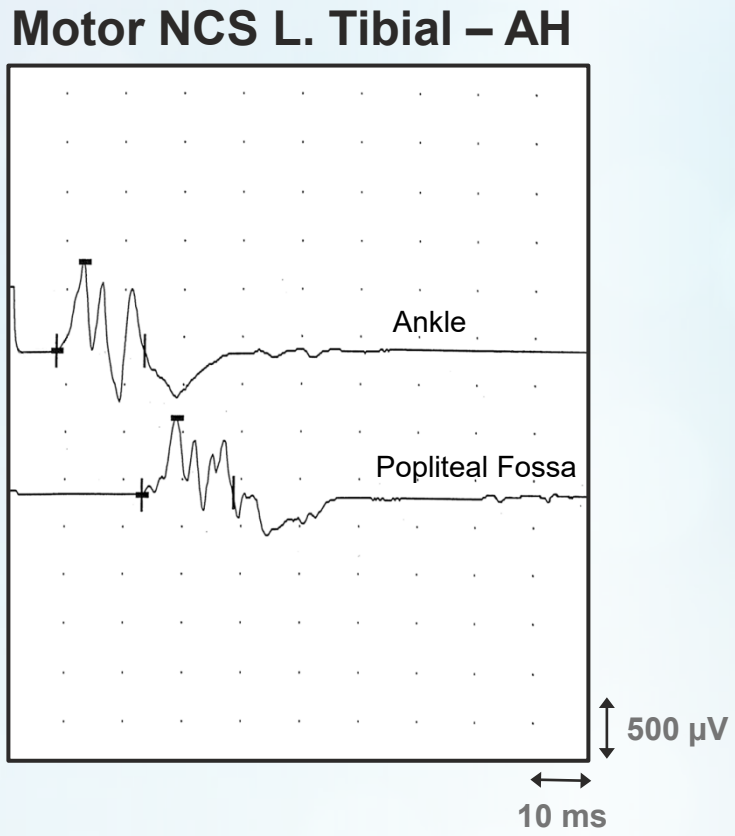
Motor NCS R. Peroneal – EDB



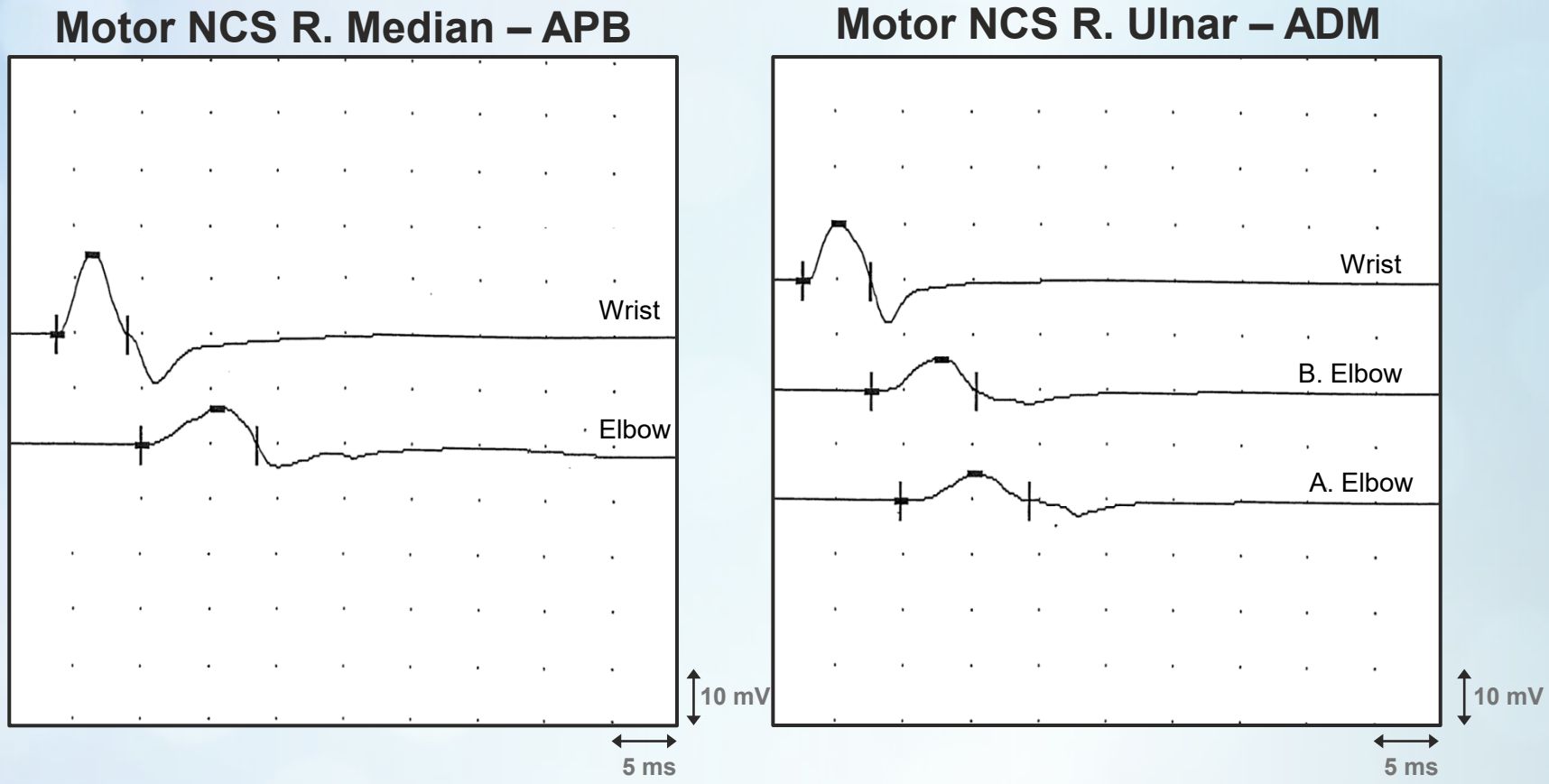
Motor NCS L. Peroneal – EDB



Temporal Dispersion (Multiphasic CMAPs and Prolonged Distal CMAP Duration) and Conduction Slowing Suggest Demyelination



Temporal Dispersion of the Proximal CMAPs Suggests Demyelination



What Features Help Confirm Diagnosis?

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Workup	Case notes
Electrophysiology	Sensorimotor polyneuropathy Evidence consistent with demyelination Severe motor conduction velocity slowing, bilateral peroneal, L. tibial Severely prolonged F-wave latencies, R. median, ulnar, peroneal, L. tibial Proximal motor responses with temporal dispersion (lower amplitude, increased duration), bilateral peroneal, R. median, and R. ulnar Absent sensory potentials in the sural, median, and ulnar nerves
Labs	• Serum labs normal, including immunofixation, glucose, creatinine, ANA, RF, Lyme, RPR, B12. Urine immunofixation normal

Diagnosis: CIDP

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Treatment Discussion: Route of Administration for IG

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What factors influence the recommended route of administration when IG is the treatment choice?

Parameter	Description/Discussion
Administration challenges	**Dexterity sensory impairment in the hands** • Impairment in proprioception, hand tremor, weakness in hand muscles
Lifestyle	• Because of active schedule and lifestyle, patient prefers IG administered intravenously to avoid the need for large supply of vials, syringes, needles, tubing, alcohol pads, gauze, tape, pump equipment
Patient preference	• Prefers IVIG • Difficulty with dexterity: multiple infusion sites; weekly frequency of multiple needle insertions

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Treatment Approach and Follow-up

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Management/ evaluation	Case notes
CIDP treatment	• IVIG-C – Loading dose: 2 g/kg (0.02 mL/kg/min) – Maintenance dose: 1 g/kg IV every 3 to 4 weeks – Alternatively, if SCIG had been chosen, at the high dose of 0.4 g/kg weekly: equivalent 35 g or 175 mL would require multiple injection sites[a]
Treatment rationale	• Patient administration challenges (dexterity issues, single without social support to help with administration) favor IVIG • IVIG-C is FDA approved for the treatment of patients with CIDP • Formulated with no sugar • Dosing defined in ICE Trial[1]

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Reference: 1. Hughes RAC, et al. *Lancet Neurol.* 2008;7(2):136-144.

Improvement With IVIG-C

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Examination	12 weeks following initiation of IVIG-C
Symptomatic improvement	• Improved gait stability and stair climbing; no longer uses cane • Decreased distal numbness at the hands • Returned to playing saxophone
Motor	• Strength improved with hand intrinsic movements now 4+
Sensory	• Vibration sense improved at the ankles, normal at DIP • Proprioception moderately improved at toes, significantly at the fingers
Reflexes	• Absent at ankles, obtained with reinforcement elsewhere

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Chronic Inflammatory Demyelinating Polyneuropathy

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Recurrent Polyneuropathies: Pathology and Corticosteroid Therapy

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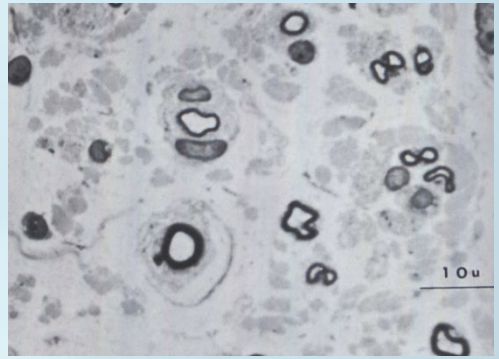
- In 1958, Austin summarized 32 cases of recurrent polyneuropathy[1]
- Presented detailed clinical picture, spinal fluid abnormalities, and pathological data[1]
- First to use the term “polyradiculoneuropathy”[1]
- Also the first to suggest that conduction block was responsible for the neurologic dysfunction[1]
- Presented a detailed case of chronic sensorimotor neuropathy with increased CSF protein and relapsing nature[1]
- In 1968, Dyck et al reported 2 more cases of chronic relapsing sensorimotor neuropathy with increased CSF protein[2]



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References: 1. Austin JH. *Brain*. 1958;81(2):157-192. **2.** Dyck PJ, et al. *Mayo Clin Proc*.

Chronic Inflammatory Polyradiculoneuropathy: Pathology and Clinical Presentation

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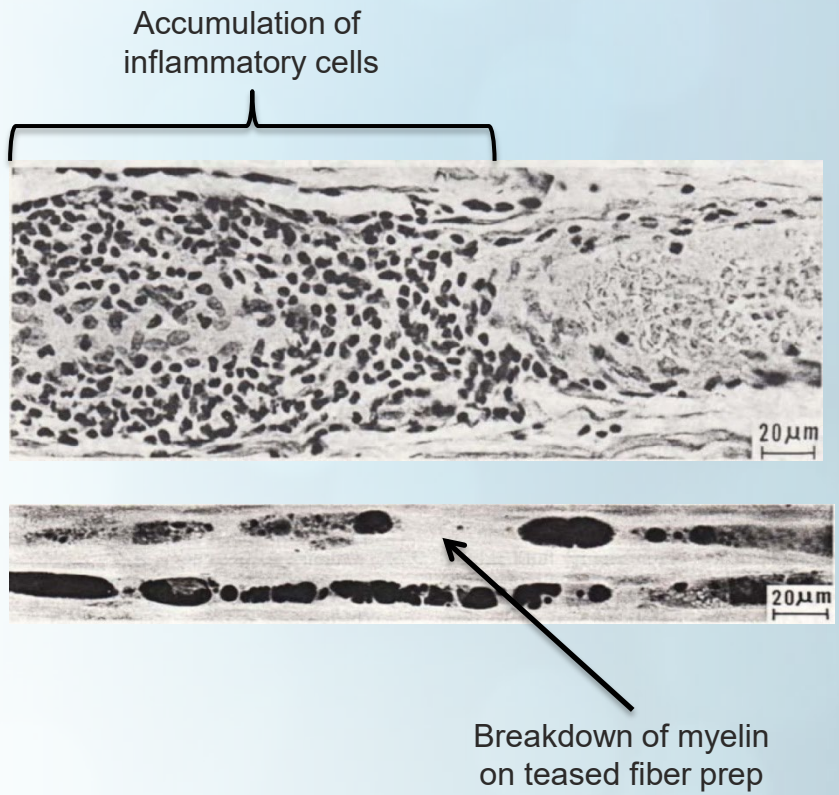
- First large case series: 53 patients with 7.5 years of follow-up
- Tendency to symmetric involvement and to involvement of proximal as well as distal limb muscles
- Diffusely slow conduction velocity of peripheral nerves
- Generalized hyporeflexia
- Albuminologic dissociation
- Demyelinating features on NCS
- Inflammation and segmental demyelination on sural nerve biopsy
- Chronicity



Reference: Dyck PJ, et al. *Mayo Clin Proc*. 1975;50(11):621-637.
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The Pathophysiology of CIDP is Multifactorial

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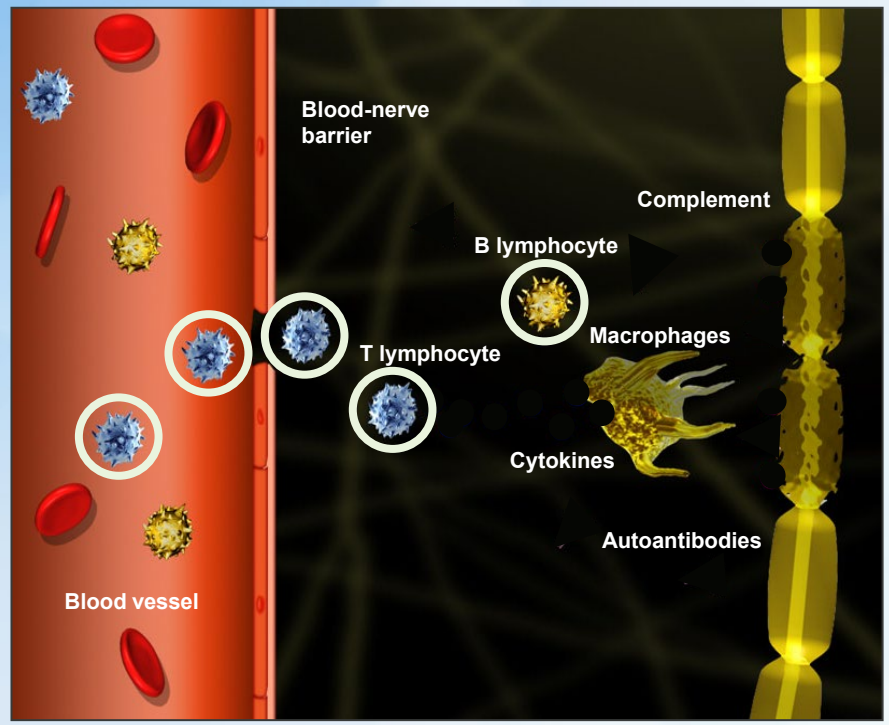

Several mechanisms play a role in the pathophysiology of CIDP, including inflammation, demyelination, axonal damage, and tissue repair[1]

- Activated T lymphocytes cross the blood-nerve barrier, increasing the activity of antigen-presenting cells (macrophages) that enhance phagocytic activity, cytokine production, and release of mediators, including proinflammatory cytokines[2]
- Autoantibodies[2]
  - **Can mediate demyelination via antibody-dependent cellular cytotoxicity**
  - **May block epitopes that are necessary for nerve conduction**
  - **Activate the complement system**

References: 1. Tackenberg B, et al. *J Clin Immunol.* 2010;30(suppl 1):S65-S69.
2. Köller H, et al. *N Engl J Med.* 2005;352(13):1343-1356.

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CIDP: Clinical Features

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- Symmetric proximal and distal muscle weakness, sensory loss, and decreased or absent DTRs[1-3]
- Common symptoms include extremity weakness and numbness[1,4]
- The disease course is steadily or stepwise progressive over at least 2 months, but can also be relapsing[1,2]
- Cranial nerves are rarely affected, and respiratory or autonomic involvement is exceptional[2,5]

DTR, deep tendon reflex.

References: 1. Saperstein DS, et al. *Muscle Nerve*. 2001;24(3):311-324. **2.** Dimachkie MM, Barohn RJ. *Curr Treat Options Neurol*. 2013;15(3):350-366. **3.** Taylor T. *Can Fam Physician*. 2013;59(4):368-371. **4.** Dyck PJB, Tracy JA. *Mayo Clin Proc*. 2018;93(6):777-793. **5.** Dalakas MC. *Nat Rev Neurol*. 2011;7(9):507-517.

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CIDP: Epidemiology

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- Typical CIDP can occur at any age, but most commonly between 40 and 60 years[1]
- Prevalence varies from 1 to 8.9 per 100,000[2,3]
- Onset during infancy and childhood can occur[1]

References: 1. van den Bergh PYK, et al. *J Peripher Nerv Syst*. 2021. doi:10.1111/jns.12455. **2.** Dimachkie MM, Barohn RJ. *Curr Treat Options Neurol*. 2013;15(3):350-366. **3.** Allen JA, Lewis RA. *Neurology*. 2015;85(6):498-504.

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Criteria for CIDP

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Diagnostic Criteria for CIDP

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	AAN 1991[1]	Saperstein 2001[2]	Koski 2009[3]	EAN/PNS 2021[4,a]
Clinical features				
Pattern of clinical involvement	Motor and/or sensory dysfunction involving more than 1 limb	Major: symmetric, proximal + distal weakness Minor: exclusively distal weakness or sensory loss	Symmetric onset or symmetric exam, with weakness in all 4 limbs and proximal weakness in at least 1 limb	Progressive or relapsing, symmetric, proximal and distal muscle weakness of upper and lower limbs, and sensory involvement of at least 2 limbs
Reflexes	Areflexia or hyporeflexia in all extremities	Areflexia or hyporeflexia in all extremities	Not mentioned	Absent or reduced tendon reflexes in all limbs
Time course	At least 2 months	At least 2 months	At least 2 months	At least 2 months
CSF studies	Mandatory; cell count <10/mm^3 Negative VDRL test Supportive: elevated proteins	Mandatory: protein >45 mg/dL Supportive: cell count <10/mm^3	Not required	Not required. May be supportive in some circumstances
Nerve biopsy	Unequivocal evidence of demyelination and remyelination	Predominant features of demyelination Inflammation	Not required	Not required. Supportive features may be seen on nerve biopsy
Requirement for "Definite" diagnostic category		Clinical major, electrodiagnostic, and CSF (biopsy supportive but not mandatory)	No serum paraprotein and no documented genetic abnormalities and either electrodiagnostic abnormalities or clinical picture as defined above	

[a] Clinical criteria are for typical CIDP.

Areas of substantial difference among guidelines

AAN, American Academy of Neurology; EAN, European Academy of Neurology; PNS, Peripheral Nerve Society; VDRL, venereal disease research laboratory.

References: 1. Cornblath DR, et al. *Neurology*. 1991;41(5):617-618. **2.** Saperstein DS, et al. *Muscle Nerve*. 2001;24(3):311-324. **3.** Koski CL, et al. *J Neurol Sci*. 2009;277(1-2):1-8. **4.** van den Bergh PYK, et al. *J Peripher Nerv Syst*. 2021. doi:10.1111/jns.12455.

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Take Home Messages About CIDP

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- According to EAN/PNS criteria, typical CIDP is a diagnosis that should be made based on clinical presentation and electrodiagnostic evidence (mandatory)[1]
- Treatment response, ultrasound imaging, MRI, CSF analysis, and nerve biopsy provide supportive evidence in possible CIDP[1]
- There are also several CIDP variants that can have slightly different clinical presentations[1]
- Awareness of these potentially treatable neuropathies is vital

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EAN, European Academy of Neurology; PNS, Peripheral Nerve Society.

Reference: 1. van den Bergh PYK, et al. *J Peripher Nerv Syst*. 2021. doi:10.1111/jns.12455.

CIDP Laboratory Features

- 3 classic laboratory studies:
  - –Cerebrospinal fluid
  - –Nerve biopsy
  - –Electrodiagnostic studies

- More recent tests
  - –MRI
  - –Ultrasound

Reference: van den Bergh PYK, et al. *J Peripher Nerv Syst*. 2021. doi:10.1111/jns.12455.

Cerebrospinal Fluid Analysis

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- The EAN/PNS guidelines suggest that CSF analysis not be performed if the diagnostic criteria for CIDP have already been met[1]
- Circumstances where CSF analysis should be considered[1]:
  - The diagnostic criteria for possible CIDP, but not CIDP, have been fulfilled
  - Acute or subacute onset of CIDP
  - Suspected or possible infectious or malignant etiology
- Elevated CSF protein should be interpreted cautiously in people with diabetes[1]
- Rigorous CSF protein cutoff values that support a diagnosis of CIDP have not been established[1]
  - Newly established higher normative values for CSF protein are 50 mg/dL for people ≤50 years of age and 60 mg/dL for those >50 years of age[1,2]
  - Levels higher than these normative values are needed to support a CIDP diagnosis[1]

EAN, European Academy of Neurology; PNS, Peripheral Nerve Society.

References: 1. van den Bergh PYK, et al. *J Peripher Nerv Syst*. 2021. doi:10.1111/jns.12455.
2. Breiner A, et al. *Muscle Nerve*. 2019;60(2):180-183.

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Nerve Biopsy in CIDP

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- The EAN/PNS guidelines suggest that nerve biopsies not be performed routinely to diagnose CIDP but that they be reserved for specific circumstances:
  - When CIDP is suspected but cannot be confirmed with clinical, laboratory, imaging, and electrodiagnostic studies
  - When CIDP is suspected but there is little or no response to treatment and another diagnosis (eg, CMT, amyloidosis, sarcoidosis, or nerve sheath tumors/neurofibromatosis) might be considered
- In addition, nerve biopsies should be considered only when
  - A skilled (neuro)surgeon and neuropathologist are available, as well as a laboratory with expertise in the handling of nerve tissue
  - The severity of the patient's symptoms justifies the potential complications associated with a nerve biopsy
  - The patient fully understands the low accuracy of the test before undergoing the biopsy

CMT, Charcot-Marie-Tooth disease; EAN, European Academy of Neurology; PNS, Peripheral Nerve Society.

Reference: van den Bergh PYK, et al. *J Peripher Nerv Syst*. 2021. doi:10.1111/jns.12455.

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Histopathological Findings in CIDP

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- Nerve biopsy findings that may support a CIDP diagnosis:
  - Thinly myelinated axons and small onion bulbs
  - Thinly myelinated or demyelinated internodes in teased fibers
  - Perivascular macrophage clusters
- Features of demyelination on electron microscopy are supportive

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Reference: van den Bergh PYK, et al. *J Peripher Nerv Syst*. 2021. doi:10.1111/jns.12455.

Sural Nerve Biopsy Findings in CIDP

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	Barohn et al, 1989 N=56[a]	Bouchard et al, 1999 N=95[a]
Demyelination/ Remyelination	48%	72%
Axonal	21%	5%
Mixed	13%	21%
Normal	18%	2%
Inflammation	11%	19% (4%[b])

[a] Number of patients in the study who had a nerve biopsy performed.
[b] Percentage of patients with conspicuous inflammatory infiltrates.

References: 1. Barohn RJ, et al. *Arch Neurol.* 1989;46(8):878-884. **2.** Bouchard C, et al. *Neurology.* 1999;52(3):498-503.

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Imaging

- Ultrasound
  - Diagnosis of CIDP is suggested by enlargement of cross-sectional area in ≥2 sites in proximal median nerve or brachial plexus
    - >10 mm2 at forearm
    - >13 mm2 upper arm
    - >12 mm2 for nerve roots
- MRI
  - Enlargement or increased signal intensity of nerve roots on T2 sequences

Reference: van den Bergh PYK, et al. *J Peripher Nerv Syst*. 2021. doi:10.1111/jns.12455.

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Misdiagnosis of CIDP

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CIDP Overdiagnosis: A Serious Issue

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- Cornblath DR, Gorson KC, Hughes RA, Merkies IS. Observations on chronic inflammatory demyelinating polyneuropathy: a plea for a rigorous approach to diagnosis and treatment[1]
  - A plea to clinicians to be thorough and cautious in diagnosis

- Allen JA, Lewis RA. CIDP diagnostic pitfalls and perception of treatment benefit[2]
  - Reviewed 59 cases of diagnosed CIDP and found **~50%** were misdiagnosed according to the 2010 EFNS/PNS guidelines
  - Despite misdiagnosis, more than two-thirds of non-CIDP cases found treatment beneficial but less than 20% of these had definite improvement in strength or sensation

EFNS, European Federation of Neurological Societies; PNS, Peripheral Nerve Society.

References: 1. Cornblath DR, et al. *J Neurol Sci.* 2013;330(1-2):2-3. **2.** Allen JA, Lewis RA. *Neurology.* 2015;85(6):498-504.

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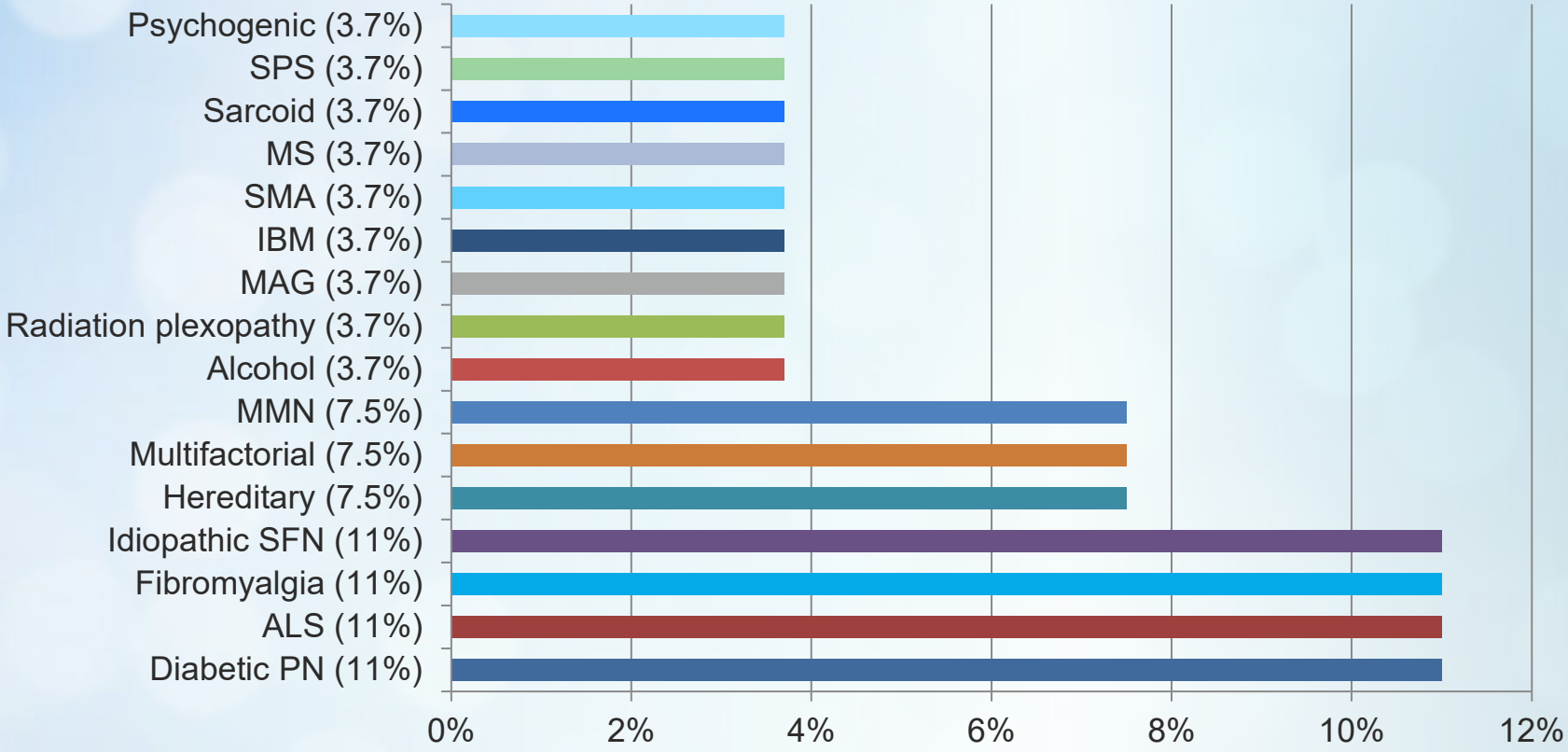
Diagnoses That Were Called CIDP



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.

Reference: Allen JA, Lewis RA. *Neurology.* 2015;85(6):498-504.

Diagnostic Data in CIDP and Not-CIDP Groups

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Patients Who Met 2010 EFNS/PNS Diagnostic Requirements for CIDP

	Clinical	NCS	CSF	MRI	Biopsy	Improve with Tx[a]
CIDP group (N= 31)	100%	100%	90.3%	75%	50%	89.6%
Not CIDP group (N=27)	44%	14.8%	50%	10.5%	0%	85.7%

[a] Subjective improvement, probable or definite.

- Objective evidence consistent with CIDP seen in a minority of not-CIDP group and yet most felt treatment helped
- Improvement was based on subjective report by patient, not by objective measures

EFNS, European Federation of Neurological Societies; PNS, Peripheral Nerve Society.

Reference: Allen JA, Lewis RA. *Neurology.* 2015;85(6):498-504.

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What Caused Misdiagnosis?

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- Clinically
  - –All misdiagnoses that met 2010 EFNS/PNS **clinical** criteria were variants (not proximal/distal symmetric weakness)
  - –Not meeting 2010 EFNS/PNS criteria
- Electrodiagnosis
  - –Misinterpreting conduction slowing when CMAP amplitude is reduced
  - –Considering slowing at entrapment sites as CIDP
  - –Accepting conduction slowing in diabetics as CIDP
- Laboratory
  - –Emphasizing mild increases in CSF protein

EFNS, European Federation of Neurological Societies; GBS, Guillain-Barré syndrome; PNS, Peripheral Nerve Society.

Reference: Allen JA, Lewis RA. *Neurology.* 2015;85(6):498-504.

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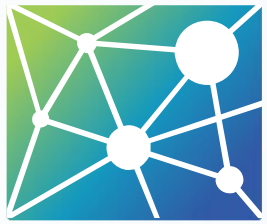

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