CIDP

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CIDP Variants

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CIDP Classification (latest guidelines, 2021)

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Typical CIDP

- Slow onset over ≥8 weeks
- May have initial acute presentation
- Chronic or stepwise progression
- Symmetrical symptoms
- Distal and proximal weakness
- Sensory dysfunction
- Absent or reduced tendon reflexes in all extremities

CIDP Variants

- Distal CIDP
- Multifocal CIDP
- Focal CIDP
- Motor CIDP
- Sensory CIDP

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

What is the defining feature of CIDP ?

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- Clinical features
- Electrophysiology showing acquired demyelination
- Pathology showing macrophage mediated demyelination
- Response to treatment

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What is a variant ?

- Differences in clinical phenotype ?
- Difference in electrophysiology ?
- Response to treatment ?
- Pathological differences ?
- Presence of antibodies ?

Clinical Features to Differentiate Typical CIDP and Selected CIDP Variants From Other Demyelinating Polyneuropathies

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Features	CIDP and CIDP Variants			Sensory	Motor
	CIDP[1]	Distal CIDP[1,2]	Multifocal CIDP[1,2]		
Weakness	• Symmetric • Proximal + distal • Steadily progressive or relapsing-remitting for >8 weeks	• Symmetric • Distally accentuated	• Asymmetric • Upper limbs > lower limbs	• None	• Yes
Sensory deficits	• Yes • Symmetric	• Yes • Symmetric	• Yes • Multifocal	• Yes	• No
Reflexes	• Reduced or absent	• Reduced or absent symmetrically	• Reduced or absent (multifocal or diffuse)	• Reduced	• Reduced or absent

MMN is not CIDP or a CIDP variant

MMN, multifocal motor neuropathy.

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.

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Electrophysiologic Findings to Differentiate Typical CIDP and Selected CIDP Variants From Other Demyelinating Polyneuropathies

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Findings	CIDP and CIDP Variants			Motor
	CIDP[1,2]	Distal CIDP[1,2]	Multifocal CIDP[1,2]	Sensory
Abnormal CMAPs: demyelinating features	• Usually symmetric	• Usually symmetric • Prolonged distal latencies	• Asymmetric (multifocal)	• Yes (cf. CISP)
Conduction block	• Frequent	• Uncommon	• Frequent	• No
Abnormal SNAPs	• Usually symmetric	• Usually symmetric	• Asymmetric (multifocal)	• Yes (cf. CISP)

MMN, multifocal motor neuropathy; SNAPs, sensory nerve action potentials.

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.

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CIDP With Acute Onset (not a variant)

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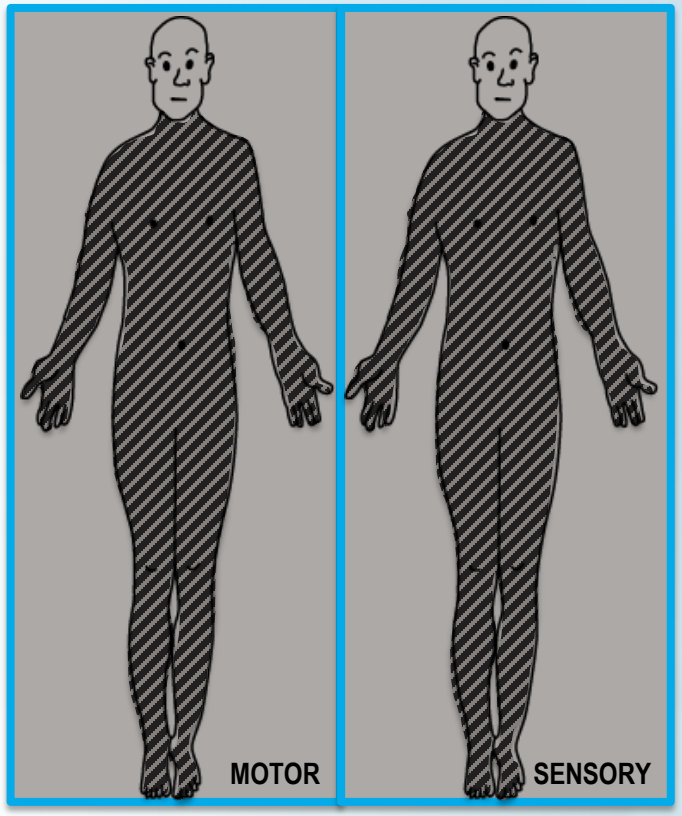
- CIDP[1,2]
  - Progression past 2 months
- Acute CIDP[1,2]
  - Presentation before 2 months
- Acute CIDP can be difficult to distinguish from GBS[1,2]
  - Like GBS, may present with limb and trunk weakness and sensory loss over trunk and limbs
  - Less likely to have facial weakness, autonomic dysfunction, severe disease, preceding illness[1,2]
- Be cautious when discharging GBS patients; further progression is possible
- May have paranodal antibodies (IgG3 subtype)



GBS, Guillain-Barré syndrome.

References: 1. Dionne A, et al. *Muscle Nerve.* 2010;41(2):202-207.
2. Ruts L, et al. *Neurology.* 2010;74(21):1680-1686.

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Distal CIDP

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What Is DADS?
Distal Acquired Demyelinating Symmetrical Neuropathy

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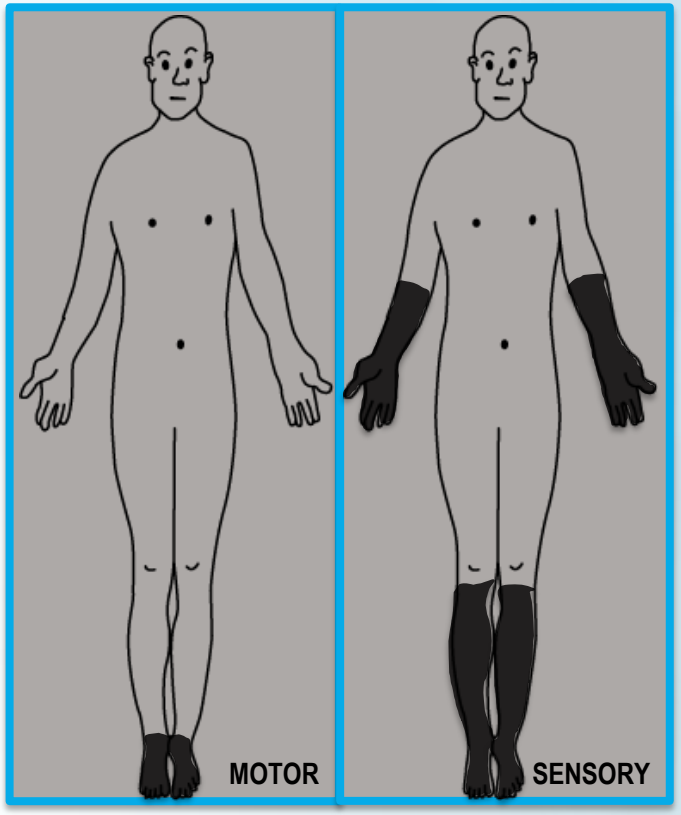
- DADS is a phenotype, not a diagnosis[1]
- Subacute or chronic onset[2]
- Length dependent (stocking-glove)[1]
- Despite the mostly sensory clinical presentation, motor nerves show demyelination on NCS[1]



References: 1. Katz JS, et al. *Neurology*. 2000;54(3):615-620.
2. Oh SJ, et al. *J Neurol Neurosurg Psychiatry*. 1992;55(8):677-680.

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Why Write About DADS?

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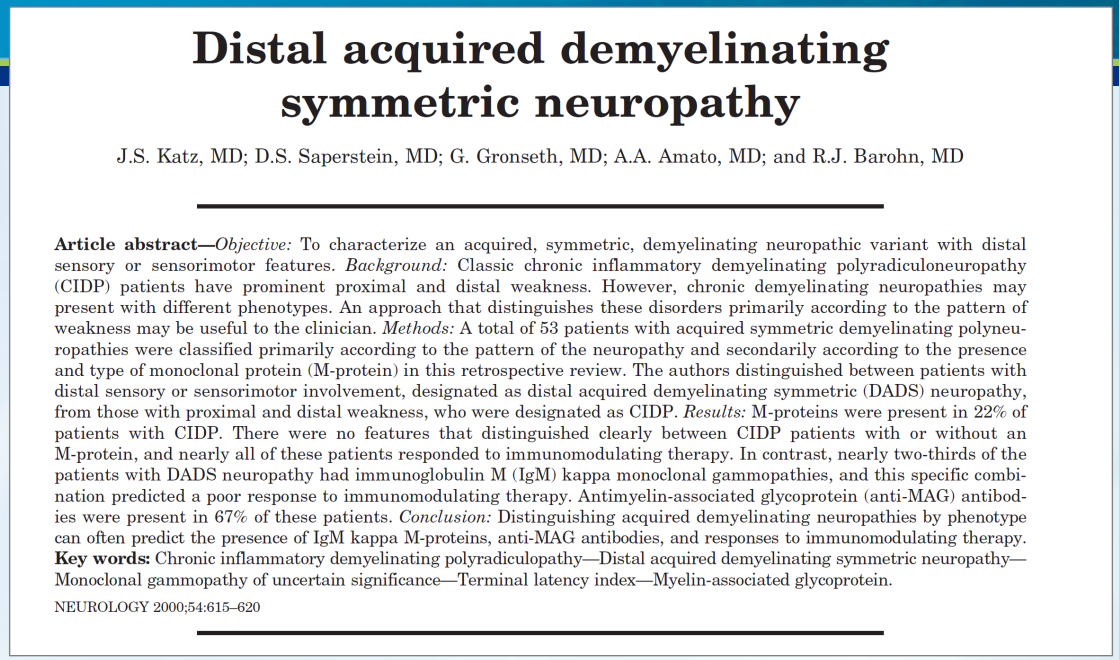

Distal acquired demyelinating symmetric neuropathy

J.S. Katz, MD; D.S. Saperstein, MD; G. Gronseth, MD; A.A. Amato, MD; and R.J. Barohn, MD

Article abstract—*Objective:* To characterize an acquired, symmetric, demyelinating neuropathic variant with distal sensory or sensorimotor features. *Background:* Classic chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) patients have prominent proximal and distal weakness. However, chronic demyelinating neuropathies may present with different phenotypes. An approach that distinguishes these disorders primarily according to the pattern of weakness may be useful to the clinician. *Methods:* A total of 53 patients with acquired symmetric demyelinating polyneuropathies were classified primarily according to the pattern of the neuropathy and secondarily according to the presence and type of monoclonal protein (M-protein) in this retrospective review. The authors distinguished between patients with distal sensory or sensorimotor involvement, designated as distal acquired demyelinating symmetric (DADS) neuropathy, from those with proximal and distal weakness, who were designated as CIDP. *Results:* M-proteins were present in 22% of patients with CIDP. There were no features that distinguished clearly between CIDP patients with or without an M-protein, and nearly all of these patients responded to immunomodulating therapy. In contrast, nearly two-thirds of the patients with DADS neuropathy had immunoglobulin M (IgM) kappa monoclonal gammopathies, and this specific combination predicted a poor response to immunomodulating therapy. Antimyelin-associated glycoprotein (anti-MAG) antibodies were present in 67% of these patients. *Conclusion:* Distinguishing acquired demyelinating neuropathies by phenotype can often predict the presence of IgM kappa M-proteins, anti-MAG antibodies, and responses to immunomodulating therapy.
Key words: Chronic inflammatory demyelinating polyradiculopathy—Distal acquired demyelinating symmetric neuropathy—Monoclonal gammopathy of uncertain significance—Terminal latency index—Myelin-associated glycoprotein.

NEUROLOGY 2000;54:615–620

- Focus on different approaches to distal versus generalized phenotypes
- Goals of paper:
  1. Distinct symmetric clinical presentations result in different bedside scenarios
  2. IgM paraprotein differentiates DADS-I from DADS-M
  3. IgM/MAG neuropathy is a distinct disease

DADS, distal acquired demyelinating symmetrical neuropathy; MAG, myelin-associated glycoprotein.
Reference: Katz JS, et al. *Neurology.* 2000;54(3):615-620. http://www.neurology.org/.
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Distal CIDP Is a Key Clinical Situation

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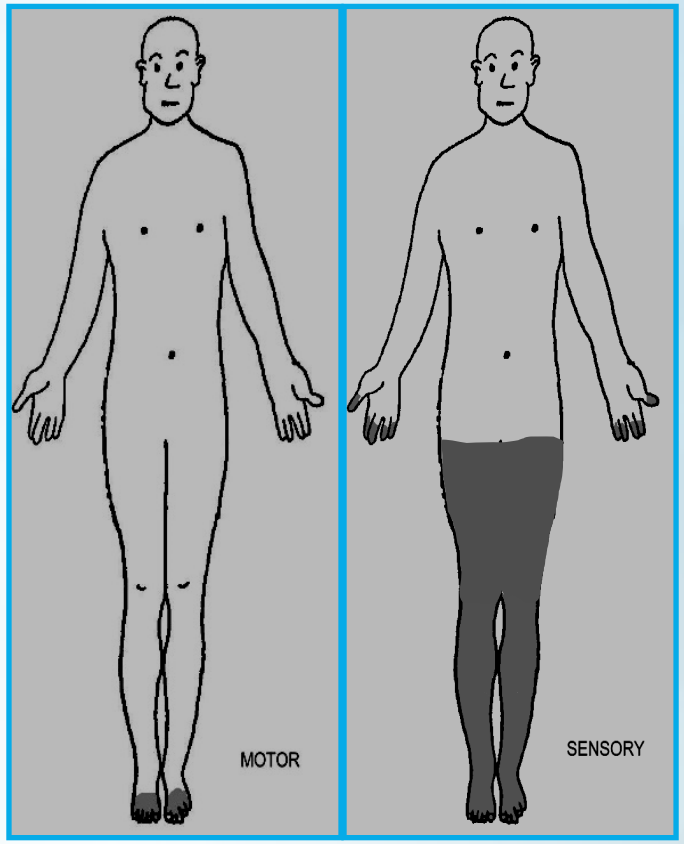
- Reason: The key differential diagnoses are the more common polyneuropathies
  - Idiopathic and diabetic
- Challenge is to define exact electrodiagnostic and CSF cutoffs that distinguish CIDP from similar clinical presentations[1]
  - Myriad criteria
- Trial of therapy sometimes needed to be sure



Images courtesy of Jonathan Katz, MD, California Pacific Medical Center, San Francisco, CA.

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Reference: Jonathan Katz, MD, personal communication.

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Sensory CIDP

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Sensory CIDP: CIDP Variant Under New EAN/PNS Classification

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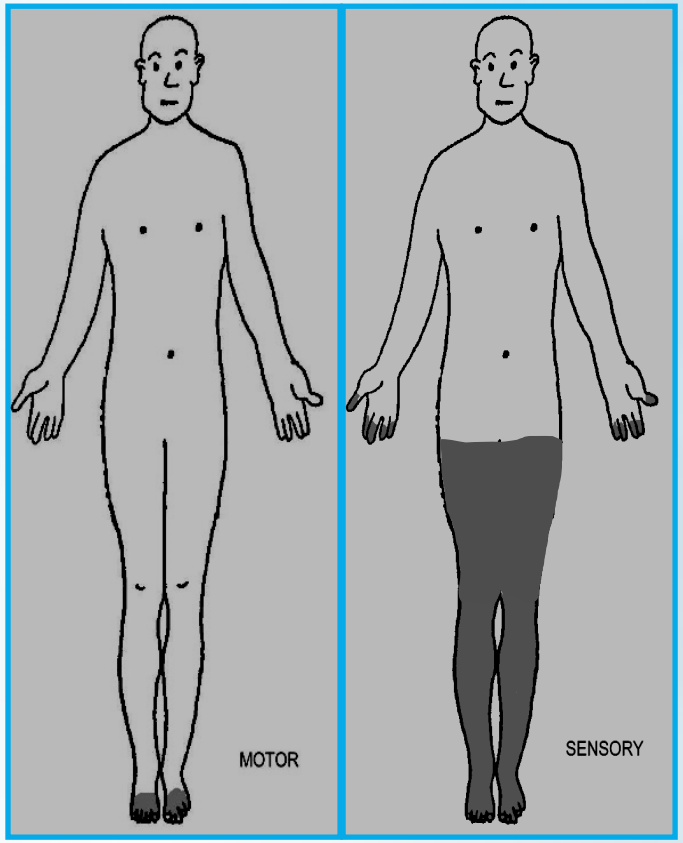
- First described by Oh et al, 1992
- Sensory clinical presentation but electrophysiology is sensorimotor
- Response to immunotherapy +
- Differentiate from CISP



Images courtesy of Jonathan Katz, MD, California Pacific Medical Center, San Francisco, CA.

CISP, chronic immune sensory polyradiculopathy; DADS, distal acquired demyelinating symmetrical neuropathy; 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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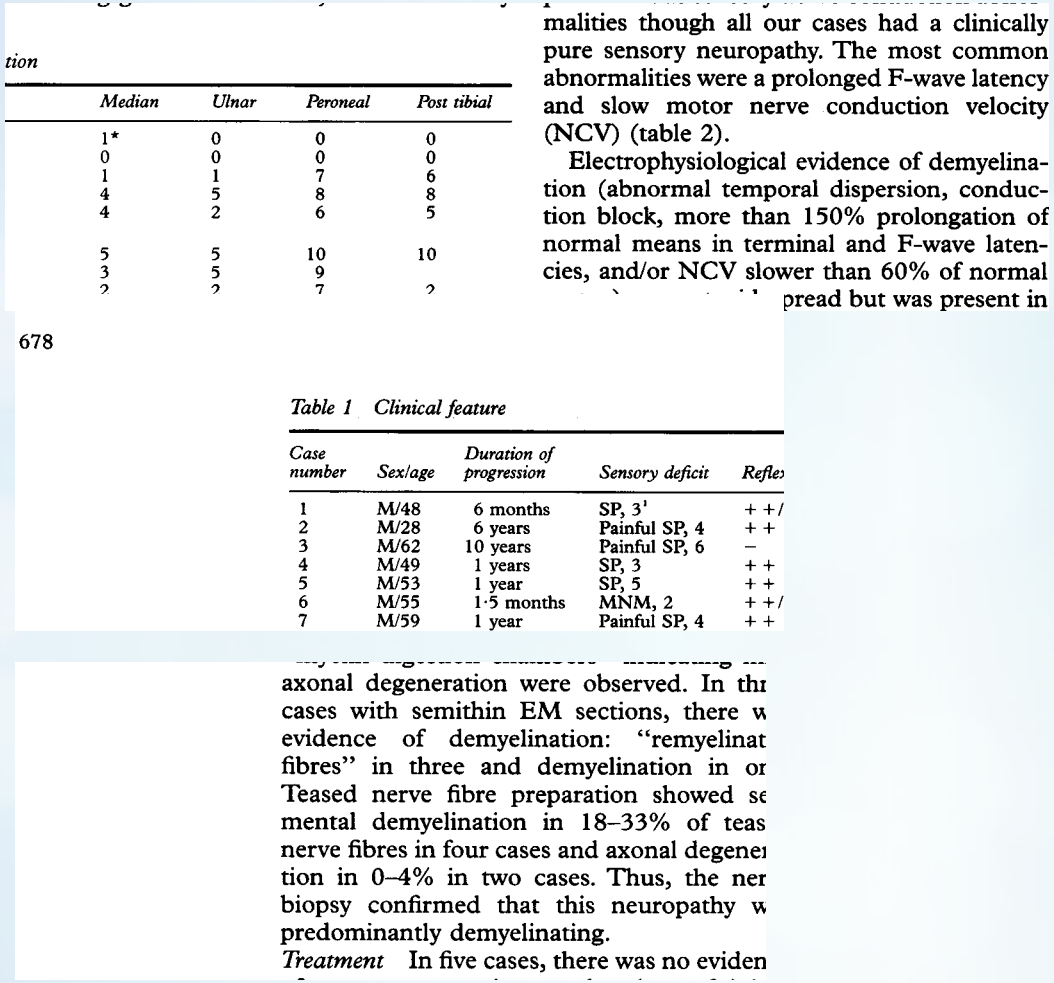
Oh et al, JNNP, 1992;55:677-680



tion

	Median	Ulnar	Peroneal	Post tibial
	1*	0	0	0
	0	0	0	0
	1	1	7	6
	4	5	8	8
	4	2	6	5
	5	5	10	10
	3	5	9	
	2	2	7	2

malities though all our cases had a clinically pure sensory neuropathy. The most common abnormalities were a prolonged F-wave latency and slow motor nerve conduction velocity (NCV) (table 2).

Electrophysiological evidence of demyelination (abnormal temporal dispersion, conduction block, more than 150% prolongation of normal means in terminal and F-wave latencies, and/or NCV slower than 60% of normal

pread but was present in

678

Table 1 Clinical feature

Case number	Sex/age	Duration of progression	Sensory deficit	Reflex
1	M/48	6 months	SP, 3'	+ +/
2	M/28	6 years	Painful SP, 4	+ +
3	M/62	10 years	Painful SP, 6	–
4	M/49	1 years	SP, 3	+ +
5	M/53	1 year	SP, 5	+ +
6	M/55	1·5 months	MNM, 2	+ +/
7	M/59	1 year	Painful SP, 4	+ +

axonal degeneration were observed. In thr cases with semithin EM sections, there w evidence of demyelination: "remyelinat fibres" in three and demyelination in or Teased nerve fibre preparation showed se mental demyelination in 18–33% of teas nerve fibres in four cases and axonal degener tion in 0–4% in two cases. Thus, the ner biopsy confirmed that this neuropathy w predominantly demyelinating.

Treatment In five cases, there was no eviden

Oh et al, 1992

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infection or event. There was no family history of a similar disease. The spinal fluid protein was high in most of cases. There were no cells in any cases. Oliogoclonal band was present in half of cases.

Diffuse nerve conduction abnormalities were invariable findings. Motor as well as sensory and mixed nerve conductions were affected. Electrophysiological evidences of

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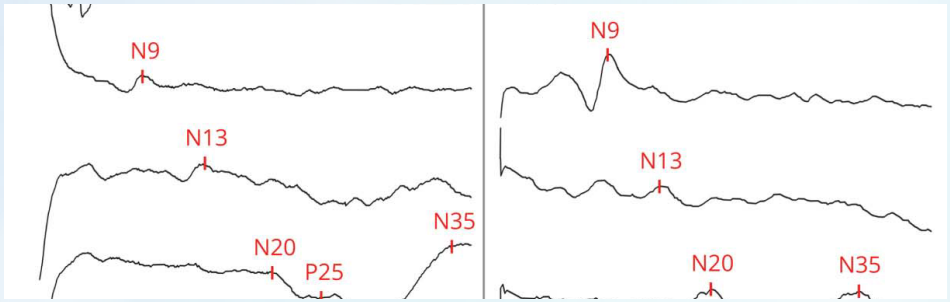
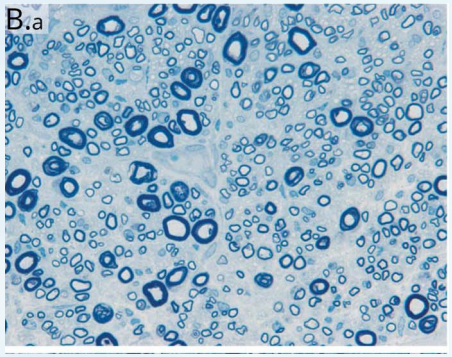
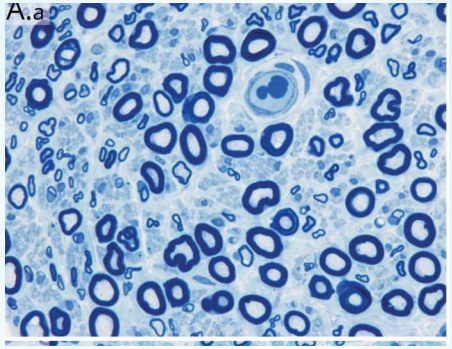
CISP and CISP-Plus, Dyck 2021





Dorsal rootlet biopsy CISP-Plus



Limb nerve CISP-Plus

Should CISP and CISP-Plus be characterized as CIDP variants ?

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- Pathology is similar to CIDP with immune mediated demyelination
- Clinical presentation is similar to sensory CIDP (sensory ataxia)
- Response to treatment with IVMP and IVIg is similar
- CISP-Plus bridges CISP to CIDP with involvement of sensory roots and distal nerve

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EAN/PNS Guidelines for CIDP: Combination of Clinical and Electrodiagnostic Criteria

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Inclusion Criteria

Typical CIDP

- Chronically progressive, stepwise, or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities
- ≥2 months duration
- Cranial nerves less frequently affected than in GBS

- Tendon reflexes absent/reduced in affected extremities

CIDP Variants

One of the following, but otherwise as in typical (tendon reflexes may be normal in unaffected limbs):

- Distal (DADS)
- Multifocal (MADSAM)
- Focal (plexus)
- Motor
- Sensory

Exclusion Criteria

- Infection, drug/toxin exposure
- Hereditary demyelinating neuropathy
- Prominent sphincter disturbance
- MMN, CISP, nodopathy
- IgM monoclonal gammopathy with high-titer antibodies to MAG
- Other causes of demyelinating neuropathy

CISP, chronic immune sensory polyradiculopathy; DADS, distal acquired demyelinating symmetrical neuropathy; EAN, European Academy of Neurology; GBS, Guillain-Barré syndrome; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; MAG, myelin-associated glycoprotein; MMN, multifocal motor neuropathy; 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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Multifocal CIDP

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Lewis Sumner Syndrome, 1982

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Table 1. Multifocal demyelinating neuropathy with persistent conduction block

Patient	Duration (years)	Clinical findings	Tinel sign	Reflexes		CSF protein (mg%)	Course and therapy
1	4	Multifocal sensorimotor neuropathy	Left ulnar n. at elbow Left axilla	Arms Legs	0 2+	Normal (21)	Slow progression No therapy
2	22	Generalized distal neuropathy with superimposed nerve trunk abnormalities	0	Arms Legs	0 0	Normal (19, 35, 45, 22)	Slow progression No therapy
3	1½	Mild generalized sensorimotor neuropathy with superimposed multifocal nerve trunk lesions Optic neuritis (VER = 120 msec)	0	Arms Legs	1+ 0	Mild increase (68, 50)	Neuropathy improved with prednisone Optic neuritis developed when steroids stopped
4	2½	Multifocal sensorimotor neuropathy	Left ulnar n. in forearm	Arms Knees Ankles	0 2+ 0	—	Clinical improvement on prednisone Relapse when dose was reduced
5	2	Mild multifocal sensorimotor	Left median n. in forearm and at	Arms Legs	0 2+	Mild increase	Condition stable without medication

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MADSAM, Saperstein et al 1999

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- 11 pts with multifocal demyelinating sensorimotor involvement
- 82% had elevated CSF protein
- Prominent demyelination on nerve biopsy
- Responded to IVIg and steroids
- Represents an asymmetric variant of CIDP cf. MMN

- Multifocal CIDP is LSS or MADSAM

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Multifocal CIDP

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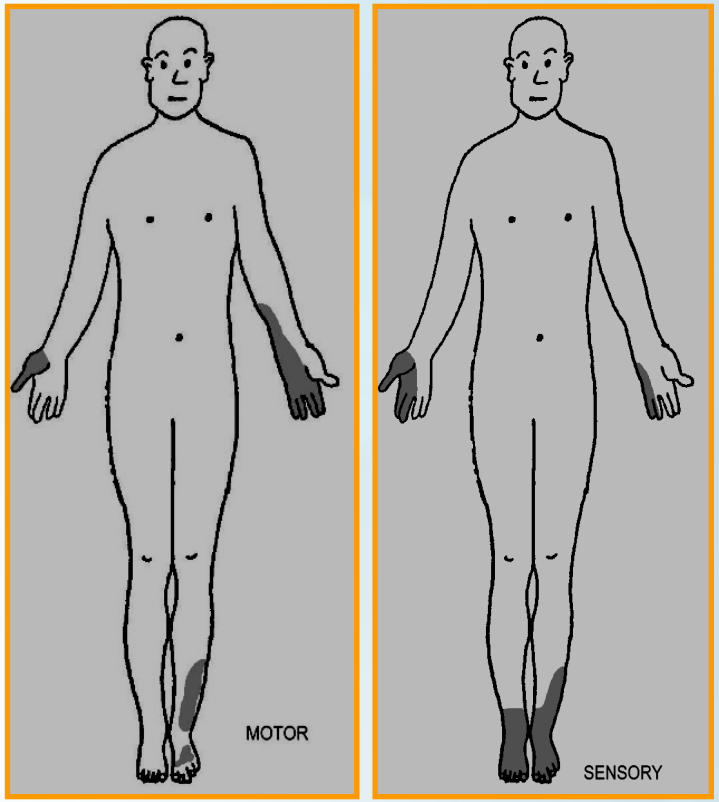
- Motor and sensory: MADSAM[1]
  - Multifocal acquired demyelinating sensory and motor neuropathy
  - Also called Lewis-Sumner syndrome
- Sensory and motor[1,2]
- Typically arms[1,2]
- Individual nerves[1,2]
- Stepwise progression[2]
- Main differential is mononeuritis multiplex from other causes and MMN[1,2]
- CSF protein elevated in 82% vs 9% in MMN[1]
- Responds to first-line treatment[1,2]



Images courtesy of Jonathan Katz, MD, California Pacific Medical Center, San Francisco, CA.

MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; MMN, multifocal motor neuropathy.

References: 1. Saperstein DS, et al. *Muscle Nerve.* 1999;22(5):560-566.
2. Dimachkie MM. *Neurol Clin.* 2013;31(2):533-555.

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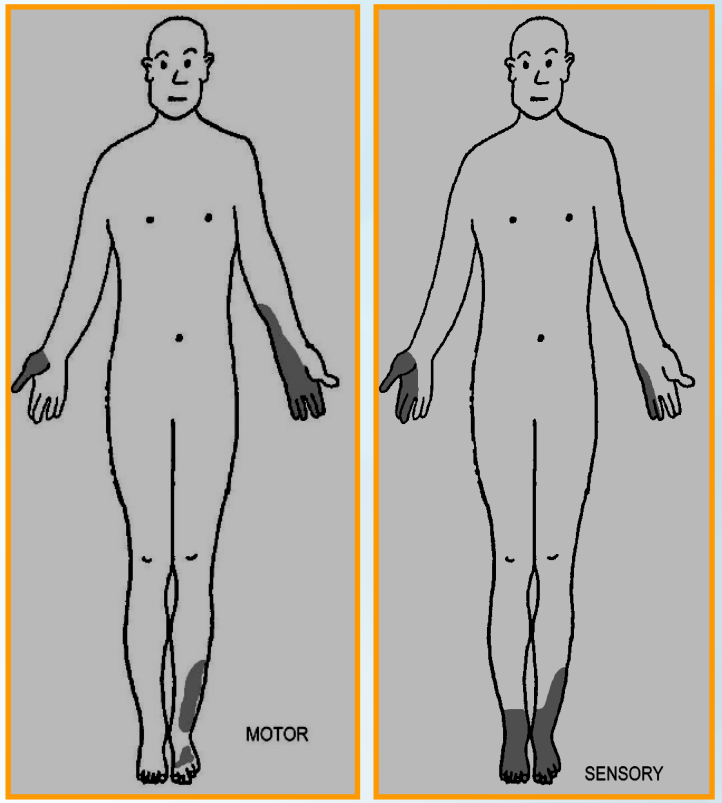
Focal CIDP

- Rare
- Usually affects brachial plexus or lumbosacral plexus
- Can affect individual peripheral nerves



Images courtesy of Jonathan Katz, MD, California Pacific Medical Center, San Francisco, CA.

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

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Motor CIDP

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Pure motor CIDP, Sabatelli 2001

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Tab. 1 Clinical features, CSF and nerve biopsy findings.

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	M	F	F	M
Age at onset (years)	12	25	29	3
Time from onset to peak severity	2 weeks	6 months	4 months	3 weeks
Rankin grade at peak severity	4	4	4	5
Clinical course	relapsing	relapsing	relapsing	relapsing
Cranial nerve involvement	No	No	Palpebral Ptosis	No
Duration of active disease (years)	11	12	4	1.5
Number of relapses	45	10	7	15
Response to therapies				
Corticosteroids	No	No	No	No
Azathioprine	Yes	No	No	No
IVIg*	Yes (0)	Yes (2)	Yes (1)	Yes (2)
Plasma exchange*	Yes (2)	No	Not done	Yes (2)
Cyclosporin A	Not done	Not done	Not done	No
Interferon alpha*	Not done	Yes (0)	Not done	Yes (0)
Present clinical status	Recovery	Recovery	Moderate weakness	Recovery
Present therapy	Azathioprine	Interferon	IVIg	None
Last relapse	1997	Sept. 1999	May 1999	1993
Myastenic-like fluctuations	Yes	No	Yes	No
CSF proteins (mg/dl) (NV < 40)	123	60	70	96
Sural nerve biopsy	Normal	Normal	Normal	Not done

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Motor CIDP

- "Relatively" symmetric
- Proximal and distal weakness
- Normal sensation and normal sensory NCS for years
- Differs from MMN, which has weakness in individual nerve territories and tends to affect the arms
- Differs from typical CIDP, which has abnormal sensation
- 50% pts responded to interferons

MMN, multifocal motor neuropathy; NCS, nerve conduction studies.

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

Multifocal Motor Neuropathy (MMN) Is Distinguished From CIDP by EAN/PNS Criteria[1]

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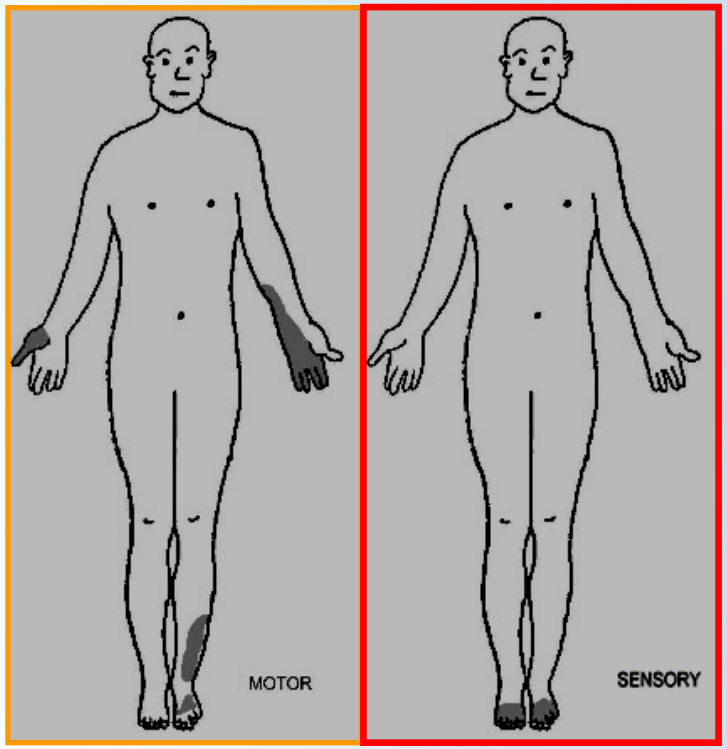
MMN

- Motor only[2,3]
  - Mild sensory symptoms are on border between MMN and MADSAM
  - No perfect divider
- Main differential of MMN is lower motor neuron ALS[3,4]
- Usually hands[3,4]
- Same stepwise progression[3]
- CSF usually normal[3]
- GM1 antibodies found in a percentage of these cases[2-4]



Images courtesy of Jonathan Katz, MD, California Pacific Medical Center, San Francisco, CA.

ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; EAN, European Academy of Neurology; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; PNS, Peripheral Nerve Society.

References: 1. van den Bergh PYK, et al. *J Peripher Nerv Syst*. 2021. doi:10.1111/jns.12455. **2.** Hahn AF, at al. *J Peripher Nerv Syst* 2013;18(4):321-330. **3.** Dimachkie MM. *Neurol Clin.* 2013;31(2):533-555. **4.** Katz J, et al. *Neurology* 1997;48:700-707.

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Demyelinating Neuropathies That Are Not CIDP

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Neuropathies that can be confused with CIDP:

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- Paraproteinemic neuropathy
  - Anti-MAG
  - IgM
  - POEMS
- Amyloid
- Inherited Neuropathy
  - CMT type 1
  - HNPP
- Diabetic Neuropathy
- Nodopathies
- CISP, CISP-Plus
- Multifocal Motor Neuropathy

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Why Do We Check for Monoclonal Proteins in Neuropathy (M Protein)?

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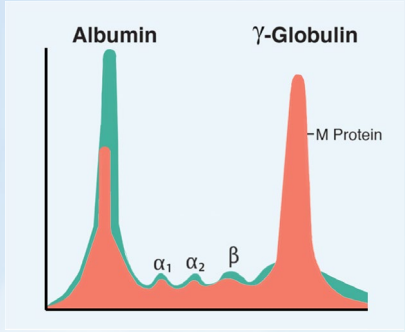
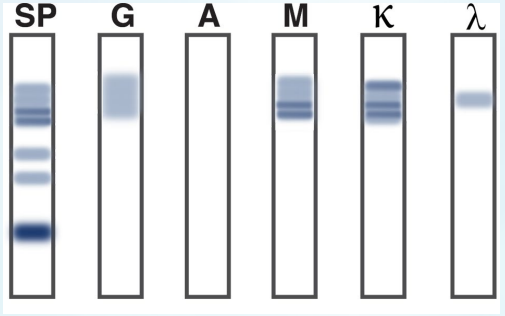
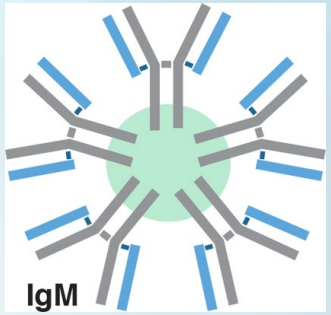


SPEP



IFE

- A monoclonal protein is simply an indicator of an underlying clone of plasma cells
- **Possibilities for what is happening:**
  1. **A benign clone (just making M proteins, usually termed "MGUS")**
  2. Malignant clone (proliferating, crowding out other cells, such as myeloma; usually IgG or IgA)
  3. ***Make antibodies that attack the nerve (typical of IgM neuropathy)***
  4. Cause hyperviscosity syndrome (Waldenström macroglobulinemia)
  5. Make amyloid
  6. Rarely, paraprotein is from a clone of cells invading nerve
  7. **Make toxic cytokines, as in POEMS**



IFE, immunofixation electrophoresis; MGUS, monoclonal gammopathy of undetermined significance; POEMS, polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes; SPEP, serum protein electrophoresis.

Reference: Cook L, Macdonald DHC. *Postgrad Med J.* 2007;83(978):217–223.

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DADS With IgM Paraprotein: Anti-MAG Neuropathy Triangle

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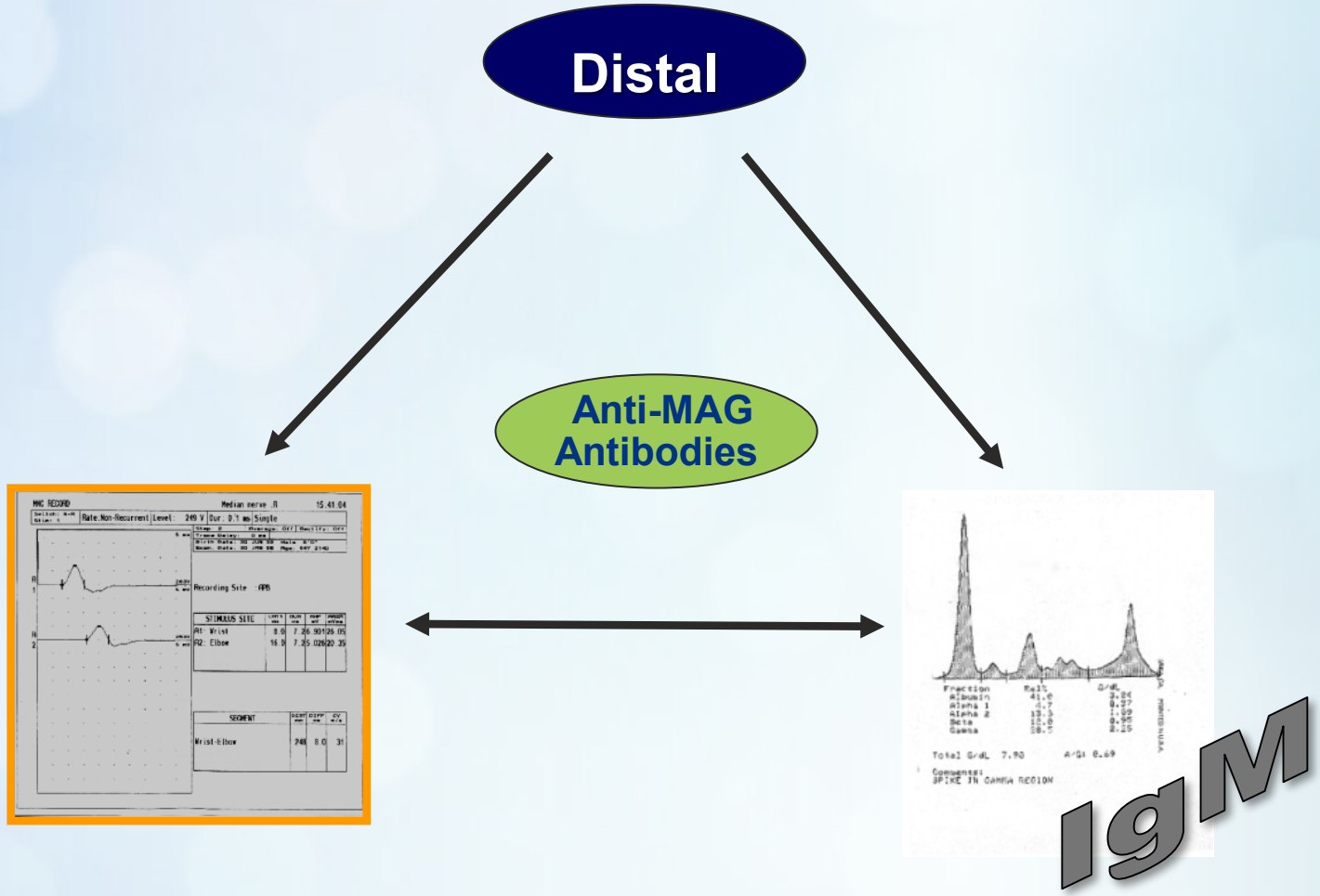

DADS, distal acquired demyelinating symmetrical neuropathy; MAG, myelin-associated glycoprotein.
Reference: Jonathan Katz, MD, personal communication.

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DADS With IgM Paraprotein: A Distinct Disorder

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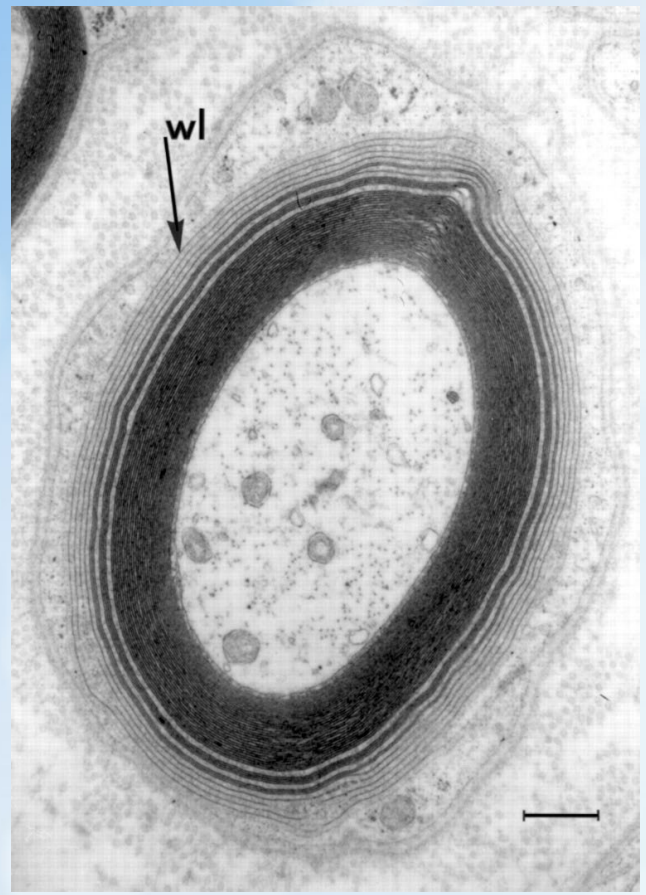

Image from Pollard JD, Young GA. *J Neurol Neurosurg Psychiatry*. 1997; 63(6):706-718. Reproduced with permission from BMJ Publishing Group Ltd.

- Older age[1]
- Mostly men[1]
- IgM paraprotein[1,2]
- Usually kappa light chains[1,2]
- Distal slowing on NCS[1,2]
- Responds poorly to immune therapies[1,2]
- Autoantibodies to MAG in many of these cases[1,2]

DADS, distal acquired demyelinating symmetrical neuropathy; MAG, myelin-associated glycoprotein; NCS, nerve conduction studies.

References: 1. Katz JS, et al. *Neurology*. 2000;54(3):615-620. **2.** Dimachkie MM, Barohn RJ. *Curr Treat Options Neurol*. 2013;15(3):350-366.

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POEMS

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- POEMS: Polyneuropathy, organomegaly, endocrinopathy, M protein, and skin changes[1]
  - Also papilledema or thrombocytosis
- Screen for osteosclerotic myeloma[1]
- Like CIDP, POEMS can present as an acquired demyelinating neuropathy[2,3]
- In general, POEMS has less involvement of distal latency and more axon loss[2,3]

References: 1. Dispenzieri A. *Am J Hematol.* 2015;90(10):951-962. **2.** Guo X, et al. *J Clin Neurosci.* 2014;21(4): 587-590. **3.** Mauermann ML, et al. *J Neurol Neurosurg Psychiatry.* 2012;83(5) 480-486.

Amyloid Neuropathy

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- Clinical picture and progression of CIDP and amyloid neuropathy may overlap[1]
- Overlap can be seen in either hereditary or acquired amyloid neuropathy[2]
- The electrophysiology of amyloid neuropathy and CIDP can be identical[2]
- CSF protein can be increased in both disorders[2]

CSF, cerebrospinal fluid.

References: 1. Cappellari M, et al. *J Peripher Nerv Syst.* 2011;16(2):119-129.
2. Mathis S, et al. *Muscle Nerve.* 2012;45(1):26-31.

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Amyloid Neuropathy (cont.)

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- Most patients (but not all) develop autonomic changes with postural hypertension, syncope, impotence, bowel and bladder incontinence, constipation[1]
- Cardiac and other organomegaly may not be present in diffuse amyloidosis causing motor weakness[2]
- Testing in suspected individuals (not routine) should include serum immunofixation, abdominal fat pad biopsy, and transthyretin gene test[1,3,4]

References: 1. Amato AA, Russell JA. *Neuromuscular Disorders.* 1st ed. New York, NY: McGraw-Hill Education; 2008:271-288. **2.** Briemberg HR, et al. *Muscle Nerve.* 2004;29(2):318-322. **3.** Mathis S, et al. *Muscle Nerve.* 2012;45(1):26-31. **4.** Shin SC, Robinson-Papp. *Mt Sinai J Med.* 2012;79(6):733-748.

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Inherited vs Acquired Demyelinating Neuropathies

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Inherited[1]

- Predominantly distal, symmetric weakness,
  pes cavus, severe atrophy
- Uniform conduction slowing in CMT-1A but conduction block less common
- Elevated CSF protein
- May not have family history
  - De novo mutations
  - Recessive disorders

Acquired[2]

- Proximal and distal weakness
- Non-uniform slowing
  - Temporal dispersion
  - Conduction block
- Elevated CSF protein

CMT-1A, Charcot-Marie-Tooth disease type 1A; CSF, cerebrospinal fluid.

References: 1. Hoyle JC, et al. *Appl Clin Genet*. 2015; 8:235-243.
2. Dalakas MC. *Nat Rev Neurol*. 2011;7(9):507-517.

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CIDP in Diabetics

- Diabetic neuropathy may have conduction slowing out of proportion to amplitude reduction
  - Diabetes itself is associated with a neuropathy marked by both axonal loss and demyelination[1]
- Diabetics also have predisposition to conduction slowing at sites of compression[2]
- CSF protein increased in diabetics up to 100 mg/dL[3]

CSF, cerebrospinal fluid.

References: 1. Tracy JA, Dyck PJ. *Phys Med Rehabil Clin N Am.* 2008;19(1):1-26. **2.** Jonathan Katz, MD, personal communication. **3.** Lotan I, et al. *Acta Neurologica Scandinavica.* 2015;132(4):278-283.

Alternative View: CIDP Is Being Missed in Diabetics

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- CIDP patients with diabetes (CIDP + DM) may present with a different clinical phenotype and electrophysiological profile than CIDP patients without diabetes (CIDP – DM)
  - CIDP + DM patients likely to have more severe abnormalities
  - But they are less likely to receive appropriate treatment
- Response rates to CIDP therapies are similar with or without DM; clinicians need to consider the possibility of CIDP + DM

DM, diabetes mellitus.

Reference: Dunnigan SK, et al. *PLoS ONE.* 2014;9(2):e89344.

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Typical CIDP Differs From Diabetic Neuropathy

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Distal and proximal weakness[1]	Distal weakness, mainly in the feet[3]
Motor and sensory loss[1]	Sensory loss, with no motor loss observed[3]
Reduced or absent reflexes[1]	Most have absent DTRs at ankles[3]
Symptoms evolve over months[1]	Symptoms generally evolve over years[3]
Significant pain is less likely[2]	Significant pain is more likely[4,5]

- Diabetic neuropathy is associated with a neuropathy marked by both axonal loss and demyelination,[6] at times with conduction slowing out of proportion to amplitude reduction due to concomitant mononeuropathies (eg, median nerve at the wrist, ulnar nerve at the elbow, peroneal nerve at the fibular head)[7]
- CSF protein increased in diabetics up to 100 mg/dL[8]

CSF, cerebrospinal fluid; DTR, deep tendon reflexes.

References: 1. Köller H, et al. *N Engl J Med.* 2005;352(13):1343-1356. **2.** Dyck PJB, Tracy JA. *Mayo Clin Proc*. 2018;93(6):777-793. **3.** Llewelyn JG. *J Neurol Neurosurg Psychiatry*. 2003;74 suppl 2(suppl 2):ii15-ii19. **4.** Galosi E, et al. *Acta Diabetol*. 2021. doi:10.1007/s00592-021-01767-x. **5.** Bouhassira D, et al. *PLoS One*. 2013;8(9):e74195. **6.** Tracy JA, Dyck PJ. *Phys Med Rehabil Clin N Am.* 2008;19(1):1-26. **7.** Jonathan Katz, MD, personal communication. **8.** Lotan I, et al. *Acta Neurologica Scandinavica.* 2015;132(4):278-283.

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Nodopathies and Antibodies Affecting Node of Ranvier

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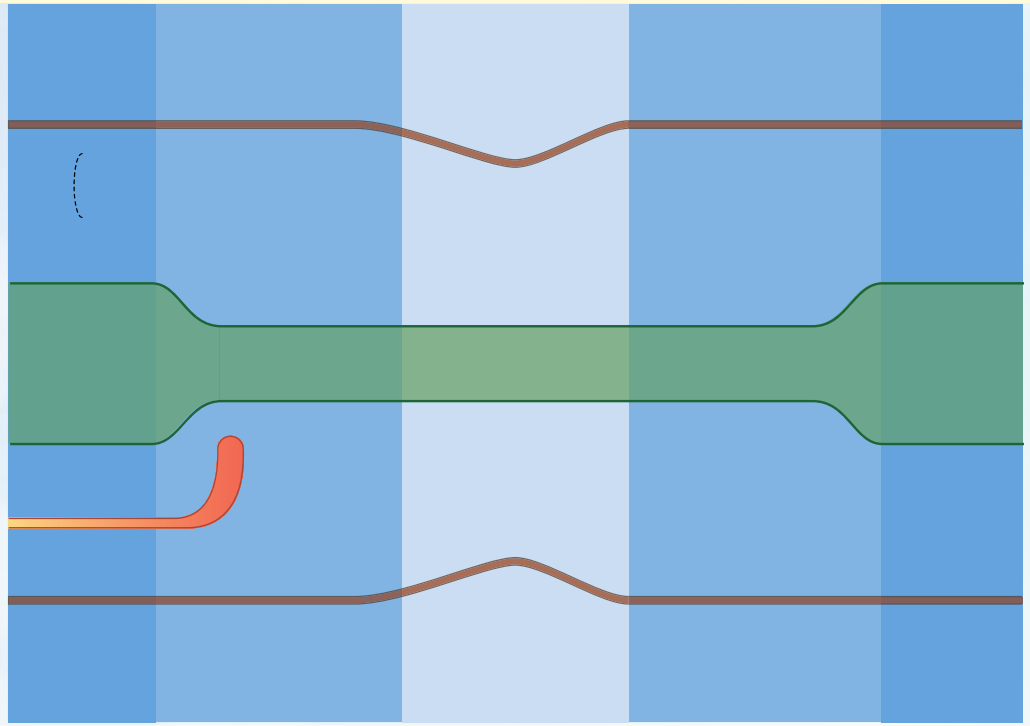
- Early reports described presentation as mainly sensory, often with tremor, and poor response to IVIg[1]
- Target antigens:
  - Concentrated at nodes of Ranvier or at paranodes[2]
  - Cell adhesion molecules such as NrCAM, gliomedin, contactin-1, NF186, and NF155[2]
- NCS with slowing and generalized conduction block typical of CIDP
- Clinical phenotypes are similar to DADS phenotype
- Subsequent papers suggested that antibodies are not so specific to a given clinical presentation, and may show up in various neuropathy types (CIDP, CMT, idiopathic)[2]

CMT, Charcot-Marie-Tooth disease; DADS, distal acquired demyelinating symmetrical neuropathy; NCS, nerve conduction studies; NF, neurofascin; NrCAM, neuronal cell adhesion molecule.

References: 1. Devaux JJ, et al. *Neurology*. 2016;86(9):800-807. **2.** Burnor E, et al. *Neurology*. 2018;90(1):e31-e38.

Brain, 2021



rom Bunschoten *et al.*[1]

Nodopathies and Antibodies Affecting Node of Ranvier

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- Consider ordering nodopathy antibodies if:
  - Resistant to standard therapy
  - Acute or subacute aggressive onset, previous diagnosis of GBS
  - Low-frequency tremor
  - Ataxia disproportionate to the sensory involvement (or other cerebellar features)
  - Predominantly distal weakness
  - Respiratory failure and cranial nerve involvement
  - Associated nephrotic syndrome
  - Very high CSF protein levels

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CSF, cerebrospinal fluid; GBS, Guillain-Barré syndrome.

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

Van Doorn et al, 2021

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ataxic variants. Although patients with autoimmune nodopathies usually meet the clinical and electrodiagnostic criteria for CIDP or its variants, they may be considered to have a disease different from CIDP because they lack classical demyelination and overt signs of inflammation on nerve biopsy, and respond differently to treatment.

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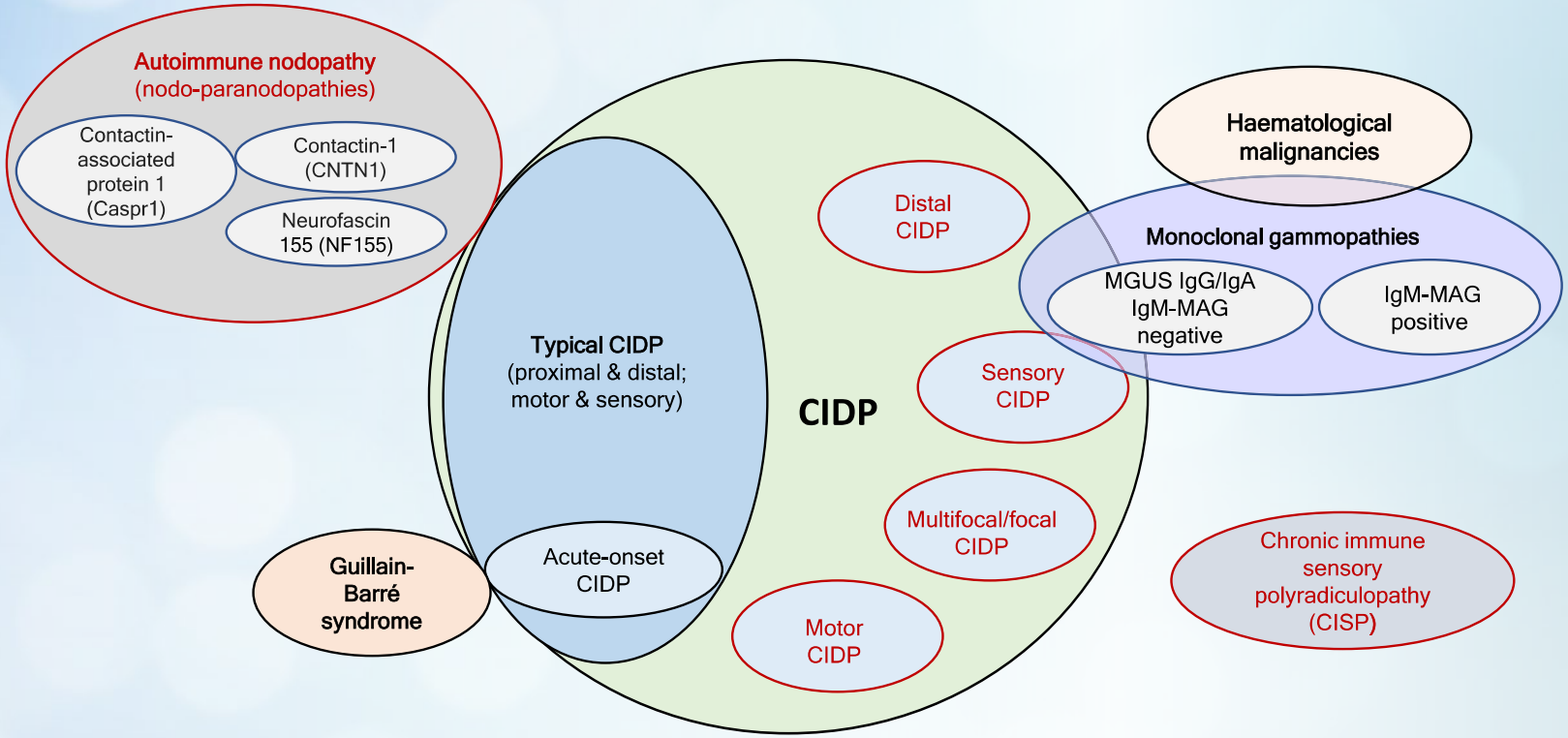
Lewis et al, Journal of the Neurol Sci, 2022



Current Guidelines for Diagnosis & Treatment of CIDP:

Van Den Bergh et al, 2021 JPNS 2021:26;242-268

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CIDP variants

One of the following, but otherwise as in typical CIDP (tendon reflexes may be normal in unaffected limbs):

- Distal CIDP: distal sensory loss and muscle weakness predominantly in lower limbs
- Multifocal CIDP: sensory loss and muscle weakness in a multifocal pattern, usually asymmetric, upper limb predominant, in more than one limb
- Focal CIDP: sensory loss and muscle weakness in only one limb
- Motor CIDP: motor symptoms and signs without sensory involvement
- Sensory CIDP: sensory symptoms and signs without motor involvement

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Unmet needs in the current guidelines:

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- If multifocal CIDP (LSS) and motor CIDP are variants of CIDP why not MMN ?
- Motor CIDP may be more diffuse MMN and response to treatment may be similar
- Should nodopathies be classified as variants ?
- Should CISP be classified as ‘sensory CIDP’ ?

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Impact of updated CIDP guideline on everyday clinical practice:

Muley and Beydoun, Ther Adv Neurol Dis 2023: 16

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Table 1. Overview of the suggested edits to the 2021 EAN/PNS CIDP guideline.

Guidelines statements	Suggested modifications	References, supporting documentation
Autoimmune nodopathies, defined by the detection of antibodies against nodal-paranodal cell adhesion molecules, should no longer be regarded as CIDP variants Testing for nodal and paranodal antibodies should be considered in all patients with clinical suspicion of CIDP when these tests are available and meet quality standards	As long as antibody testing is not readily available to confirm the diagnosis, nodopathies should be considered as a CIDP variant to avoid confusion, diagnostic, and treatment delays Future guidelines should include advice on treatment strategies when nodopathies diagnoses are made after antibody testing, to avoid a lack of practical guidance for this patient population	Lewis *et al.*[6]: review confirming the lack of availability of good quality antibody testing
There is not enough evidence to determine if CISP is demyelinating or related to sensory CIDP, and CISP has therefore not been included in the CIDP variant classification	Given the clinical resemblance to sensory CIDP, responsiveness to IVIg, and similar cerebrospinal fluid findings, classifying CISP as a separate entity might further delay diagnosis and treatment. Therefore, CISP should be classified as a CIDP variant	Rajabally *et al.*[7]: editorial discussing the inclusion of chronic immune polyradiculopathies in the CIDP classification

CIDP, Chronic inflammatory demyelinating polyneuropathy; CISP, chronic immune sensory polyradiculopathy; EAN/PNS, European Academy of Neurology/Peripheral Nerve Society; IVIg, intravenous immunoglobulin.

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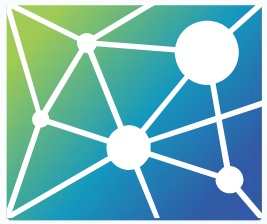

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