UT Southwestern
O'Donnell Brain Institute

Chronic Inflammatory Demyelinating Polyneuropathies (CIDP) and Mimics: Diagnosis and Treatment Updates

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Disclosures

- UCB pharma

Peripheral nervous system

Neuron Cell Body

- Anterior Horn Cell (motor)
- Dorsal Root Ganglion (sensory)

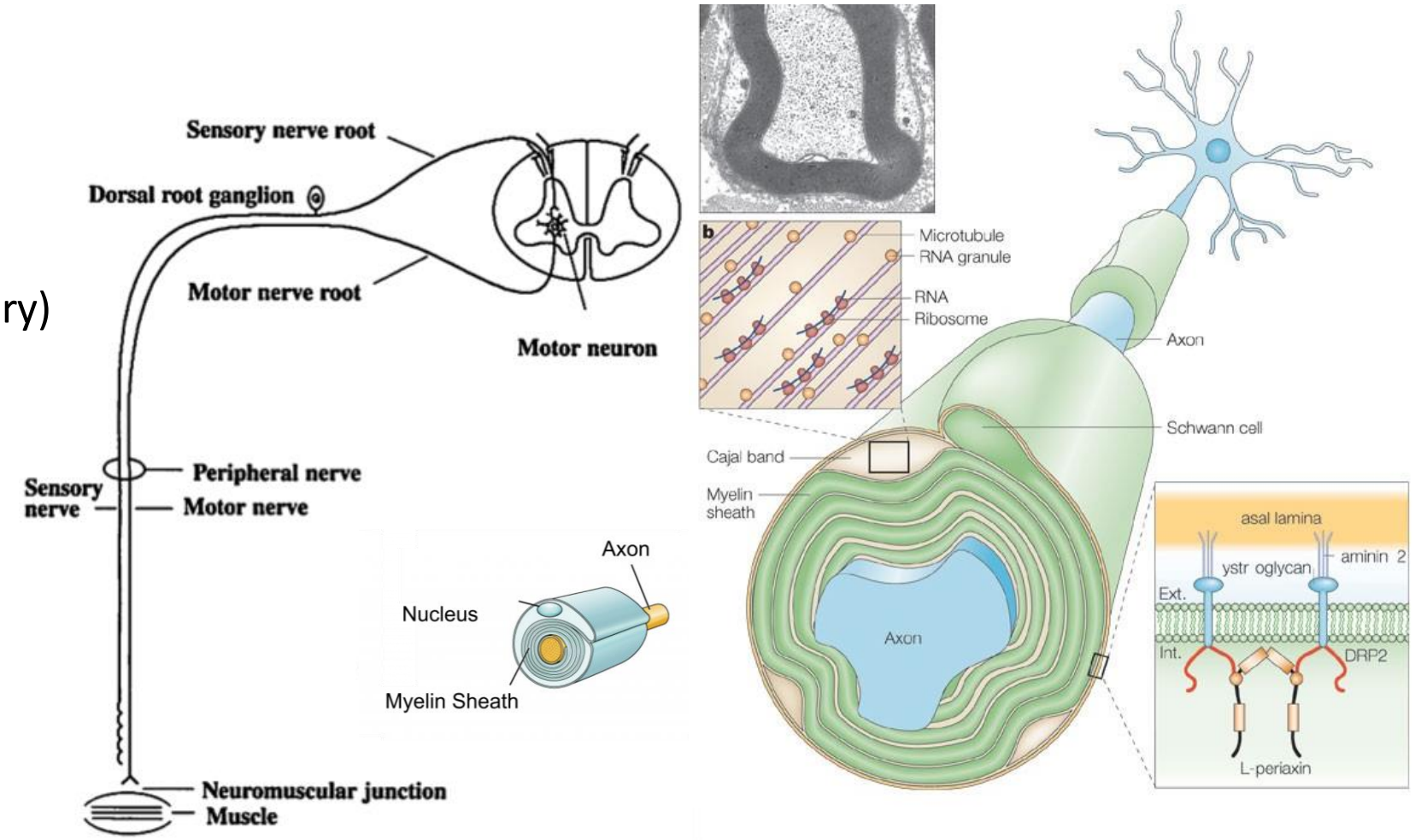
Nerve Root

Peripheral Nerve

- Axons
- **Myelin**

Neuromuscular Junction

Muscle



Sherman, D., Brophy, P. Mechanisms of axon ensheathment and myelin growth. *Nat Rev Neurosci* **6**, 683–690 (2005)

https://openbooks.lib.msu.edu/introneuroscience1/chapter/cells-of-the-nervous-system-glia/

Neuropathy – *suggesting exam features*

Demyelinating

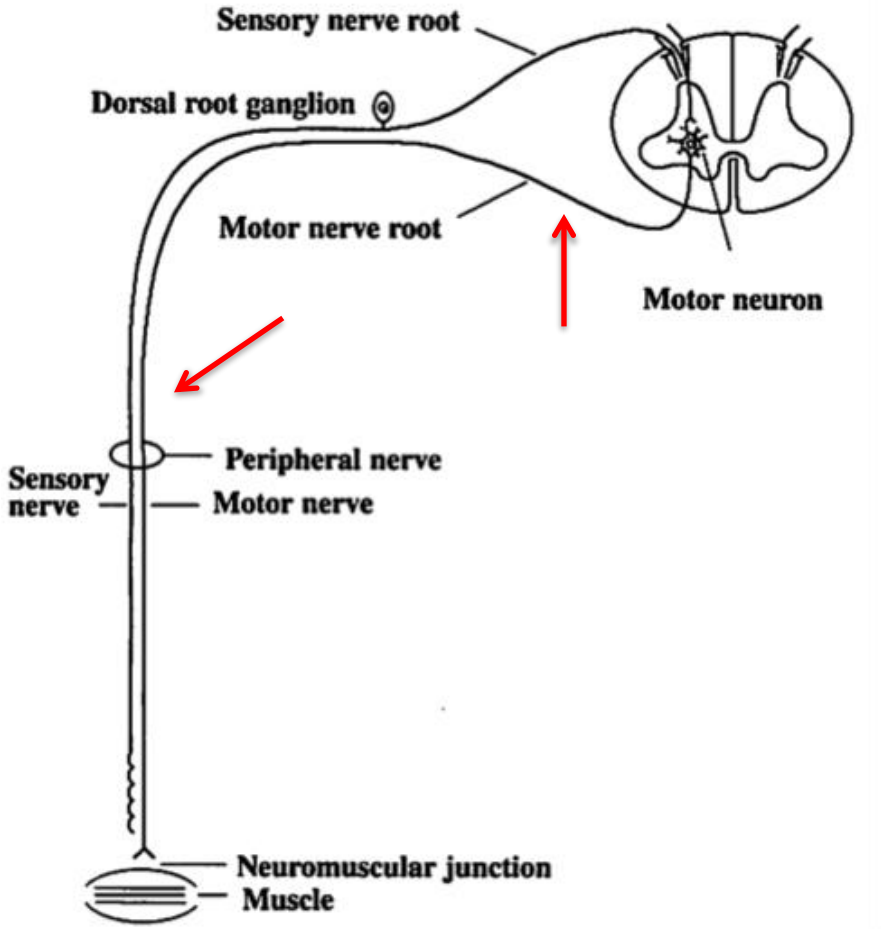
- Weakness without atrophy
- Motor predominant
- Radicular pain
- Non-length-dependent - **distal + proximal**
  - **Hallmark of typical CIDP**
- Patchy, asymmetric or symmetric
- Usually acute to subacute in onset

Axonal

- **Distal** > proximal symmetric sensorimotor disturbances
  - Sensory predominant, small + large fiber abnormalities
  - Weakness of flexion/extension of great toe + small toes early
- Legs (**feet**) > arms (hands) - longer axons more susceptible
- Muscle atrophy
  - Intrinsic hand + foot muscles

CIDP

- Immune-mediated demyelinating poly*radiculo*neuropathy - inflammation of nerve roots + peripheral nerve
- RARE, incidence of 0.33 per 100,000 population
- Cell mediated & antibody mediated inflammation
  - Causes *demyelination/remyelination*
  - Predilection for spinal roots + proximal nerve trunks, large fiber peripheral nerve
  - More vibration/proprioception loss vs pain/temp sensory changes (ie small fiber)



CIDP Diagnostic Criteria

- Mostly idiopathic, can be triggered
- Various clinical presentations
  - Can affect cranial nerves

Typical CIDP

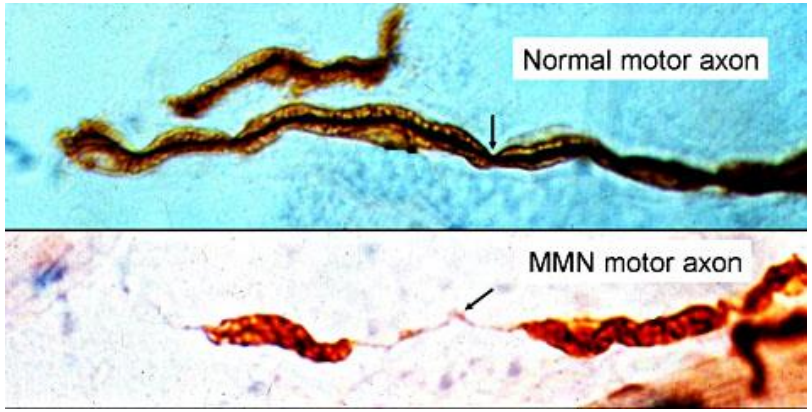
Atypical CIDP (**"CIDP variant"**) based on sx + exam findings

1. Distal CIDP or "DADS"
2. Multifocal CIDP (Lewis-Sumner variant or MADSAM)
3. Focal (brachial or LS plexus or ≥ 1 nerve in 1 limb)
4. Motor CIDP
5. Sensory CIDP

TABLE. SUMMARY OF EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES/PERIPHERAL NERVE SOCIETY DIAGNOSTIC CRITERIA (2010) FOR CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY (CIDP)

	Typical	Atypical
Clinical criteria	Chronically progressive, stepwise or recurrent symmetric proximal and distal weakness and sensory dysfunction of all extremities that developed over ≥2 months with absent or reduced tendon reflexes in all extremities	Predominantly distal (distal acquired demyelinating symmetric [DADS])
		Asymmetric (multifocal acquired demyelinating sensory and motor neuropathy [MADSAM], Lewis-Sumner syndrome)
		Focal (involving brachial or lumbosacral plexus or ≥1 nerves in 1 limb)
		Pure motor
		Pure sensory
	NOT caused by *Borrelia* infection (Lyme disease), diphtheria, drug, or toxin Nonhereditary Without prominent sphincter disturbance	
	Not meeting criteria for multifocal motor neuropathy, IgM with high titer antiMAG antibodies, POEMS syndrome, osteosclerotic myeloma, diabetic or nondiabetic lumbosacral radiculoplexus neuropathy, lymphoma, amyloidosis	

83% sensitivity, 94% specificity



https://neuromuscular.wustl.edu/antibody/pnimdem.html

MMN: segmental demyelination but not a CIDP

Electrodiagnostic criteria

- *Not all slowing on NCS is demyelinating*
- Axonal loss leads to slowing – prolonged latencies, slowed CV's

(EFNS/PNS) 2021 diagnostic criteria

Electro-physiologic criteria	**Definite:** includes at least 1 of the following:
	Prolonged motor distal latency ≥50% above upper limit of normal (ULN) in 2 nerves (not including median neuropathy at wrist from carpal tunnel syndrome), or
	Reduced motor conduction velocity ≥30% below lower limit of normal (LLN) in 2 nerves, or
	Prolonged F-wave latency ≥30% above ULN in 2 nerves (≥50% if amplitude of distal negative peak compound muscle
	demyelinating parameter is seen in ≥1 other nerve(s)
	Possible: any of the electrophysiologic criteria for definite CIDP, but in 1 nerve only

NCS VALUES NEEDED TO BE CONSIDERED "DEMYELINATING"

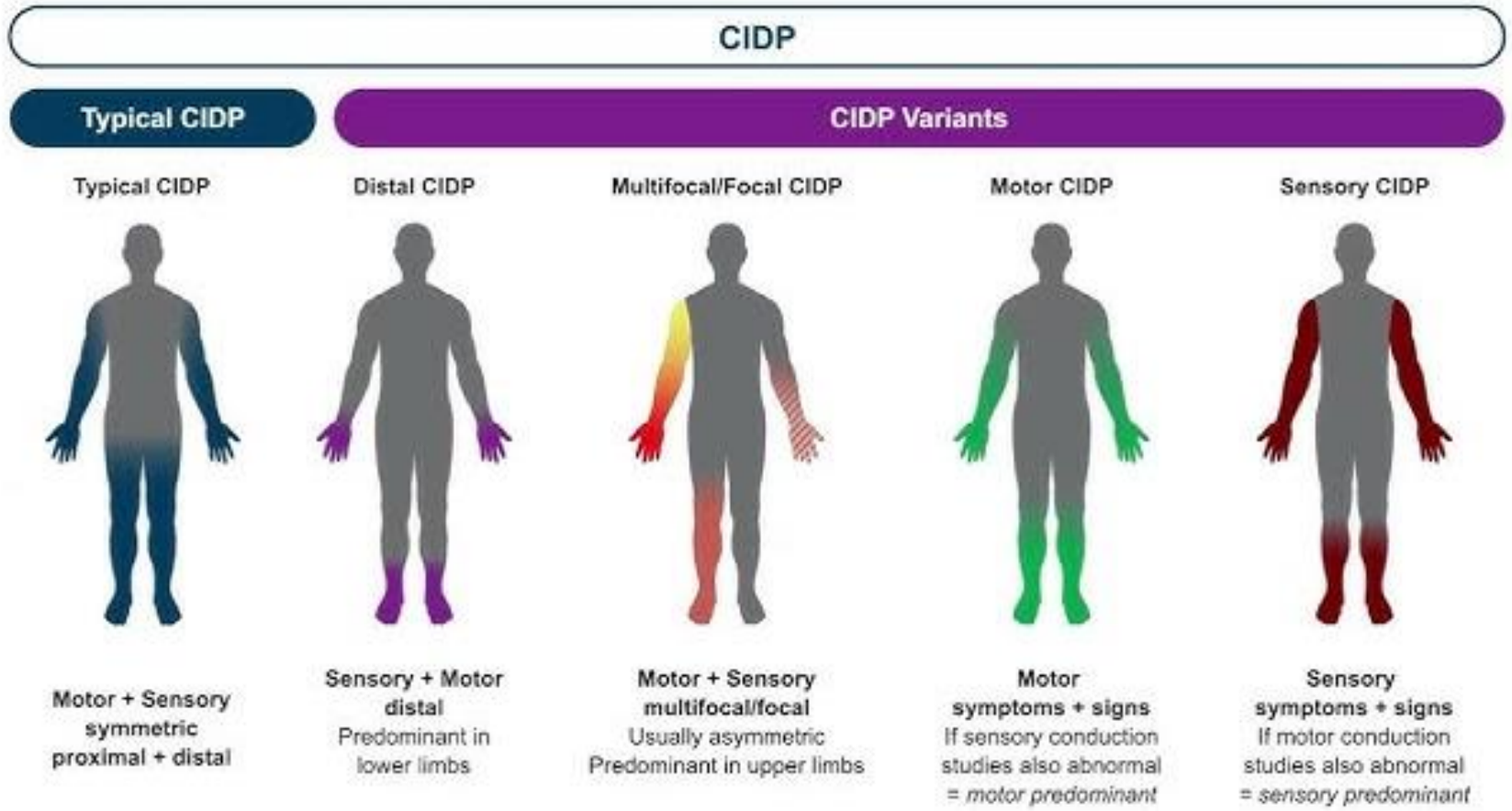
	NCV			DL			F-W			CMAP	
	LLN	80%	70%	ULN	125%	150%	ULN	120%	150%	LLN	80%
Median	49	39	34	4.4	5.5	6.6	31	37.2	46.5	4 mV	3.2
	48	38.4	33.6	4.5	5.6	6.7				3	2.4
Ulnar	49	39	34	3.3	4.1	4.9	32	38.4	48	6.6	5.2
	48	38.4	33.6	3.6	4.5	5.4				5	4
Peroneal	44	35.2	30.8	6.5	8.1	9.7	56	67.7	84	2	1.6
	42	33.6	29.4	6.6	8.2	9.9					
Tibial	41	32.8	28.7	5.8	7.2	8.7	58	69.6	87	4	3.2

If Amp > 80% use 1st column and if < 80% use 2nd column

Supportive tests for CIDP

Supportive tests	Elevated CSF protein with leukocyte count <10/mm^3
	MRI gadolinium enhancement and/or hypertrophy of cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses
	Abnormal sensory nerve conduction study (NCS) in at least 1 nerve: a. Normal sural with abnormal median (excluding median neuropathy at wrist from carpal tunnel syndrome) or radial sensory nerve action potential (SNAP) amplitudes; or, b. sensory conduction velocity <80% of LLN (<70% if SNAP amplitude <80% of LLN); or, c. delayed somatosensory evoked potentials without central nervous system involvement
	Evidence of demyelination /remyelination by nerve biopsy with electron microscopy or teased fibre analysis

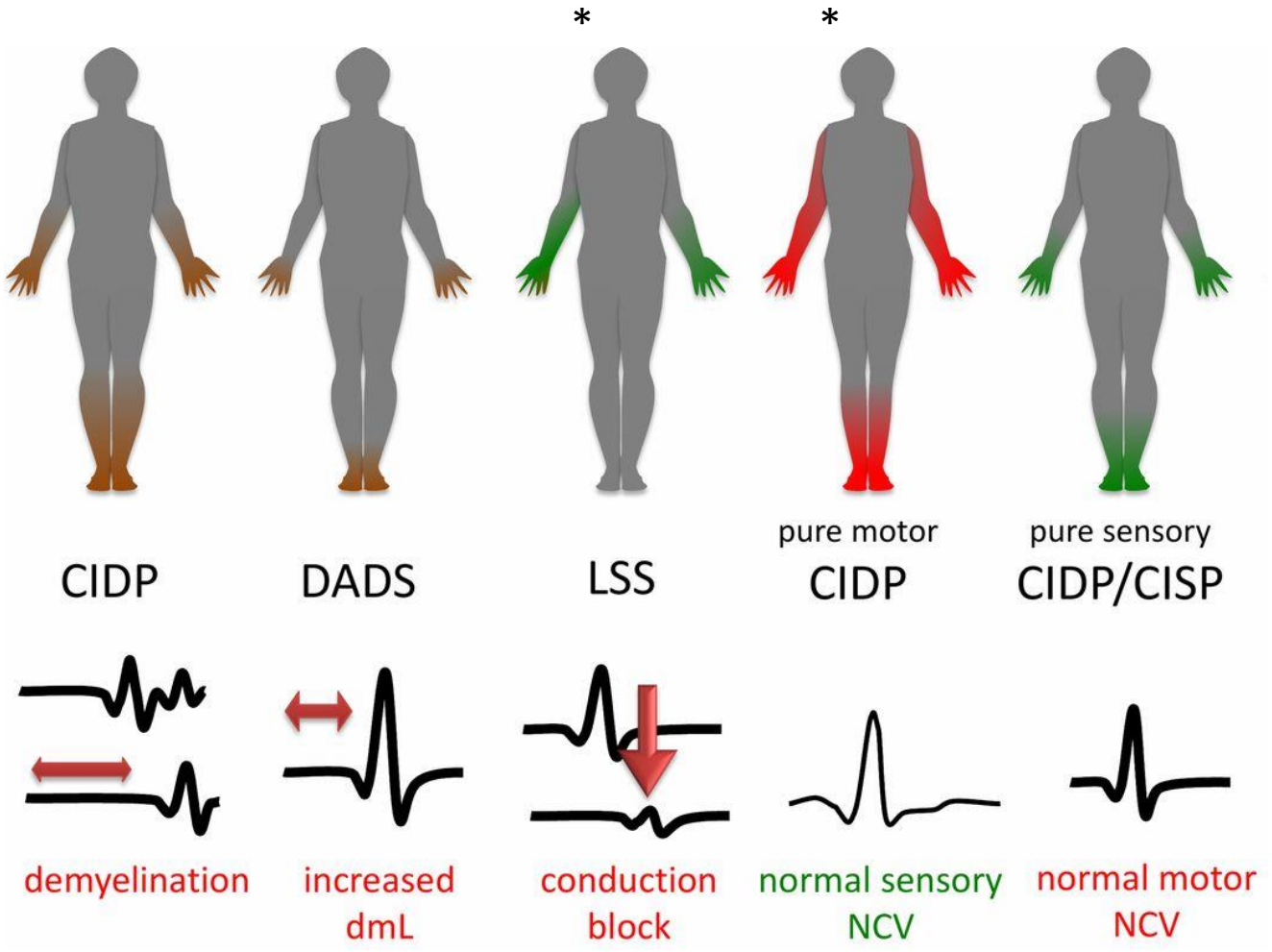
Clinical manifestations of CIDP and variants



aka “Lewis-Sumner variant” (LSS)

https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2021.665136/full

EDx manifestations of CIDP and variants



*Upper limb predominant

https://www.frontiersin.org/journals/neurology/articles/10.3389/fneur.2021.665136/full

Typical CIDP

- >50% of all CIDP cases
- Chronic onset, sensorimotor, symmetric proximal > distal
  - ~18% are acute onset
  - GBS mimic; can resemble NF155 and CNTN1 antibodies
- Treatment: IVIG, steroids
  - immune suppressive therapy (IST), PLEX (severe cases)

Randomized Controlled Trial > Lancet Neurol. 2008 Feb;7(2):136-44.
doi: 10.1016/S1474-4422(07)70329-0.

Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo-controlled trial

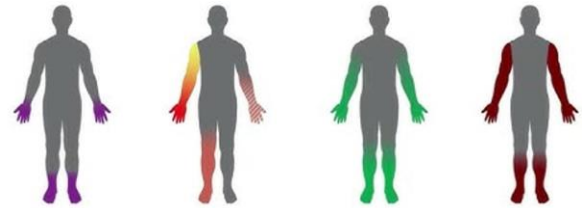
Richard A C Hughes [1], Peter Donofrio, Vera Bril, Marinos C Dalakas, Chunqin Deng, Kim Hanna, Hans-Peter Hartung, Norman Latov, Ingemar S J Merkies, Pieter A van Doorn; ICE Study Group

Collaborators, Affiliations + expand

PMID: 18178525 DOI: 10.1016/S1474-4422(07)70329-0

Atypical CIDP

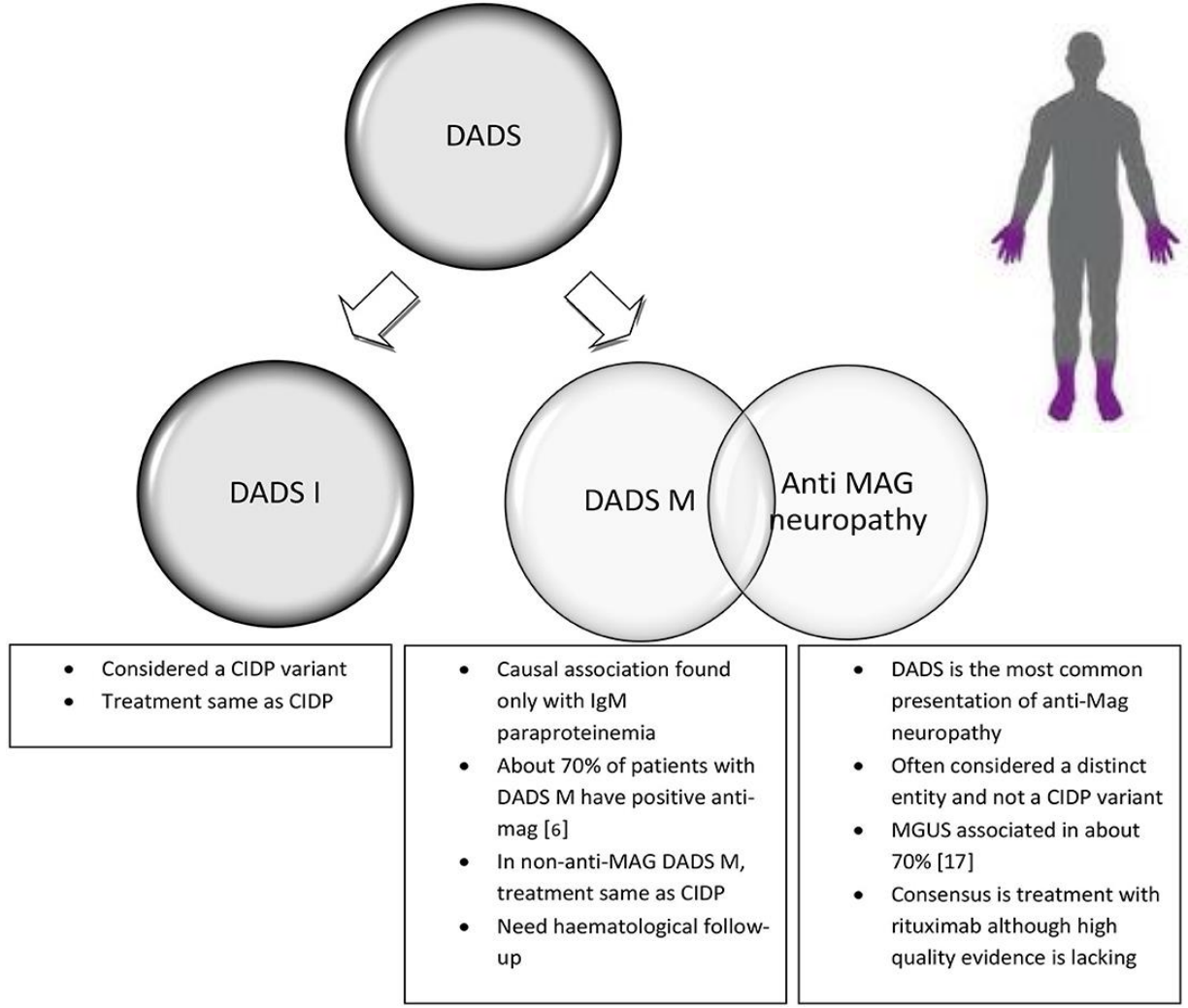
- In a series of 376 CIDP pts, atypical cases constituted **18%**
- No universally accepted diagnostic criteria for these entities
- High quality evidence for efficacy of immunomodulatory therapies lacking
- Getting any data for evidence-based management of CIDP variants is challenging



CIDP variant	Treatment	Prognosis	Special considerations
DADS-I	First-line IMT	Similar to CIDP	Need for hematological evaluation and monitoring
DADS MAG	Rituximab	Less favorable for DADS M	Rare worsening with rituximab reported
MADSAM	First-line IMT Consider 2nd line agents, rituximab, in refractory cases	Generally less favorable	
Pure sensory	First-line IMT	Similar to CIDP	Responds well to IVIG or steroids
CISP	First-line IMT	Mostly similar to CIDP	Prone to relapse on tapering IMT
Pure motor	IVIG recommended as first line	Similar to CIDP	Steroid found to be equally efficacious but distinction from MMN needed
Focal variant	First-line IMT, may need maintenance therapy	Comparable to CIDP	Prone to relapse on tapering IMT
CIDP with IgG4 antibodies	Rituximab or cyclophosphamide (refractory to first-line IMT)	Poor compared to CIDP	

Atypical CIDP: DADS

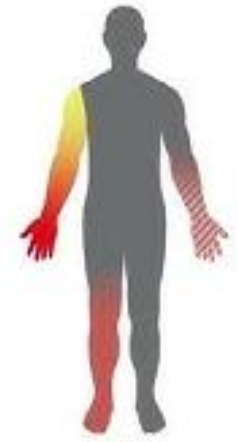
- DADS-M: discrete entity with distinctive pathology and tx response
- NCS and exam help distinguish this
  - Prolonged distal latencies
  - ***Absent*** distal responses
- About 50–70% of DADS-M patients have **anti-myelin associated glycoprotein (MAG) Ab**
- *Presence of elevated IgM & anti-MAG are exclusionary criteria for the diagnosis of CIDP*
- Overlapping clinical presentation, lack of accepted criteria blur distinction btwn these 3



Menon D, Katzberg HD, Bril V. Treatment Approaches for Atypical CIDP. Front Neurol. 2021 Mar 15

MADSAM

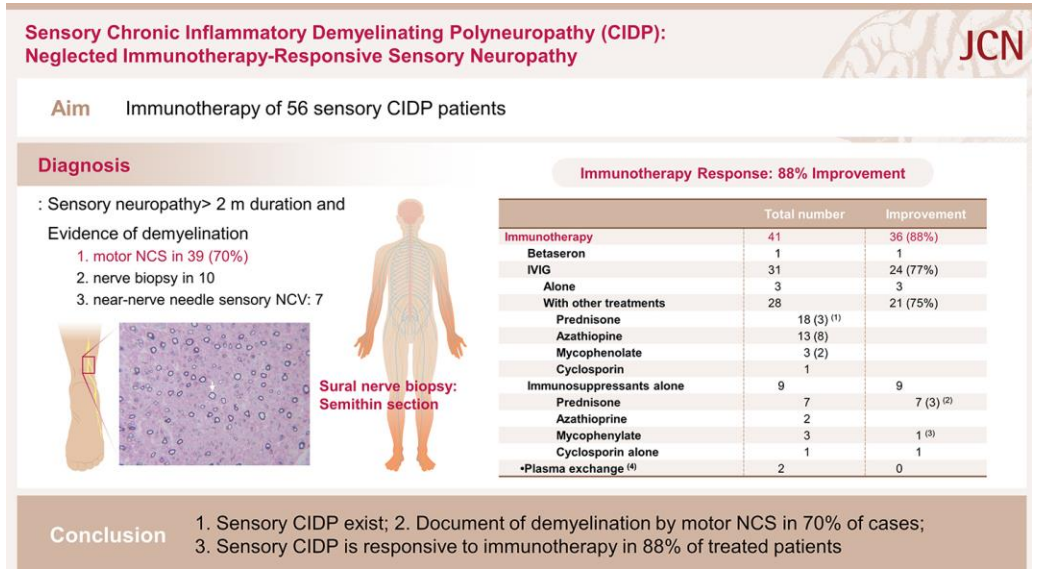
- Painless, demyelinating, mononeuropathy multiplex
- ***Most frequently encountered variant of CIDP*** in most series
- Macrophage mediated demyelination is multifocal, distributed mainly in mid-limb or proximal nerve segments



- Treatment responses to first line agents, long term outcomes, rates of remission are inferior compared to typical CIDP
- Response rates to IVIG, PLEX, and prednisone similarly effective
- Conventional immunotherapy is first-line (IVIG, steroids); chemo agents or rituximab are second-line agents in refractory cases

Pure sensory CIDP

- Progressive pure sensory neuropathy
- Rare, labeled often as “idiopathic”
- Demyelinating features on NCS affecting sensory + *motor* nerves



Sensory Chronic Inflammatory Demyelinating Polyneuropathy (CIDP): Neglected Immunotherapy-Responsive Sensory Neuropathy

JCN

Aim Immunotherapy of 56 sensory CIDP patients

Diagnosis

: Sensory neuropathy> 2 m duration and
Evidence of demyelination
1. motor NCS in 39 (70%)
2. nerve biopsy in 10
3. near-nerve needle sensory NCV: 7

Sural nerve biopsy: Semithin section

Immunotherapy Response: 88% Improvement

	Total number	Improvement
Immunotherapy	41	36 (88%)
Betaseron	1	1
IVIG	31	24 (77%)
Alone	3	3
With other treatments	28	21 (75%)
Prednisone	18 (3) [1]	
Azathiopine	13 (8)	
Mycophenolate	3 (2)	
Cyclosporin	1	
Immunosuppressants alone	9	9
Prednisone	7	7 (3) [2]
Azathioprine	2	
Mycophenylate	3	1 [3]
Cyclosporin alone	1	1
•Plasma exchange [4]	2	0

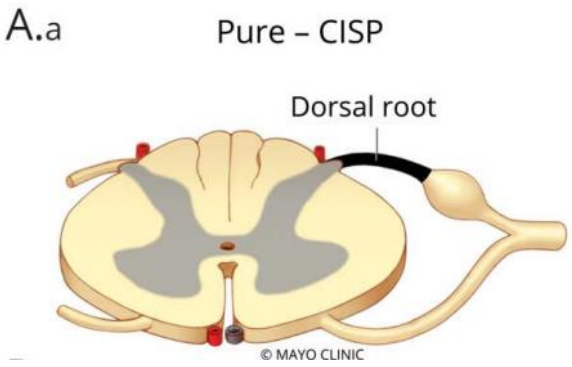
Conclusion 1. Sensory CIDP exist; 2. Document of demyelination by motor NCS in 70% of cases; 3. Sensory CIDP is responsive to immunotherapy in 88% of treated patients

- No difference in treatment response in comparison with typical CIDP
- About **90% of pts reported to respond to IVIG or steroids** in most series, only very few pts requiring PLEX or alternate immunological agents
- IVIG and steroids equally efficacious

Oh SJ, King P. Sensory Chronic Inflammatory Demyelinating Polyradiculoneuropathy: Neglected Immunotherapy-Responsive Sensory Neuropathy. J Clin Neurol. 2024 May

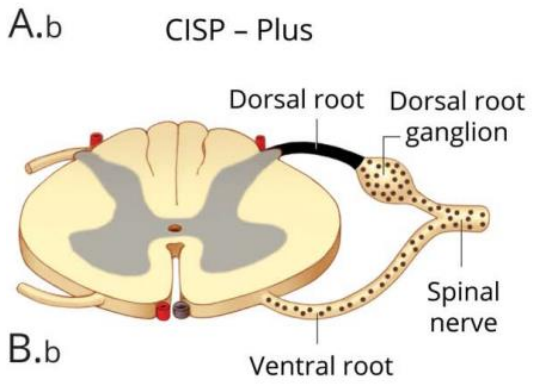
CISP

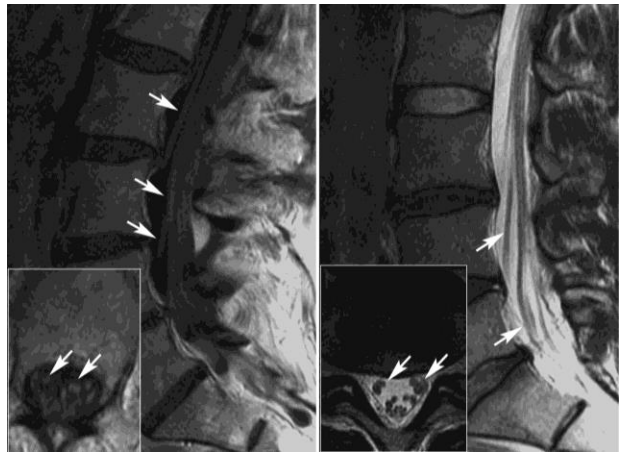
- Clinical presentation: sensory loss, gait ataxia, falls, large fiber sensory deficits, reduced/absent reflexes, preserved muscle strength
- Often considered a pure sensory CIDP because of similarities in clinical presentation, but **pathology confined to sensory roots** (*pre*-ganglionic) **with sparing of motor nerves**
    - **Normal sensory NCS**, abnormal SSEP, **thickened spinal roots on MRI**, high CSF protein



CISP-plus

- Predominant sensory syndrome with no weakness or only mild distal weakness
- Mild abnormalities on NCS/EMG (motor or sensory) *that do not fully explain clinical syndrome* (including reduced CMAPs & SNAPs)
- Exclude CNS or compressive nerve root lesions that could explain clinical syndrome

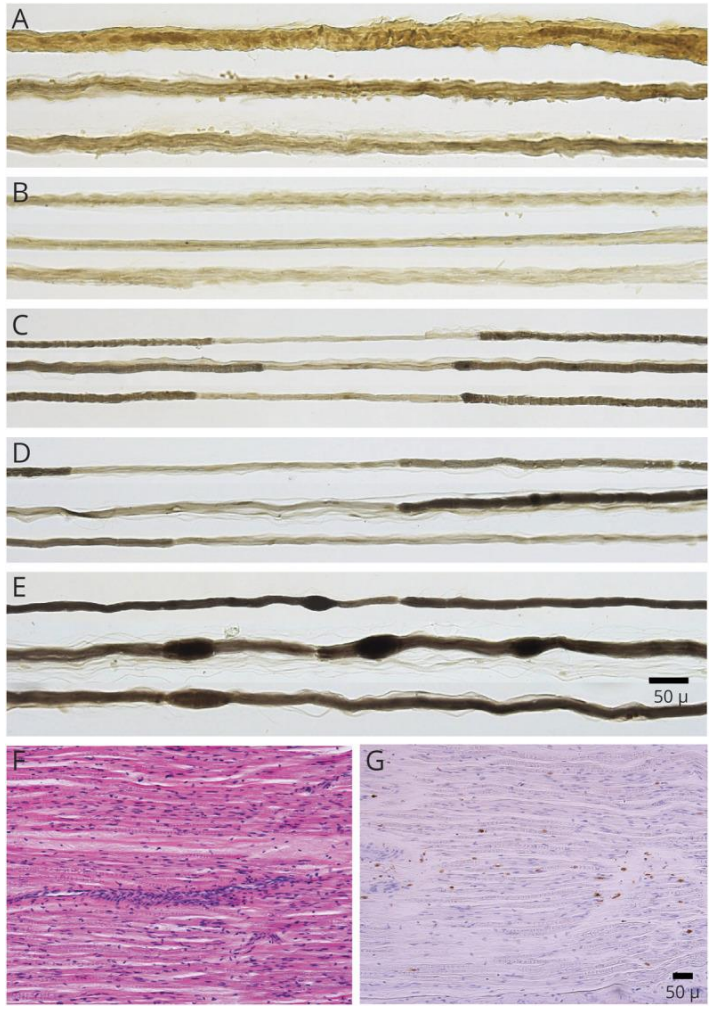




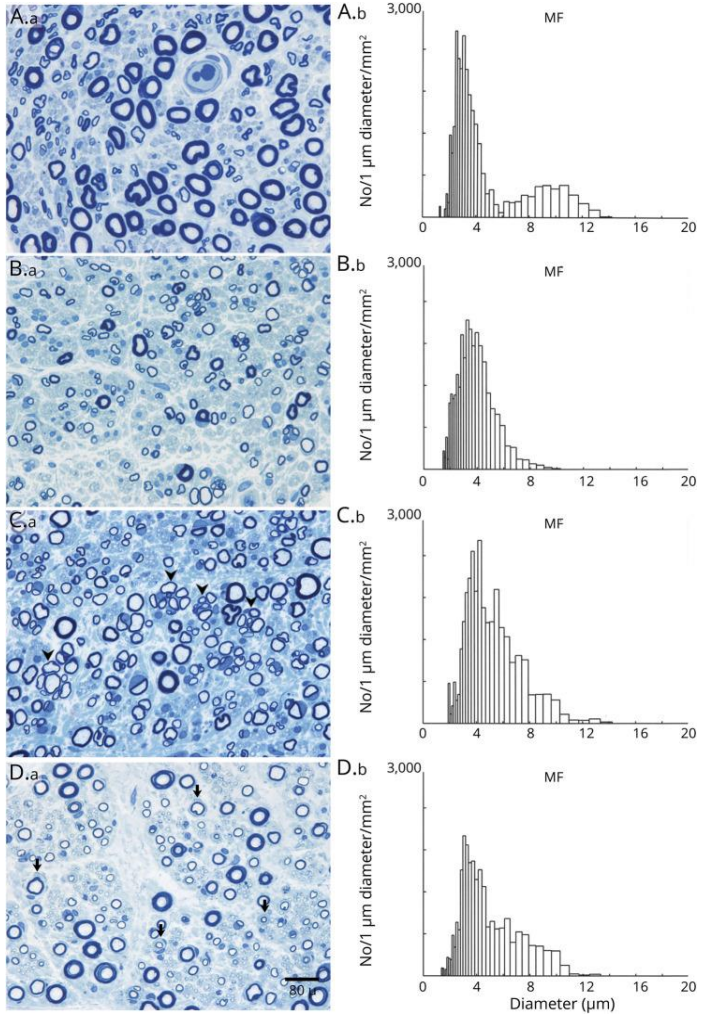
SSEP or imaging abnormalities (usually MRI) consistent with nerve root involvement

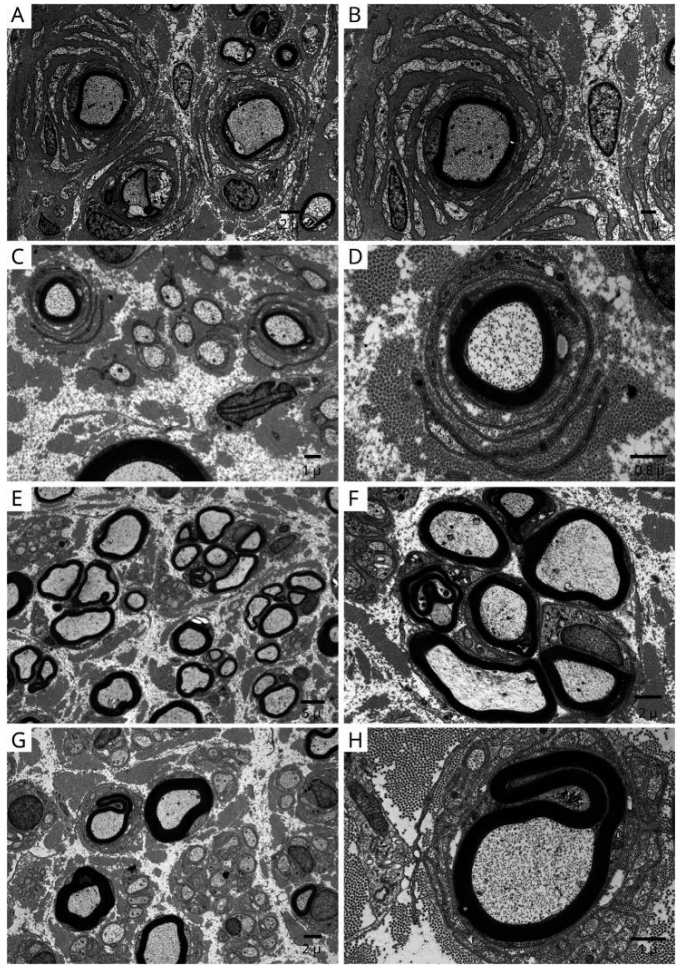
CISP-plus

Teased myelinated nerve fiber preparations



Loss of Large Myelinated Fibers & Onion-Bulbs in Limb Nerves





Shelly S et al. Expanding the Spectrum of Chronic Immune Sensory Polyradiculopathy: CISP-Plus. Neurology. 2021

Pure motor CIDP

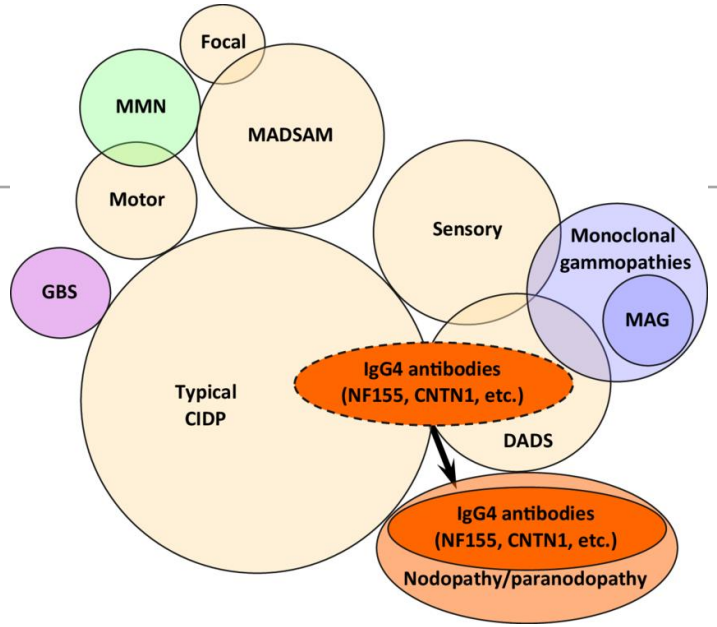
- Resembles MMN clinically but is more **symmetric** clinically (*MMN is not a form of CIDP*)
  - MMN does not respond to steroids
- Motor conduction blocks are most common finding on NCS, absence of sensory abnormalities
- Can also mimic MND (ie ALS)
  - Absence of any bulbar involvement + demyelinating features on NCS helpful to distinguish pure motor CIDP from MND
- Treatment response rate to immunotherapy 70–90% in most series (comparable to classic CIDP)
- Given that a clear distinction often difficult to establish between pure motor CIDP and MMN, IVIG (not steroids) may still be the ideal initial choice, if all other factors are equal

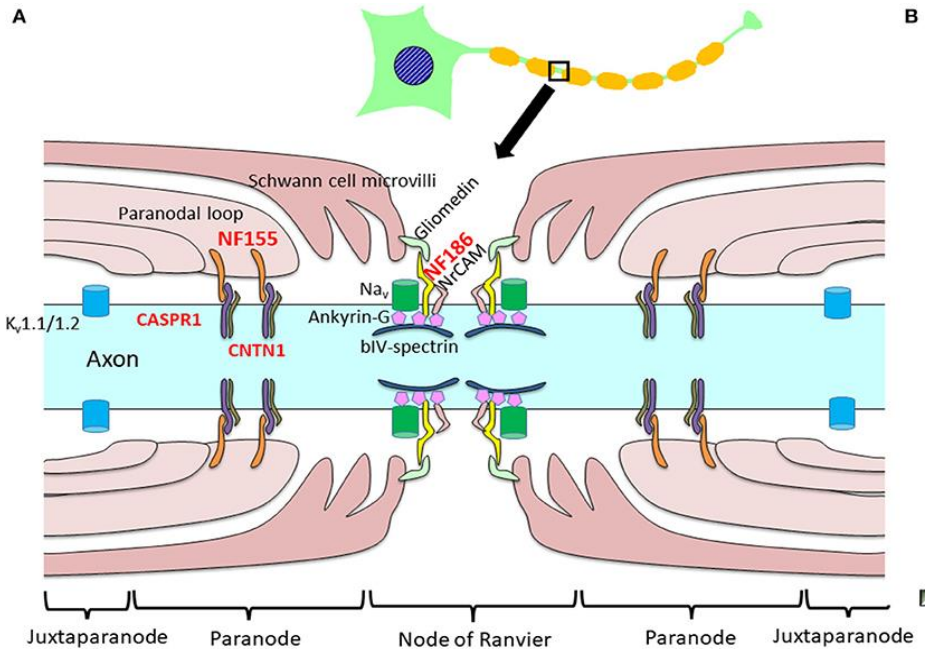
Focal CIDP

- *Least defined, least frequent* (focal CIDP was not seen in two large cohorts of pts with CIDP variants from Italy (*n* = 84) & Japan (*n* = 40))
- Initial reports of a monomelic demyelinating polyneuropathy with hypertrophy of the involved nerves and biopsy showing characteristic “onion bulb” changes led to recognition of this focal form of CIDP
- *Distinct from MMN*: has **sensory** involvement, negative GM1 Ab, favorable response to steroids
- May be considered at one end of a spectrum of disease (ie an arrested form of MADSAM or typical CIDP) → so would respond to similar treatment strategies
- Treatment: IVIG, steroids
- Long-term maintenance therapy required in many pts due to higher chances of relapse with attempted tapering

CIDP with IgG4 antibodies

- Certain pathogenic autoantibodies in a subset of CIDP (also GBS) identified
- IgG4 Ab directed against several nodal & paranodal antigens: **neurofascin** (Nfasc 155 + Nfasc 140/186), **contactin-1** (CNTN1), & **contactin associated protein-1** (Caspr1)
  - Only a small number of pts with refractory CIDP have one of these autoantibodies
  - *Clinical features: early age of onset, subacute presentation, presence of disabling tremor + ataxia*
- Can show **CNS** demyelination
- Poor response to IVIG and other first-line agents
- Small case series show cyclophosphamide or rituximab favorable refractory CIDP (+/- IgG4 Ab)
  - Rituximab favored





Kira, Anti-Neurofascin 155 Antibody-Positive Chronic Inflammatory Demyelinating Polyneuropathy/Combined Central and Peripheral Demyelination: Strategies for Diagnosis and Treatment Based on the Disease MechanismFront. Neurol., 09 June 2021

News | Article | June 21, 2024

FDA Approves Efgartigimod Alfa and Hyaluronidase for CIDP

Author(s): Rose McNulty

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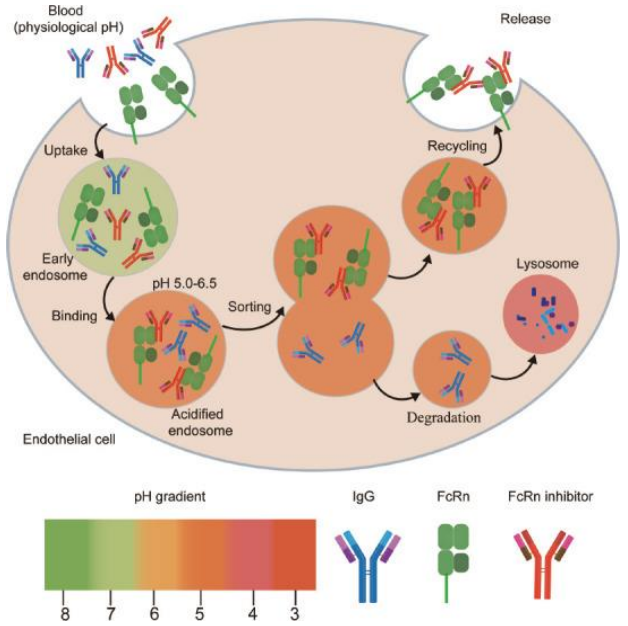
Safety, tolerability, and efficacy of subcutaneous efgartigimod in patients with chronic inflammatory demyelinating polyradiculoneuropathy (ADHERE): a multicentre, randomised-withdrawal, double-blind, placebo-controlled, phase 2 trial

Jeffrey A Allen, MD [a] · Jie Lin, MD [b] · Ivana Basta, MD [c] · Tina Dysgaard, MD [d] · Christian Eggers, MD [e] · Jeffrey T Guptill, MD [f,g] · et al. Show more

Affiliations & Notes Article Info Linked Articles (1)



Zhu et al. Neural Regen Res, 2023

- Human IgG1 antibody Fc fragment
- Enrolled CIDPD patients from 146 clinical sites – North America, Europe, Asia-Pacific

ADHERE TRIAL: RESULTS

Evidence of clinically meaningful deterioration entered open label phase

Confirmed evidence of clinical improvement (ECI), treatment responders

Stage A

Treatment cycle
Weekly Efgartigimod PH20 1000 mg subQ vs placebo up to 12 wks

322 pts: 214 (**66%**) confirmed ECI

Primary endpoint: *confirmed clinical improvement:* ≥1 pt aINCAT ↓, ≥4 pts inflammatory Rasch-built overall disability scale ↑, or >8 kPa grip strength ↑ after 4 injections & 2 consecutive visits

Stage B

Randomized withdrawal phase
Weekly 1000 mg subQ vs placebo, maximum 48 weeks

221 randomized: 111 SC efgartigimod PH20, 110 placebo

Primary endpoint: ***risk of relapse*** -- time to first aINCAT increase of ≥1 point

- SC efgartigimod PH20 significantly reduced the risk of relapse vs placebo (p<0·0001)
- 31 **(28%)** of those who received SC efgartigimod PH20 had a relapse versus 59 **(54%)** placebo

Treatment-emergent adverse events (TEAEs)

- In stage B, 64% of those on SC efgartigimod PH20 had TEAEs vs 56% on placebo
  - Serious TEAEs in 6 (5%) on SC efgartigimod PH20 & 6 (5%) on placebo

Questions?