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SNEMA
Svenska Neuromuskulära Arbetsgruppen
Swedish Neuromuscular Association

Karolinska Institutet

Immune-mediated neuropathies:

How to identify in an ocean of polyneuropathies?

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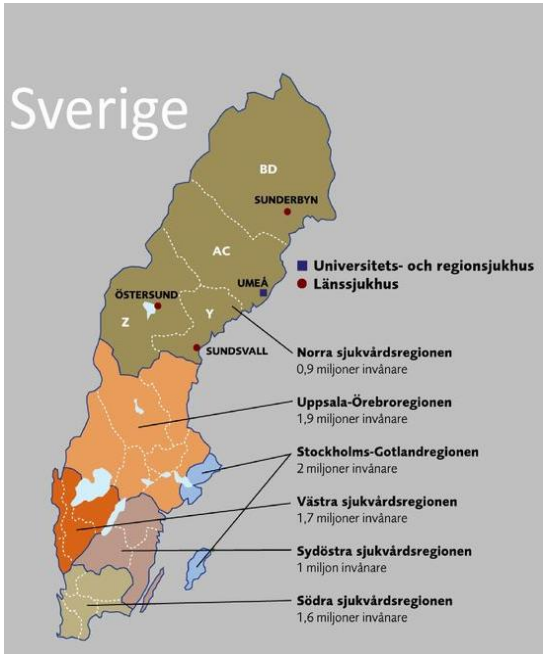
Specialized neuromuscular centers in Sweden

All regions care for their own patients with neuromuscular diseases, but refer advanced cases to the university hospitals in:

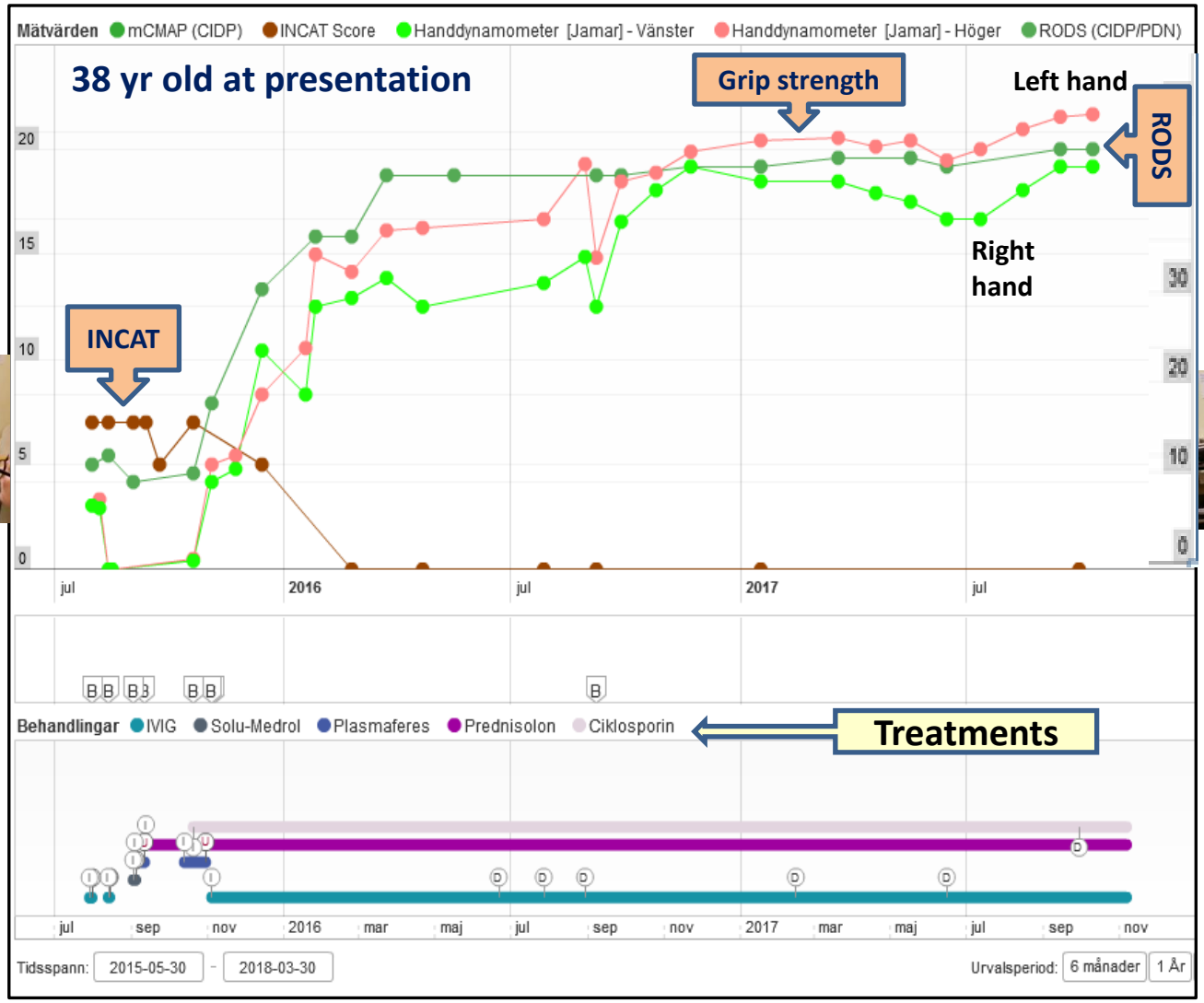
-Lund/Malmö (SUS)
-Göteborg (Sahlgrenska)
-Linköping (US)
-Stockholm (Karolinska). *Population base 2.3 milj*

Metabolic / mitochondrial diseases and pediatric cases:
- Göteborg & Stockholm



Patient with Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Patient overview in Swedish Neuro Registries (www.neuroreg.se)



Immune-mediated neuropathies

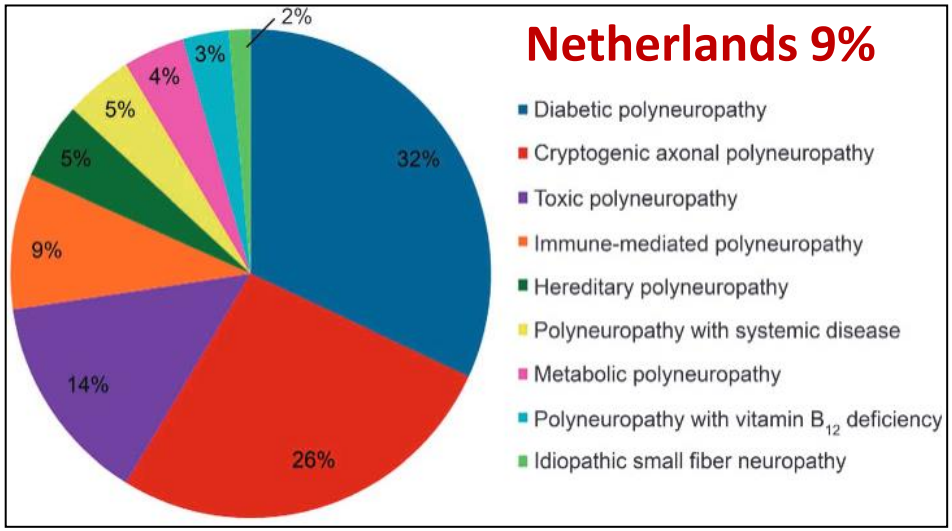
Definition

- Inflammatory disorders of the PNS (+ rarely even CNS simultaneously)
- Treatable neuropathies

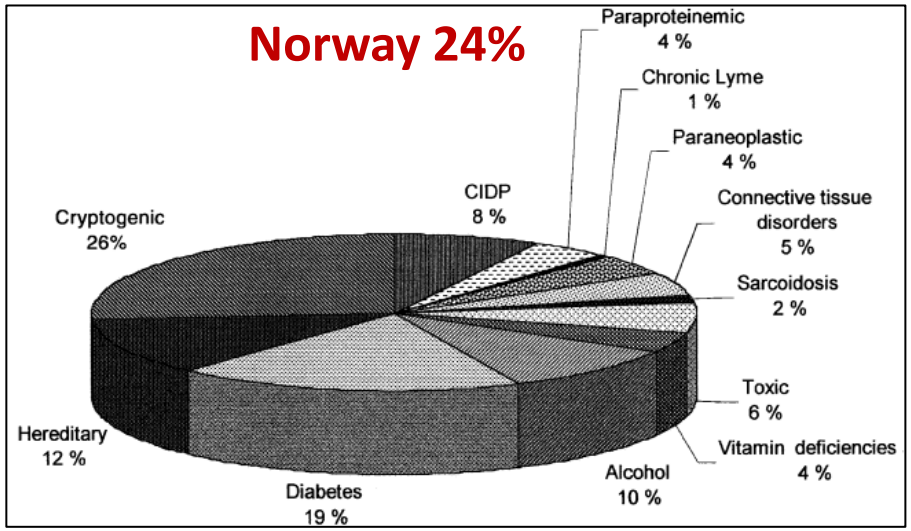
Contents

- Classification of immune-mediated neuropathies
- The pattern recognition approach to investigating neuropathies
- Acute onset neuropathies diff. diagnosis
  including pan-neurofascin autoimmune nodopathy
- Chronic immune-mediated neuropathies
  CIDP, MMN and paraproteinemic neuropathies & diff. diagnosis

9-30% of all neuropathies are immune-mediated



Visser et al., Neurology, 2015;84 :259-264



Mygland & Monstad, Eur J Neurol 2001; 2001 8:157-65.

-> **27% of "idiopathic" neuropathies** refered to the 3° center at Columbia, NY had an inflammatory etiology (CIDP, IgMGUS, Sjögren …)

USA

Farhad et al. Muscle & Nerve 2016

Cause of peripheral neuropathy	Number of patients	Percent
Idiopathic	19	19%
Diabetes mellitus	17	17%
Vitamin B12 deficiency	9	9%
Dysimmune neuropathies		
Associated or not with autoimmune disease (other than CIDP)	7 + 3 associated with autoimmune disease (1 vasculitis, 2 connective tissue diseases)	7% + 3%
CIDP	8	8%
Paraproteinemia-related neuropathy	8	8%
Celiac disease	6	6%
Multifocal motor neuropathy (MMN)	3	3%
Paraneoplastic neuropathy	3	3%
Hypothyroidism	6	6%
Toxic causes	4	4%
Genetic polyneuropathy	3	3%
Infective causes	2	2%
Alcohol	1	1%
Chronic kidney disease	1	1%
Total	100	

Italy 30%

Ricci et al. Neurol Sci 2019

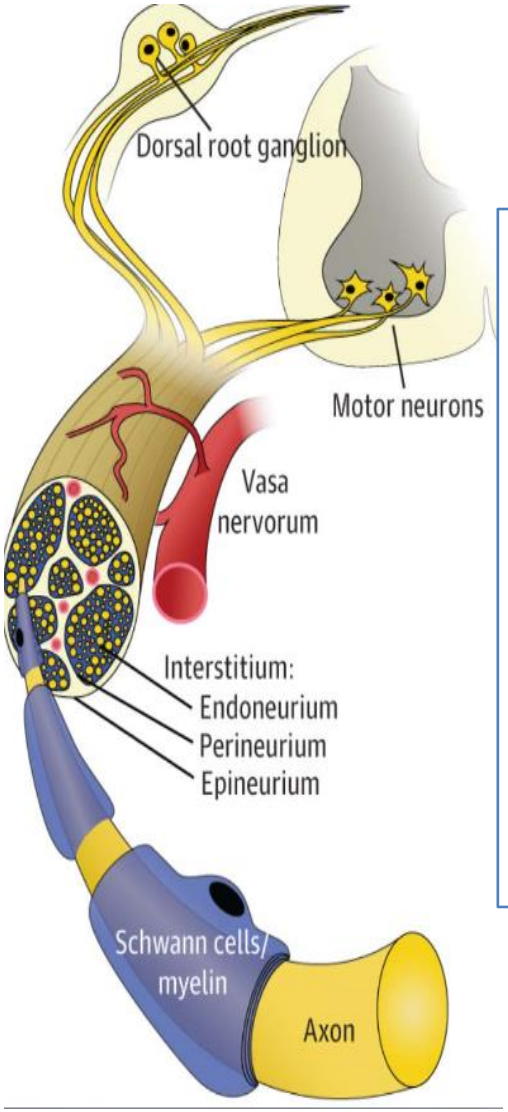
Inflammatory neuropathies – Etiologies

SECONDARY
Systemic

Systemic diseases
Sjögren, sarcoidosis,…
Paraproteinemia (DADS)
Non-Hodgkin lymphoma
Osteosclerotic myeloma (POEMS)

Immuntherapy-related
Anti-TNF-α
Tacrolimus
Immune checkpoint inhibitors
GVHD-neuropathy

Paraneoplastic
Anti-Hu, CASPR2 ….



PRIMARY
Non-systemic

GBS
CIDP
MMN
PNS-vasculitis

Autoimmune nodopathies

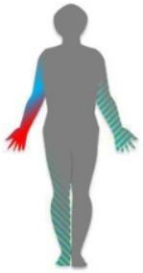
- Chronic: CIDP-like
- Acute: GBS-like
  Pan-neurofascin autoimmune nodopathy

The Pattern Recognition approach: aid in the etiological hunt

Pool of all neuropathies

History
Nerve exam
Neurophysiology

CSF analysis
Nerve imaging
Antibody testing
Nerve biopsy



Published in final edited form as:
Neurol Clin. 2013 May ; 31(2): 343–361. doi:10.1016/j.ncl.2013.02.001.

Pattern Recognition Approach to Neuropathy and Neuronopathy

Richard J Barohn, M.D.[a] and **Anthony A. Amato, M.D.**[b]
[a]Chairman, Department of Neurology, and Gertrude and Dewey Ziegler Professor of Neurology, University of Kansas Medical Center, Kansas City, Kansas
[b]Vice-chairman, Department of Neurology, Brigham and Women's Hospital, Professor of Neurology, Harvard Medical School, Boston, MA

Peripheral Neuropathy: Asking the Right Questions

Careful evaluation can reveal the cause of peripheral neuropathy in more than half of all cases.

By Charlene Hoffman-Snyder NP-BC and Benn Smith MD
Practical Neurology, 2009

Karolinska Polyneuropati Vårdprogram 2021
www.snema.se

Immune-mediated neuropathy

Other etiologies

Features which set inflammatory neuropathies apart

- Acute/subacute onset, relapsing-remitting course
- Demyelinating polyneuropathy (differential CMT1)
- Unsual neuropathy phenotypes / patterns:

  Proximal muscle weakness
  Pure sensory
  Pure motor
  Asymmetrical (mononeuritis multiplex)

- Systemic features

  - Paraprotein (IgM>> IgG > IgA)
  - Systemic inflammatory disease
  - Malignancy
  - Use of drugs which induce autoimmunity

Patterns based on mode of onset and course of disease

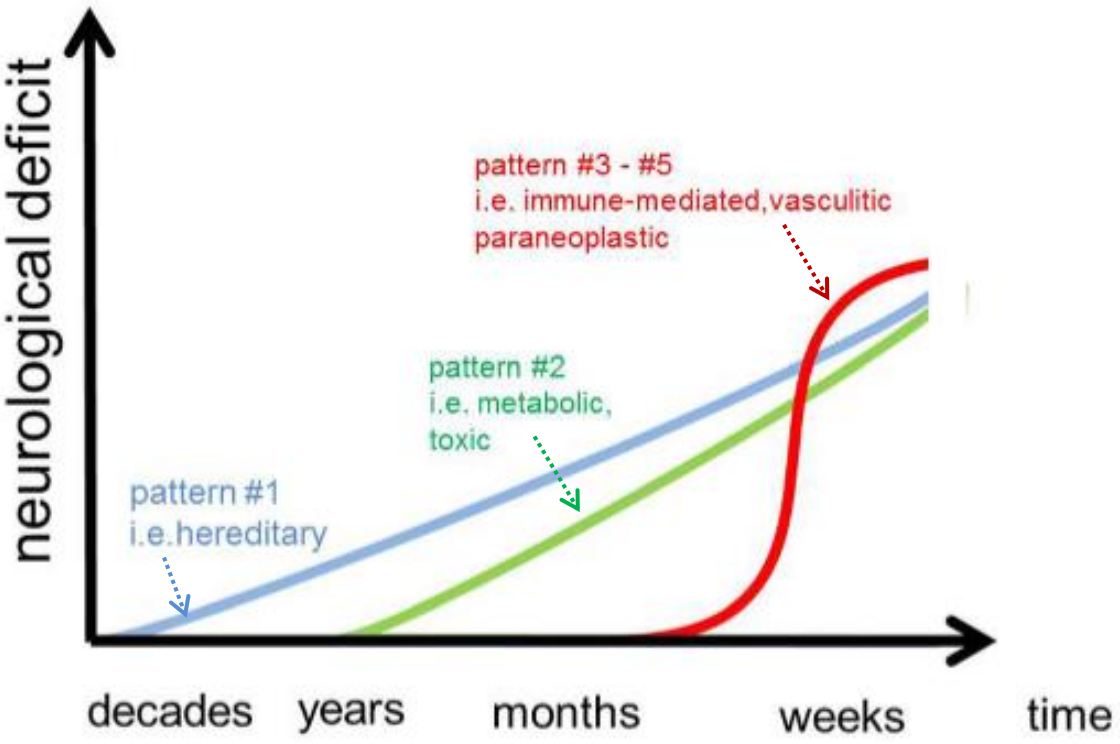
Lehmann *et al. Neurological Research and Practice* (2020) 2:20
https://doi.org/10.1186/s42466-020-00064-2

Neurological Research and Practice

STANDARD OPERATING PROCEDURE Open Access

Diagnosis of peripheral neuropathy

Helmar C. Lehmann[1*], Gilbert Wunderlich[1,2], Gereon R. Fink[1,3] and Claudia Sommer[4]



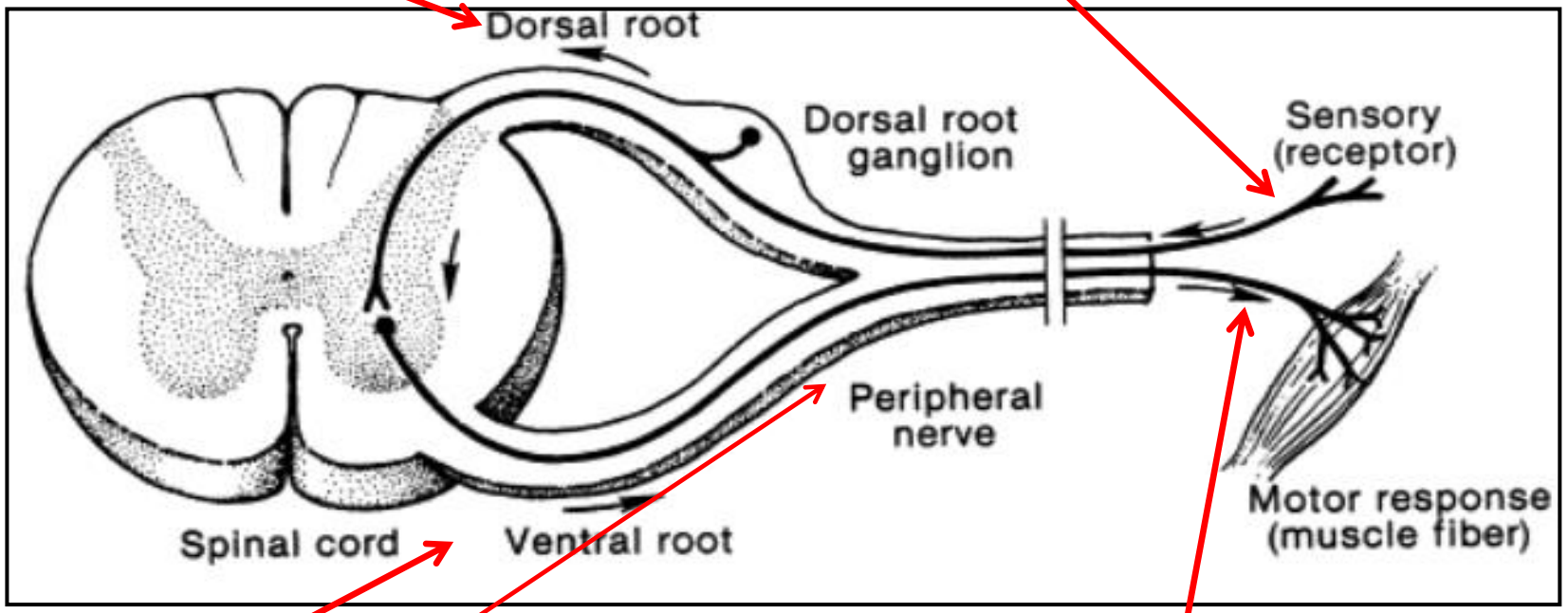
Patterns based on neurophysiological findings

Pure sensory axonal features
↓ *SNAP amplitudes*

Dorsalroot ganglia
Ganglionopathy
- Paraneoplastic
- Sjögren

QST
↑ warm & cold *thresholds*

Unmyelinated fibers
Vasculitis, Sjögren, Sarcoidosis



Demyelinating features
Slow NCV, conduction blocks, prolonged F-waves

Proximal roots/distal myelin
GBS (AIDP)
CIDP
Autoimmune nodopathies
MMN
DADS (PDN)

Axonal features
↓ *CMAP/SNAP*

Axon
GBS (AMAN /AMSAN)
Vasculitis
Sarcoidosis
Paraneoplastic

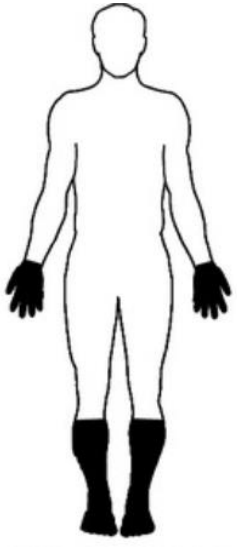
Patterns based on mode of onset vs. neurophysiological findings

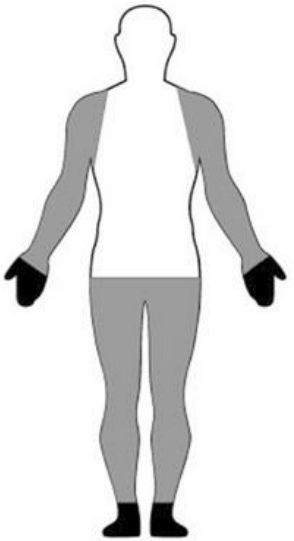
	Acute	Chronic
Demyelinating	**AIDP (GBS)** Acute-CIDP Panneurofascin autoimmune nodopathy	**- CIDP** - MMN - Paraprotein-related neuropathy
Axonal	- AMAN - AMSAN = Axonal GBS	- Vasculitic neuropathy - Paraneoplastic neuropathies

GBS = Guillain-Barré syndrome *MMN= Multifocal Motor Neuropathy*
AM(S)AN = Acute Motor (Sensory) Axonal Neuropathy
CIDP = Chronic Inflammatory Demyelinating Polyradiculoneuropathy

Patterns based on topography and type of symptoms

The typical non-inflammatory polyneuropathies





Slowly progressive
Sensorymotor
Axonal or demyelinating

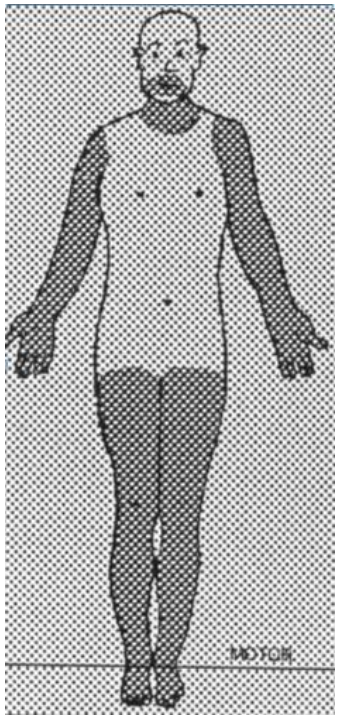
Etiologies

Diabetes, B-vit difficiency, toxic, CMT, ATTRv amyloidosis,…

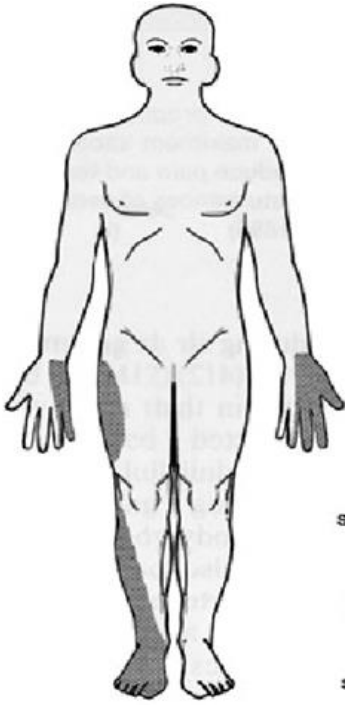
25% are chronic idiopathic axonal polyneuropathies (**CIAP**)

Patterns based on topography and type of symptoms

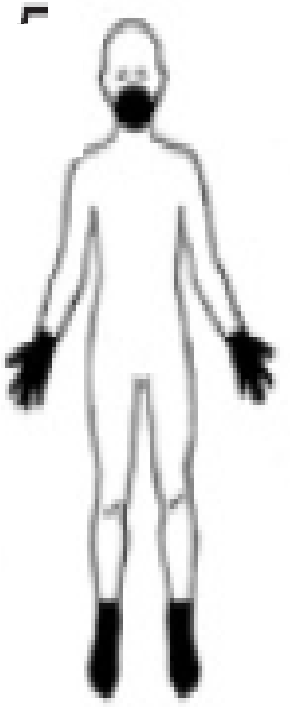
The typical inflammatory polyneuropathies



GBS
CIDP



MMN
MADSAM
Vasculitis



Pure sensory neuropathy

MADSAM: Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (CIDP-variant)

Differential diagnosis of multifocal neuropathies

Based on clinical and neurophysiological findings

Sensorimotor

Axonal

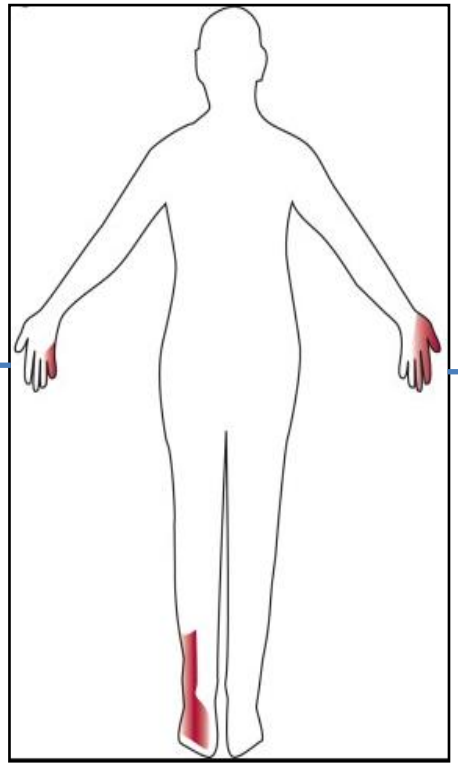
Diabetes

Vasculitis

Demyelinating

MADSAM

HNPP



Pure motor

Demyelinating

MMN

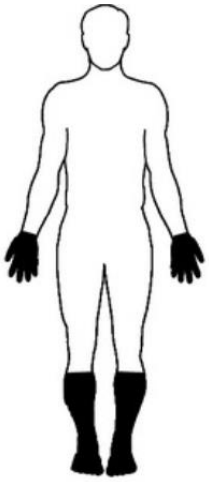
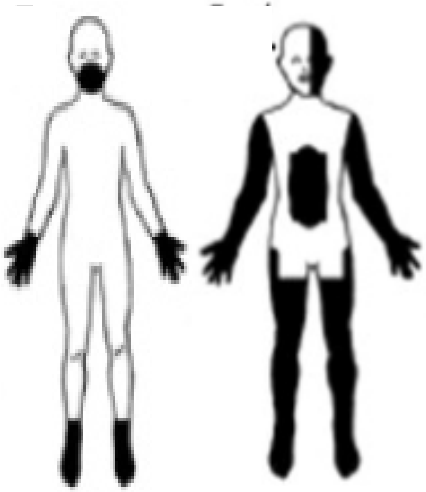
Axonal

PSMA (ALS)

MADSAM: Multifocal Acquired Demyelinating Sensory and Motor Neuropathy (CIDP-variant)

HNPP: Hereditary Neuropathy with Pressure Palsies

Pure sensory neuropathies- *based on electrophysiological findnings*

	Axons: Aα and Aβ fibers	C- and Aδ fibers	Dorsal root ganglia
			
Neuro-physiology	**Pure sensory axonal** symmetrical neuropathy	Normal ENeG **Small Fiber Neuropathy (SFN)** Pathol QST	Pure sensory axonal patchy neuropathy **Ganglionopathy**
SNAP	Reduced	Normal	Reduced
Nerve exam	**Areflexia** Sensory ataxia	**Normoreflexia** Allodynia Autonomic	**Normoreflexia** Hypoesthesia No sensory ataxia

Etiologies Vasculitis (Sjögren…), sarcoidosis, paraneoplastic, postinfectious, covid vaccine
Genetic: HSAN, CANVAS

SNAP = Sensory Nerve Action Potentials


Acute onset
neuropathies

Differential diagnosis of acute onset neuropathies

- **Toxic**

- Chemotherapy-induced axonal neuropathy
- GBS-like onset axonal + demyelin.: Amiodarone, nitrofurantoin, vincristine
- Lead poisoning

- **Metabolic**

Porphyria

- **Immune-mediated**

- Guillain-Barré Syndrome (GBS)
  AIDP, AMAN/AMSAN, Miller-Fisher Syndrome
- Acute-CIDP
- Acute post-infectious (post-vaccination) small fiber neuropathy (SFN)
- Pan-neurofascin autoimmune nodopathy

Anti–pan-neurofascin IgG3 as a marker of fulminant autoimmune neuropathy

Helena Stengel, Atay Vural, MD, PhD, Anna-Michelle Brunder, Annika Heinius, Luise Appeltshauser, MD, Bianca Fiebig, Florian Giese, MD, Christian Dresel, MD, Aikaterini Papagianni, MD, Frank Birklein, MD, PhD, Joachim Weis, MD, Tessa Huchtemann, MD, Christian Schmidt, MD, Peter Körtvelyessy, MD, Carmen Villmann, PhD, Edgar Meinl, MD, Claudia Sommer, MD, PhD, Frank Leypoldt, MD,* and Kathrin Doppler, MD*

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Dr. Doppler
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Neurol Neuroimmunol Neuroinflamm 2019;6:e603. doi:10.1212/NXI.0000000000000603

J Neurol Neurosurg Psychiatry 2021;**92**:1089–1095.

IgG_1 pan-neurofascin antibodies identify a severe yet treatable neuropathy with a high mortality

Janev Fehmi ,[1] Alexander J Davies,[1] Jon Walters,[2] Timothy Lavin,[3] Ryan Keh,[3]

Pan-Neurofascin autoimmune nodopathy – a life-threatening, but reversible neuropathy

Luise Appeltshauser and Kathrin Doppler

Current Opinion in Neurology, 36 (5), 394-401. 2023

Autoimmune nodopathies

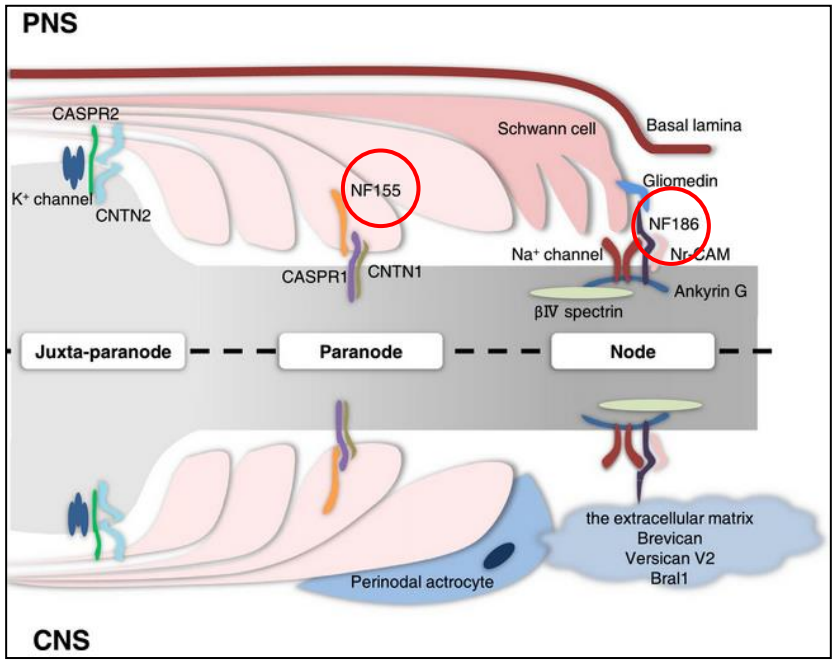
Antibody-mediated disease where adhesion molecules are attacked at the nodes and paranodes

Subtypes: Acute and chronic

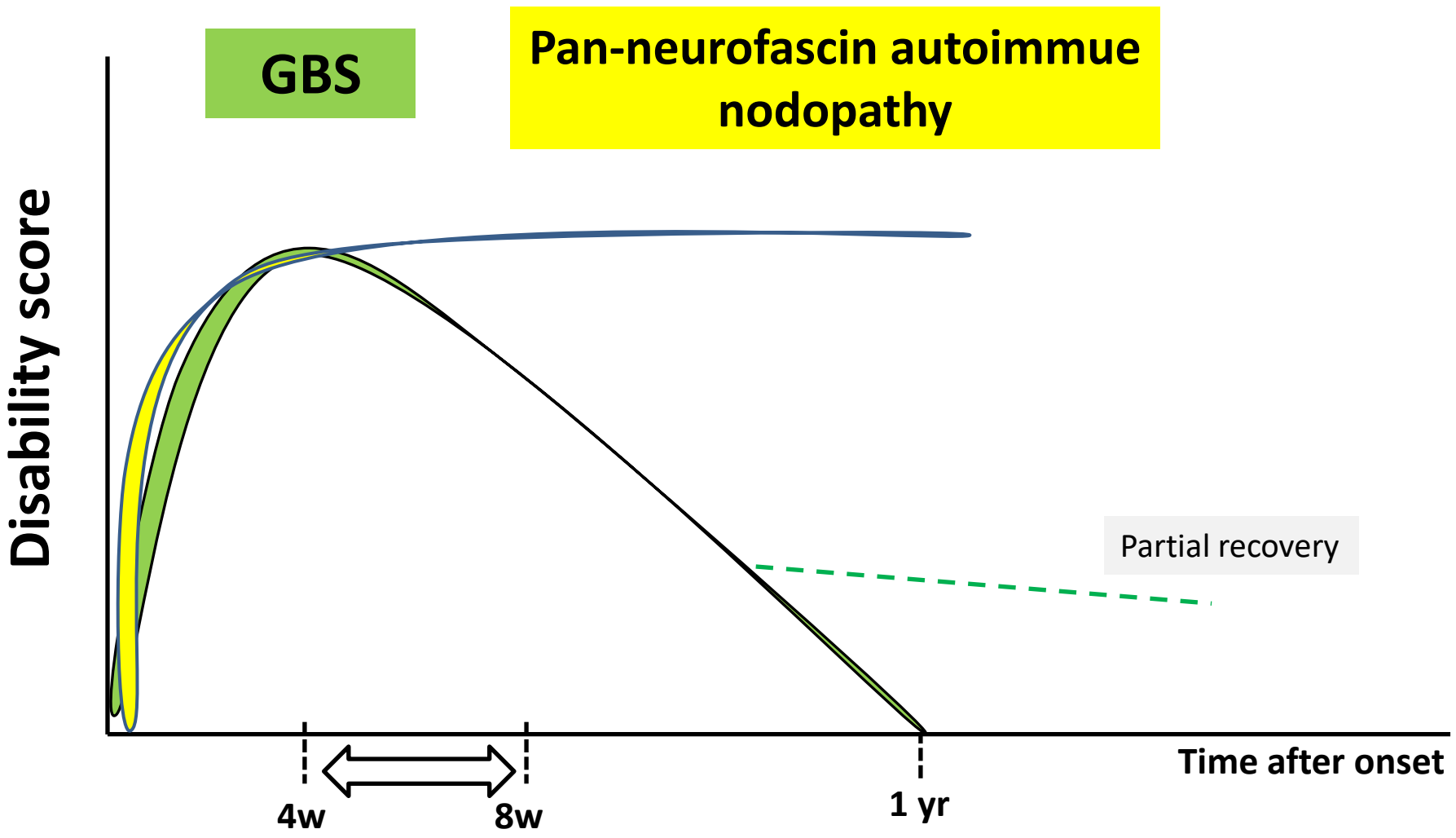
Pan-neurofascin nodopathy (acute)

Diagnosis: Serum antibodies to NF-155, -186 and -140

- GBS-like acute onset
- Tetraplegia, cranialnerve paresis
- Autonomic failure
- Respiratory failure
- Long-term invasive ventilation
- (Locked-in)
- High mortality
- Demyelinating + axonal
- Poor response to IVIg / PE
- Good response to rituximab
- Monophasic



Differential diagnosis of acute onset sensorimotor immune-mediated neuropathies




Chronic
neuropathies

Chronic Inflammatory Demyelinating Polyradiculoneuropathy - CIDP

Demyelinating motor and sensory polyneuropathy
Subacute-, or acute onset!

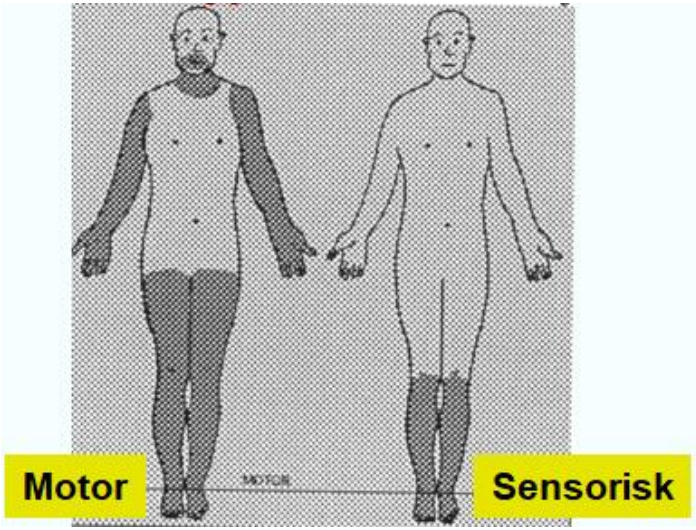
Prevalence: 2-9/100,000; ♂>♀
Age of onset 4-90, median 50 yrs

Associated rarely with IgG paraprotein, lymphoma, GVHD and immune checkpoint inhibitors

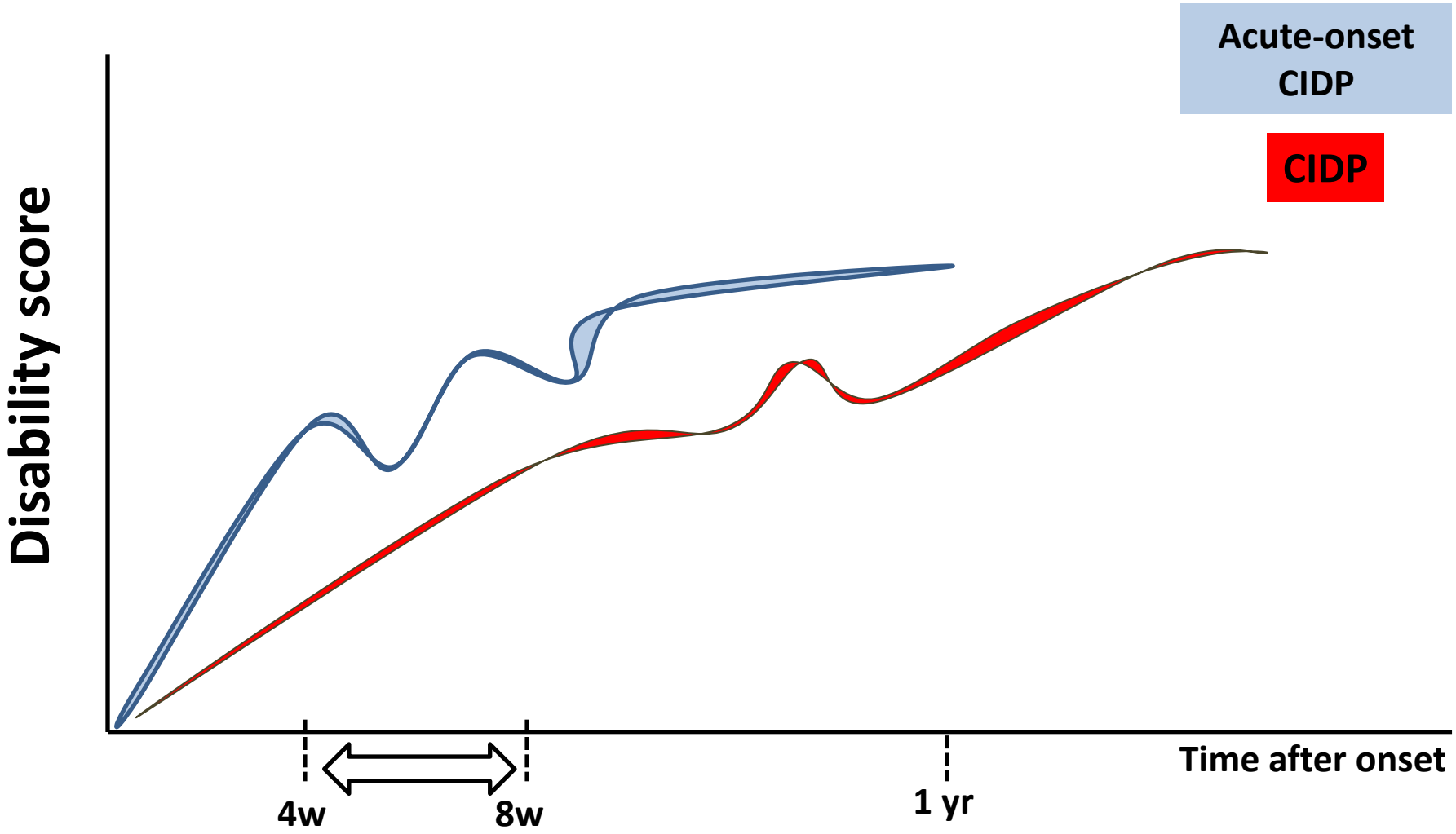
Signs:
-Motor weakness in all 4 extremeties, including proximally
-Areflexia
-Progressive phase >8w

Diagnosis:
-Neurophysiology
-CSF analysis and nerve imaging (supportive)

Treatment:
IVIg, kortison, plasma exchange, cyclophosphamaide, HSCT


Motor
Sensorisk

Differential diagnosis of subacute onset sensorimotor immune-mediated neuropathies



Multifocal Motor Neuropathy (MMN)

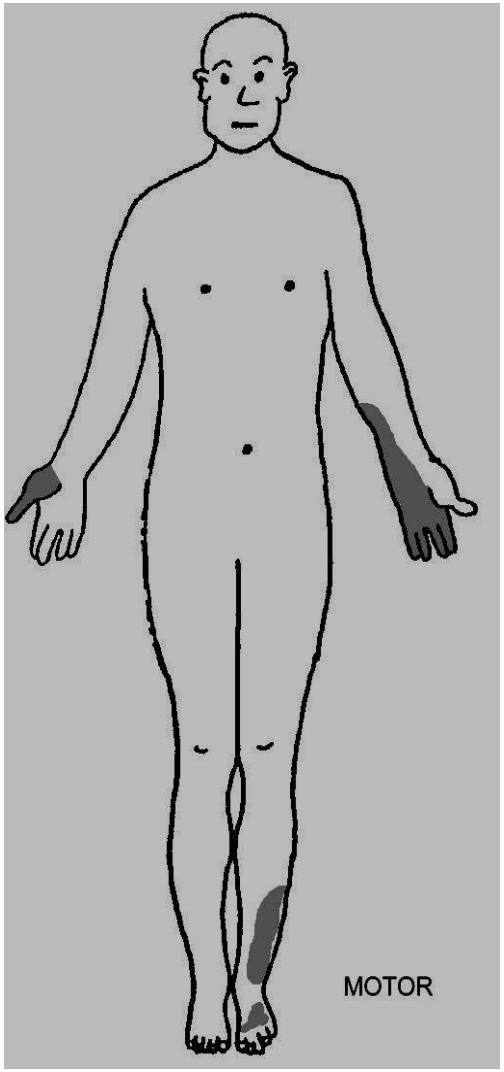
Multifocal immune-mediated **demyelinating motor** neuropathy, often with multipel conduction blocks

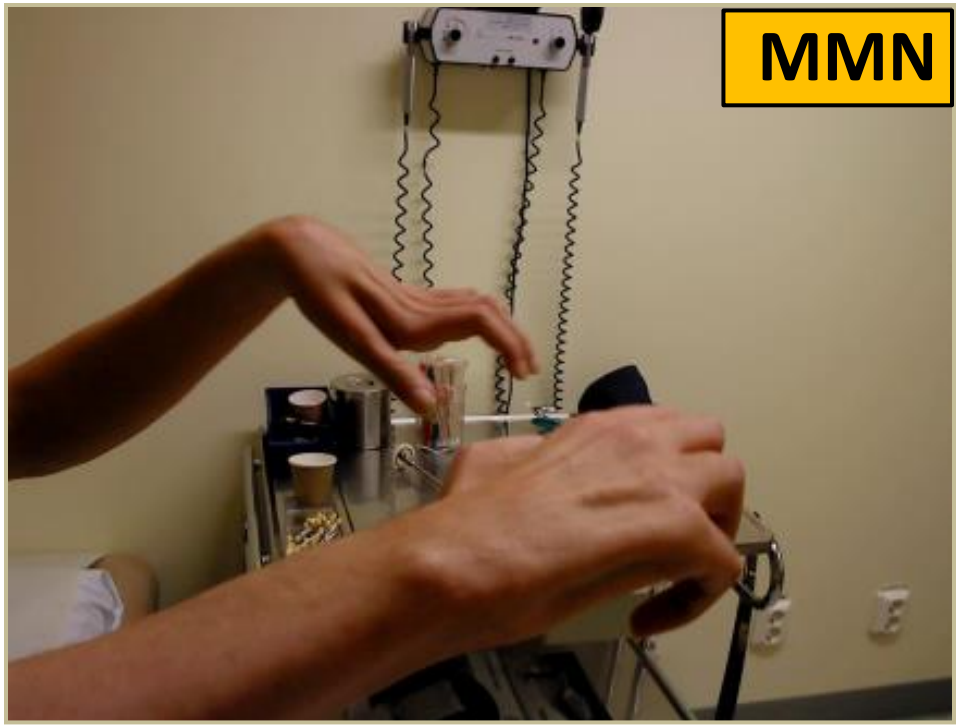
Prevalence: 0.5 /10^5, ♂>♀

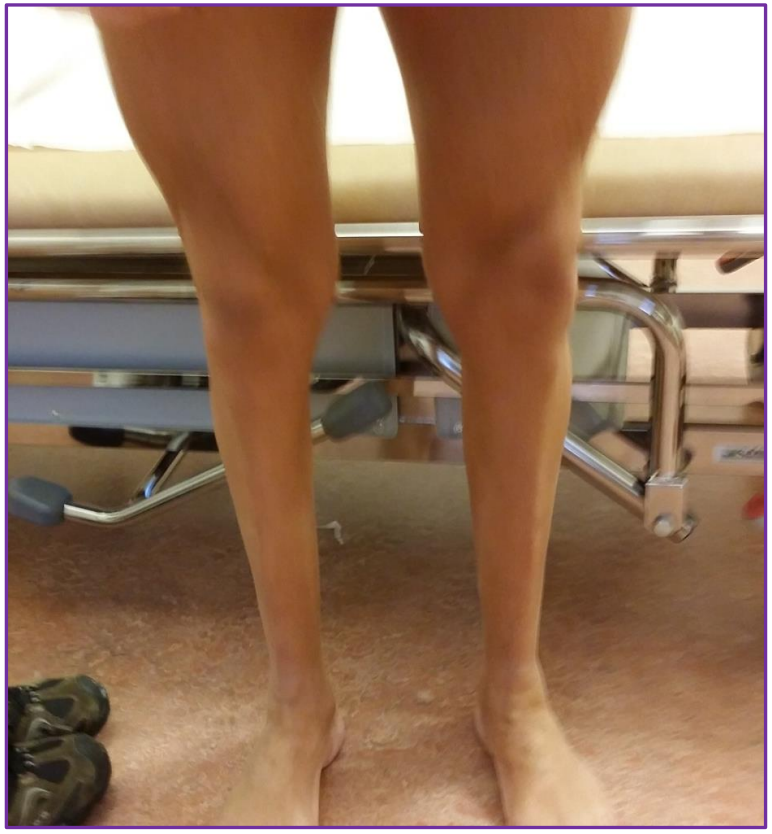
- Onset often distally in one arm
- Asymmetrical spread
- Slow progression
- Hypo- or normoreflexia
- Muscle atrophy, fasciculations (diff: PSMA)
- Treatable: IVIg

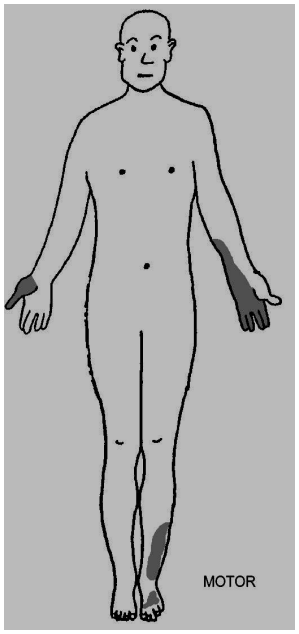
<u>Diagnosis</u>:

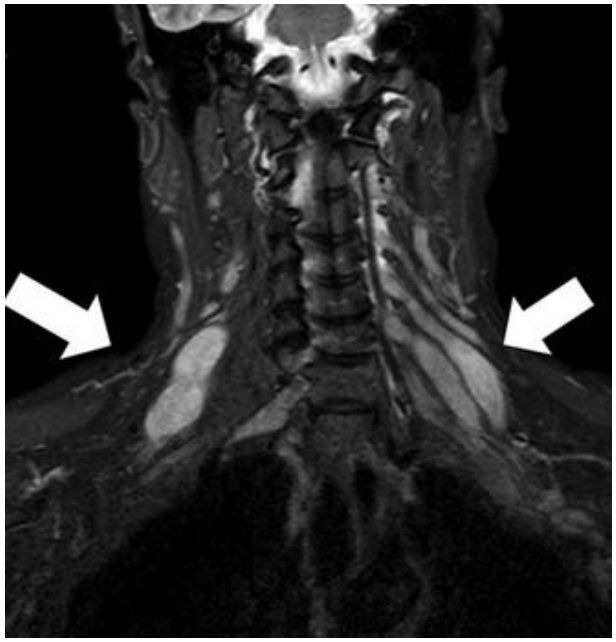
- ENeG: **Pure motor demyelinating** neuropathy, +/- conduction blocks
- S- GM1 IgM antibiodies in up to 80% of cases
- Imaging: MRI or nerve ultrasound

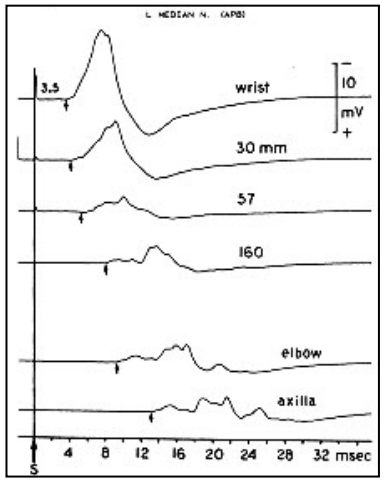












Kuwahara et al. Neuroimmunol & Neuroinflam, 2019

Paraprotein + polyneuropathy: Causality?

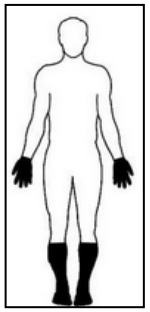
IgM paraproteins may induce an immune-mediated demyelinating neuropathy

Associated with: MGUS, lymphoma, Waldenström, Myeloma

Mechanism: Myelin-associated glycoprotein (MAG) antibodies. 50% of IgM parapr.

Distal Acquired Demeylinating Symmetric Neuropathy (DADS)

Slowly progressive
Sensory>motor
Distal
Sensory ataxia, tremor



ENeG: *Demyelinating* neuropathy, extremely prolonged distal latencies

Treatment: Cortison, IVIg, Rtx

Other paraproteins:

- IgG-**κ** -> No causality in chronic axonal neuropathies
- IgG-**λ** and IgA-**λ** -> POEMS -> Sensorimotor demyelinating + axonal PNP
- Light chains -> AL amyloidosis -> Severe sensorimotor axonal PNP

Antibody testing

Condition	Autoantibody (serum)	Clinical application
MFS	anti-GQ1b	90% are seropositive
Autoimmune nodopathy	Neurofascin antibodies, CASPR1, Contactin 1	100% are seropositive
MMN	Anti-GM1 IgM	30-80% are seropositive
DADS + IgM-κ pararotein	Anti-MAG	Ca 50% are seropositive
POEMS (IgG / IgA-λ)	S-VEGF	Yes (but low titers are unspecific)
Vasculitic neuropathy	Vasculitis panel	Yes
Ganglionopathy	SSA/SSB, anti-Hu TS-HDS	Yes Sometimes (moderate specificity)
Subacute sensory and ataxic axonal neuropathy	Anti-Hu, CV2, amphyphisin, Vasculitis panel	Yes

Karolinska vårdprogram för utredning av polyneuropati (2021)

www.snema.se/dokument

PNP Kategori	*Vanligaste* orsak	Förlopp - progress	Sens / Motor/ Autonom	Utbredning	Neurofysiologiska fynd
1	*Idiopatisk*	Mycket långsamt	Sens >> Motor	Distal	Lätt axonal
2	*Varierande: Systemiska sjd / CMT mm*	Långsamt	Sens ≥ Motor; ev autonom	Distal >>Prox	Axonal eller Axonal + demylin. (Ren Demyelin.)
3	*Immunologisk* GBS / CIDP	Akut Subakut (långsamt)	Motor ≥ Sens, ev autonom	Distal ≥ Prox	Demyelin. eller Demyelin. + axonal
4	*Immunologisk* MMN	Subakut Långsamt	Motor	Distal > Prox	Demyelin. eller Demyelin. + axonal
5	*Bindvävs sjd / Paramalign.*	Subakut Långsamt	Sens	Distal > Prox	Axonal
6	*Idiopatisk* Fintrådsneurop.	Subakut Långsamt	Sens, ev autonom	Distal	Fintrådspåverkan
7	*Vaskulit* Mononeuritis Multiplex, HNPP	Akut Subakut Långsamt	Sens ≥ Motor	Distal	Axonal eller Axonal + demylin.

Tid för debut av symtom till maximal-symtomnivå: =Akut: < 4 veckor; =Subakut: ca 2 månader- 1 år (3 år); Långsamt: ca 3-5 år; =Mycket långsamt: ca 6-15 år

PNP Kategori	Etiologi	Utredningsförslag
1	Axonal degeneration som är idiopatisk, hereditär, åldersrelaterad, eller sekundär till diabetes, B-vitaminbrist, alkohol och toxiska faktorer	Basala prover ENeG/EMG utom hos ”äldre-äldre”
2	Axonal degeneration med sekundär myelinskada, alt primär demyelinisering med en sekundär axonal skada. Ofta idiopatisk, men kan bero på systemiska sjukdomar såsom diabetes mellitus, njursvikt, vitaminbristtillstånd mm. Ärftliga tillstånd som ATTRv-amyloidos samt både axonala och demyeliniserande former av CMT. Toxiska orsaker som alkohol och läkemedel. Systemiskt- eller isolerad PNP-vaskulit, IgM paraprotein, sekundär amyloidos, lymfom, samt senstadium av CIDP där sekundär axonal degeneration överväger.	- Basala prover - ENeG/EMG - Ev. KST och/eller autonoma tester - Ev. genetisk utredning (CMT) **Yngre pat + snabb progress även:** - Vaskulitprover (se kategori # 5!) - Paramalignitetsutredning (se # 5!) - Muskelbiopsi (vaskulit?) - Fettbiopsi (amyloid?) - U-elfores, anti-gangliosid antikroppar (ak) i serum - Mutationsanalys- ATTRv-amyloidos? - Muskel, och ev. även nervbiopsi (vaskulit? Amyloidos?)
3	Immunologiskt angrepp mot myelin i PNS	Basala prover, ENeG/EMG LP, ev MRT rygg + kontrast eller nervultraljud, ev MAG-antikroppar
4	Immunologiskt angrepp mot myelin i PNS	Basala prover, ENeG/EMG LP, anti-gangliosid ak i serum. Ev nervultraljud
5	Axonal degeneration i grova sensoriska nervfibrer inklusive de proprioceptiva banorna. Bakomliggande orsaker är bindvävssjukdom (oftast Sjögrens syndrom) samt paramalignitet.	Basala prover, ENeG/EMG Vaskulitprover: CCP, SSA/ SSB, ANCA. B-celler; komplement; Kryoglobiner; HCV, HIV. Läppslemhinnebiopsi (Sjögren?) Malignitet: DT thorax/buk; riktad malignitetsutredning efter symtom. Paraneoplastiska ak. Muskel, och ev. nervbiopsi (vaskulit?)
6	Degeneration av småkalibriga sensoriska kutana (Aδ + C) & ev. autonoma (C) fibrerna. I de flesta fall är fintrådsneuropatin idiopatisk. Identifierbara orsaker utgörs av metabola sjd såsom nedsatt glukostolerens, diabetes mellitus, Fabry och Tangiers sjd; Immunopatier (MGUS, vaskulit, SLE, Sjögrens syndrom, celiaki, paramalignitet och amyloidos). Toxiska faktorer (alkohol, vissa cytostatika, anti-HIV läkemedel, metronidazol och alkohol) samt Hereditära tillstånd (HSAN I, IV,V; CMT-IIb & ATTRv amyloidos)	Basala prover; ENeG/EMG inklusive KST & ev. autonoma tester. Vaskulitprover (se # 5) Peroral glukosbelastning **Prog. måttligt-uttalade symtom även:** Celiakiutredning (transglutaminas ak, px duodenum); Fettbiopsi (amyloidos); ev DNA analys för ATTRv amyloidos Ev Metabol-utredning: Serum α-galaktosidase /u-trihexosid (Fabry); Blodfetter (Tangier)
7	Axonal skada sekundärt till inflammation/ ischemi vid bindvävssjukdom, vaskulit och diabetes samt myelinskada på hereditär basis (HNPP).	Basala prover, ENeG/EMG; LP Vaskulitprover (se # 5); ev. DNA analys-HNPP. Muskel, och ev. även nervbiopsi (vaskulit?)

Summary & Take Home

- Treating a patient with immune-mediated neuropathy is quite gratifying

- Ca 10-15% of polyneuropathies seen by neurologists at hospitals have an immue-mediated etiology

- Pattern recognition based on neurophysiology and topography:
  - Increases chanses of etiological diagnosis and of treatment
  - More stimulating to investigate polyneuropathies!

- All that shines is not gold

Consider CMT1, HNPP, ATTRv, CANVAS, PSMA as diff. diagnosis

- Consider pan-neurofascin autoimmune nodopathy the next time you consult on a ”GBS” patient with prolonged invasive ventilation in the ICU