Consider Rare: Suspecting and Diagnosing CIDP

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Continuing Education Information

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Learning Objectives: 1) Describe the early symptoms of CIDP. 2) List best practices which can be used to diagnose CIDP more efficiently..

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Agenda

- CIDP prevalence and challenges with timely diagnosis
- Key clinical diagnostic features of CIDP
- Role of supportive testing to improve diagnostic accuracy

CIDP: An overview

An immune mediated peripheral nerve disorder

Prevalence[1,2]	Age[3,4]	Gender[4]
1-9 per 100,000, which means in the United states, about 40,000 people are affected	Any age can be affected, but incidence and prevalence increase later in life	Both genders can be affected, but men are affected almost twice as often as women

1. Lunn M et al. JNNP. 1999:66(5);677-680; 2. Mathey EK. JNNP. 2015:86; 973-985; 3. Broers MC. Neuroepidemiology 2019:52(3-4);161-172; 4. Brun S et. Immuno. 2022:2(1);118-131

Diagnosing CIDP

The journey to CIDP diagnosis:

Delay, disability & prognosis

Delayed diagnosis is common

- Mean time from symptom onset to diagnosis: 10 to 40 months[1-2]

Disability is common

- Mean disability "moderate" at time of diagnosis[3]
- Requires help with day-to-day tasks, but walks without assist
- Disability worsens as the disease goes undiagnosed
- At some point in disease, half are unable to live independently[4]

Predictors of worse long-term prognosis[5-7]

- Older age, Progressive course, Prominent axon loss

1. Hughes RA et al. Lancet Neurol 2008; 2. Laughlin RS et al. *Neurology* 2009; 3. Cocito D et al. Eur J Neurol 2010; 4. Lunn MP et al. JNNP 1999; 5. Bouchard C et al. Neurology 1999; 6. Simmons Z et al. Brain 1995; 7. Sghirlanzoni A et al. Neurol Sci 2000

Why is CIDP a difficult diagnosis to make?

1. Rare disease with heterogenous clinical presentations
2. Requires integration of many clinical and laboratory components, each of which has a potential for error
3. No single diagnostic test
4. Diagnostic mimics are common

Why is early and accurate diagnosis important?

CIDP is treatable

- Overall, 80-90% respond to one of the first line therapies[1]

But when diagnosis is delayed, treatment is delayed

- Axon loss accumulates
- Disability accumulates

As treatment is delayed

- Disease progression is common
- Axon loss may worsen

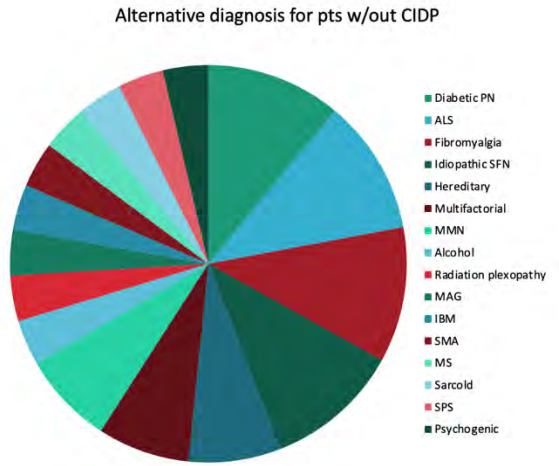
Consequences

- Increased disability
- Poorer prognosis

1. Cocito D et al. *Eur J Neurol 2010.*

Misdiagnosis of CIDP is also common

CIDP diagnostic pitfalls and perception of treatment benefit[1]



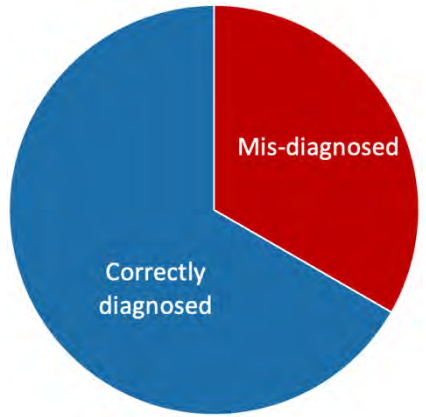
Almost half **(47%)** did not have CIDP (n=58)

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

Clinical condition	Assessment	No. of cases	% of total cases
Immune neuropathy present	Yes	80	32.2
	No	115	46.4
	Unable to determine	53	24.1
Appropriate candidate for therapy	Yes	80	32.2
	No	119	48.0
	Unable to determine	49	19.8
Positive response to IVIg predicted	Yes	37	14.9
	No	149	60.1
	Unable to determine	62	25.0
Evidence for demyelination	None	82	33.0
	Some – does not meet EFNS criteria	42	16.9
	Meets EFNS criteria	26	10.4
	Uninterpretable	20	8.0
	No NCV submitted	78	31.4

68% did not have CIDP or other immune neuropathy

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



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

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

1. Figure recreated from Allen JA and Lewis RA. Neurology. 2015; 2. Table recreated from Levine et al. Neurology Clinical Practic. 2018; 3. Broers M et al. European Journal of Neurology. 2021

Why is avoiding misdiagnosis important?

1. Patients wrongly diagnosed with CIDP are often exposed with expensive and potential harmful immunotherapies
2. Delays treatment or management of their “real” condition
3. Creates malalignment between treatment, expectations for improvement and prognosis

Core clinical features of CIDP

Typical CIDP and the variants

- Typical CIDP phenotype
  - Symmetric proximal and distal numbness and weakness in the upper and lower limbs
  - Reduced or absent deep tendon reflexes
  - Progressive or relapsing over at least 2 months
- Recognized variants of CIDP include
  - Distal CIDP
  - Multifocal CIDP
  - Sensory CIDP
  - Motor CIDP

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

Core clinical features of CIDP

The variants

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

All should have reduced reflexes, be progressive or relapsing over > 8 weeks, and have electrophysiologic evidence of peripheral nerve demyelination.

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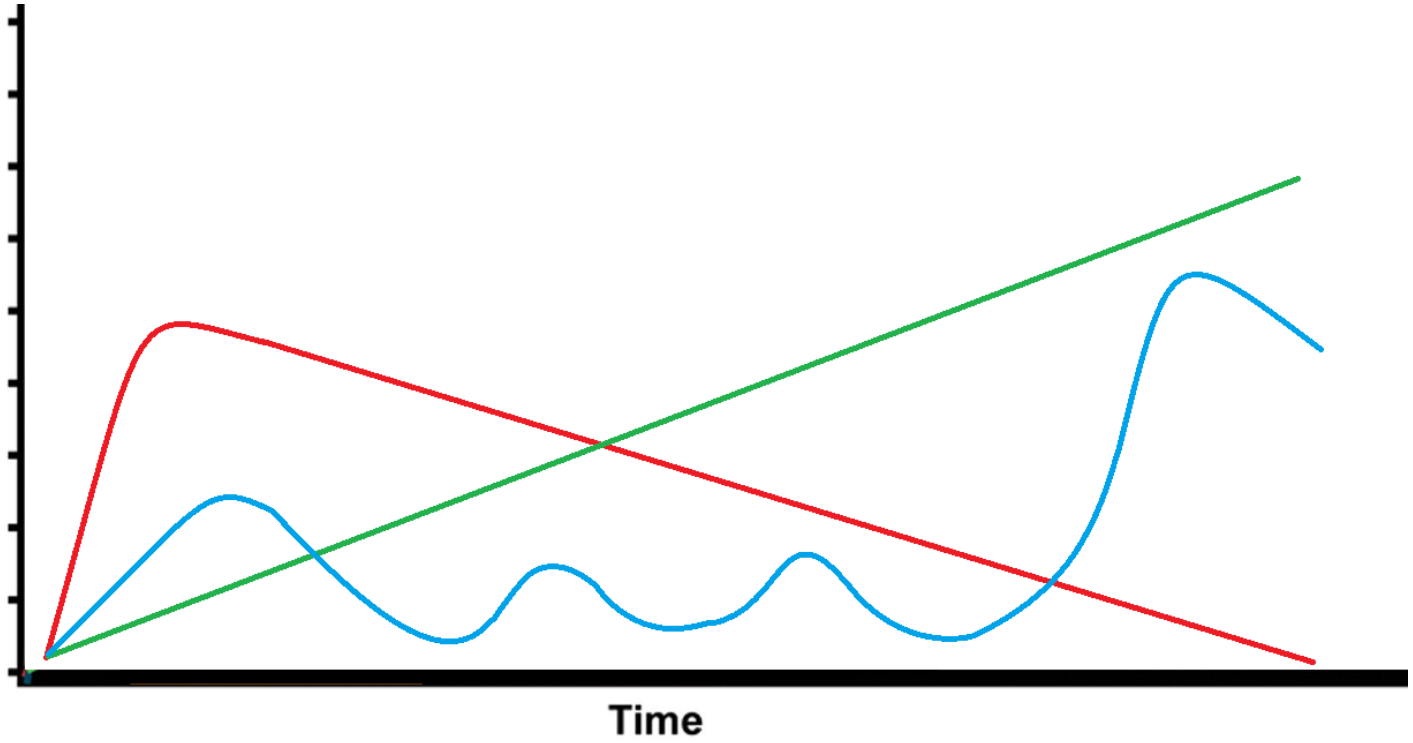
Other symptoms of CIDP

Symptom	Frequency	Comment
Fatigue	Up to 75%	Can be hard to differentiate from weakness
Pain	30-40%	Can be moderate to severe
Tremor	Up to 50%	
Autonomic dysfunction	20-25%	Usually mild
Cranial nerve dysfunction	5-20%	Facial nerve most common
Respiratory failure	Rare	

Although other symptoms can occur, CIDP is always defined first and foremost by the motor and sensory deficits.

CIDP clinical course

Evolves over **2 months or more** in a progressive or relapsing pattern.



An illustrative patient

- 62-year-old man developed numbness and paraesthesias bilaterally in feet and hands
- Other than hyperlipidemia and hypertension he was previously healthy
- 3 months after symptom onset needed a cane to walk, and at 6 months was having trouble leaving his house due to gait instability
- Neurological examination 6 months after onset
  - Bilateral and symmetric weakness in her proximal and distal lower limbs and distal upper limbs
  - Reduced vibration perception in the hands, feet and toes
  - Diffusely reduced or absent deep tendon reflexes

An illustrative patient

Meets the clinical definition of “typical” CIDP:

- Proximal and distal motor and sensory deficits
- Relatively symmetric
- Reduced reflexes
- Evolves over more than 2 months

Electrophysiology findings in CIDP

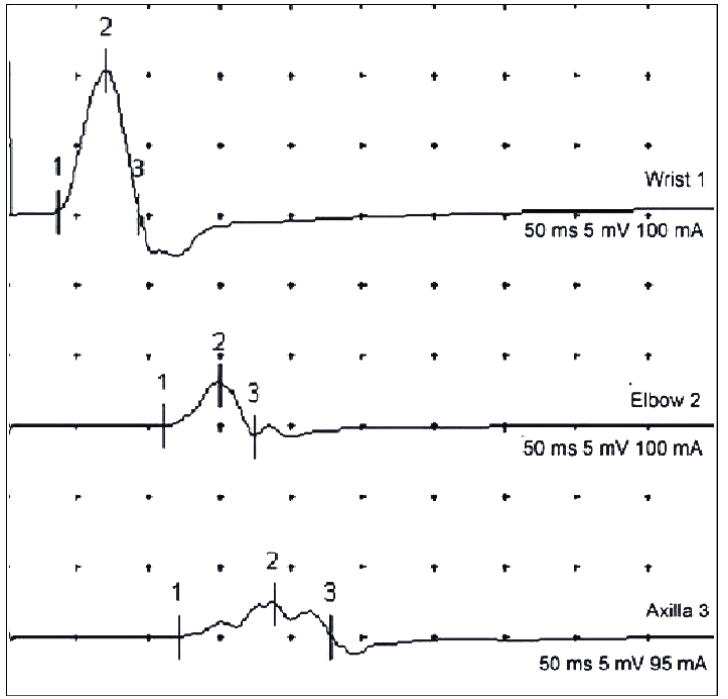
Finding evidence of peripheral nerve demyelination

May include:

- Motor conduction slowing
- Conduction block
- Temporal dispersion
- Distal latency prolongation
- F-wave prolongation

EAN/CIDP diagnostic guidelines[1]

- Mild or moderate changes may not be diagnostic of a demyelinating polyneuropathy
- Guidelines are an excellent resource to understand if a change supports a CIDP diagnosis



Median nerve conduction block in a demyelinating neuropathy[2]

1. Van den Bergh PY et al. European Academy of Neurological Societies/Peripheral Nerve Society guideline on management of CIDP - second revision. J Peripher Nerve Syst 2021;26(3):242–268.
2. Ahn SW. Annals of Clinical Neurophysiology. 2018: 20(2):71. Creative commons.

EAN/PNS Electrodiagnostic Criteria

- ≥50% prolongation of motor distal latency
- ≥30% reduction of motor conduction velocity
- ≥20% prolongation of F-wave latency, or ≥50% if amplitude of distal negative peak CMAP is <80% of LLN
- Motor conduction block: ≥30% amplitude reduction if distal amplitude > 1 mV
- Abnormal temporal dispersion: >30% duration increase
- Distal CMAP duration prolongation (median ≥6.6 ms, ulnar ≥6.7 ms, peroneal ≥7.6 ms, tibial ≥8.8 ms)

Electrodiagnostic findings may be classified as:

Strongly supportive of peripheral nerve demyelination: Two or more nerves affected
Weakly supportive of peripheral nerve demyelination: Only one nerve affected

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

An illustrative patient

Sensory NCS

	Rec. Site	CV (m/s)	Amplitude (uV)
L ulnar – Dig V			
Wrist	Dig V	44	7
L sural – Lat mall			
Calf	Ankle	NR	NR

Motor NCS

	Rec. Site	Latency (ms)	Amplitude (mV)	Duration (ms)	CV (m/s)
L ulnar – ADM					
Wrist	ADM	6.94	5.1	7.61	
B elbow	ADM	12.10	3.3	8.76	31.2
A elbow	ADM	14.69	3.1	9.66	38.0
L peroneal – EDB					
Ankle	EDB	7.11	2.9	6.75	
Fib head	EDB	14.69	2.2	9.69	22.7
Pop fossa	EDB	17.92	2.1	10.52	29.8

An illustrative patient

Meets the electrophysiologic definition of “strongly supportive” of demyelination

- Greater than 30% CV slowing in 2 nerves
- Conduction block in 1 nerve
- Sensory abnormalities in 2 nerves

Supporting data in CIDP

Increasing or decreasing diagnostic confidence

Supportive Criteria for CIDP
• Elevated CSF protein with leukocyte count <10/mm^3
• MRI showing gadolinium enhancement and/or hypertrophy of the cauda equina, lumbosacral or cervical nerve roots, or the brachial or lumbosacral plexuses
• Ultrasound showing nerve, plexus or root enlargement
• Nerve biopsy showing unequivocal evidence of demyelination and/or remyelination by electron microscopy or teased fiber analysis
• Objective clinical improvement following immunomodulatory treatment

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

Common pitfalls when considering supportive data

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

Key messages when integrating clinical and laboratory components

- **Core clinical and electrophysiologic features are still needed**
- **Supportive CIDP findings are not diagnostic of CIDP in isolation**
  - Beware of mild or moderately elevated CSF protein
  - Beware of “subjective” responses to treatment
- **Supportive data is <u>not needed</u> if:**
  - Clinical and electrophysiologic findings are clear
  - No “red flags” for alternative diagnosis
- **Supportive data <u>can be helpful</u> if:**
  - Electrophysiologic findings are only weakly supportive of CIDP
  - If there are mimics that need to be excluded

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

EAN/PNS CIDP diagnostic criteria

The two diagnostic classifications

CIDP

Clinical criteria + Strongly supportive electrodiagnostic criteria

Possible CIDP

Clinical criteria + Weakly electrodiagnostic criteria

Supportive criteria

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

Possible CIDP can be upgraded to CIDP if:

- 2 or more supportive features are present
- No alternative explanation is present

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

CIDP diagnostic challenges

A common diagnostic dilemma

- No CIDP diagnostic biomarkers are known
- Recognizing characteristic clinical and electrophysiologic features is key for early and accurate diagnosis
- Failure to identify “red flags” and to consider diagnostic alternatives may lead to misdiagnosis

“Red flags” that it might not be CIDP

The phenotype helps narrow the differential

Distal CIDP

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

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

“Red flags” that it might not be CIDP

The phenotype helps narrow the differential

Sensory CIDP

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

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

“Red flags” that it might not be CIDP

The phenotype helps narrow the differential

Multifocal CIDP

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

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

“Red flags” that it might not be CIDP

The phenotype helps narrow the differential

Motor CIDP

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

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

An illustrative case

Meets EAN/PNS CIDP diagnostic criteria

High confidence that this patient has a diagnosis of CIDP

CIDP

- Clinical criteria + Strongly supportive electrodiagnostic criteria
- Also 2 supportive criteria

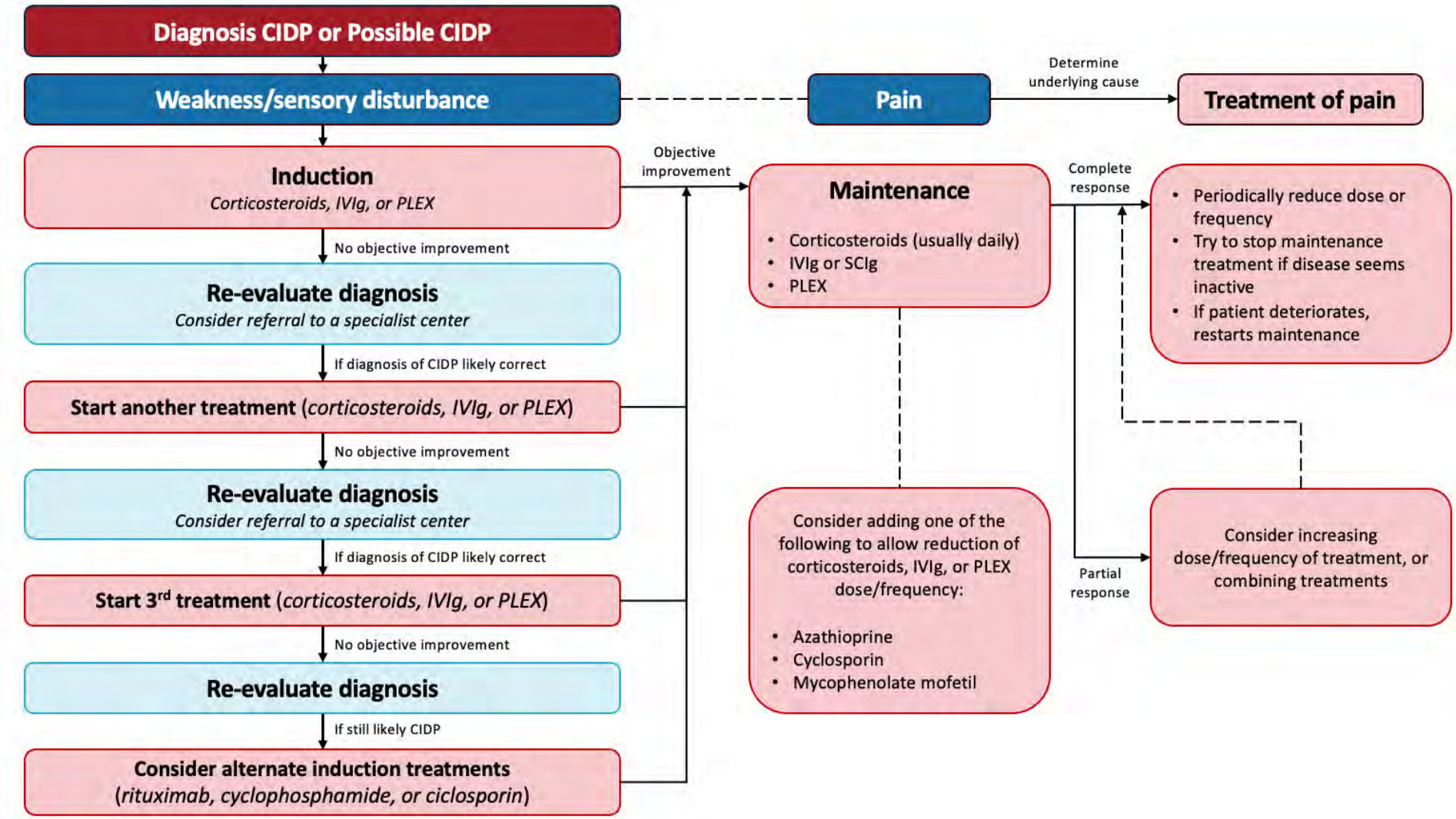
An illustrative case

- CSF protein 89 ng/ml with 1 WBC and 3 RBC
- MRI of the showed enlargement and increased T2 signal in portions of the brachial plexus
- Serum immunofixation showed no monoclonal gammopathy
- No other “red flags” were observed

High confidence that this patient has a diagnosis of CIDP

Managing CIDP

Recommendations from EAN/PNS Guidelines



1. Van den Bergh PYK, *et al. Eur J Neurol.* 2021;28(11):3556–3583; 2. van den Berg B, *et al. Nat Rev Neurol.* 2014;10:469–482.

CIDP treatments

Corticosteroids in CIDP

- Mimic the action of naturally occurring hormones[1]
- Decreasing inflammation and suppress the immune system[1]
  - Suppresses migration of polymorphonuclear leukocytes[2]
  - Reversal of capillary permeability[2]
  - Inhibition of proinflammatory[1] and promotion of anti-inflammatory cytokines[3]

Pros

- ✓ Convenient (oral or IV)
- ✓ Inexpensive
- ✓ Broadly effective for many conditions
- ✓ Easily accessible

Cons

- ✕ High blood pressure
- ✕ High blood sugar
- ✕ Bone loss
- ✕ Weight gain and edema
- ✕ Stomach ulcers
- ✕ Restlessness and irritability
- ✕ Others

1. Samuel S, *et al*. *J Neurocrit Care.* 2017;10(2):53–59; 2. Puckett Y, *et al*. Prednisone. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan; 3.Léger J-M, *et al*. *Neurotherapeutics*. 2016;13:96–107

CIDP treatments

Corticosteroids in CIDP

- Little evidence of a beneficial effect of corticosteroids in CIDP from clinical trials[1,2]
  - One small randomized controlled trial compared corticosteroids to no treatment (not placebo!)[3]
  - Open label studies suggest a response rate of about 60%[4]
  - Studies comparing pulse vs daily oral corticosteroids appear similar in efficacy, but pulsed corticosteroids are generally better tolerated [5]
- Commonly used in clinical practice

1. Hughes RA, et al. Cochrane Database Syst Rev. 2016;10(10):CD001446; 2. Hughes RA, et al. Cochrane Database Syst Rev. 2017;11(11):CD002062; 3. Dyck PJ et al. Ann Neurol. 1982; 4. van Lieverloo GGA, et al. J Neurol. 2018;265:2052–2059; 5. Van Schaik I et al. Lancet Neurol. 2010;9:245–253.

CIDP treatments

IVIG and SCIG in CIDP

- Immunoglobulins: Antibodies obtained from pooled blood donors
- Multiple possible immunologic mechanisms[1,2]
  - Regulate autoreactive B-cell clones
  - Competes with disease-associated antibodies
  - Impairs T-cell activation
  - Blocks Fc receptors
  - Interferes with complement activation

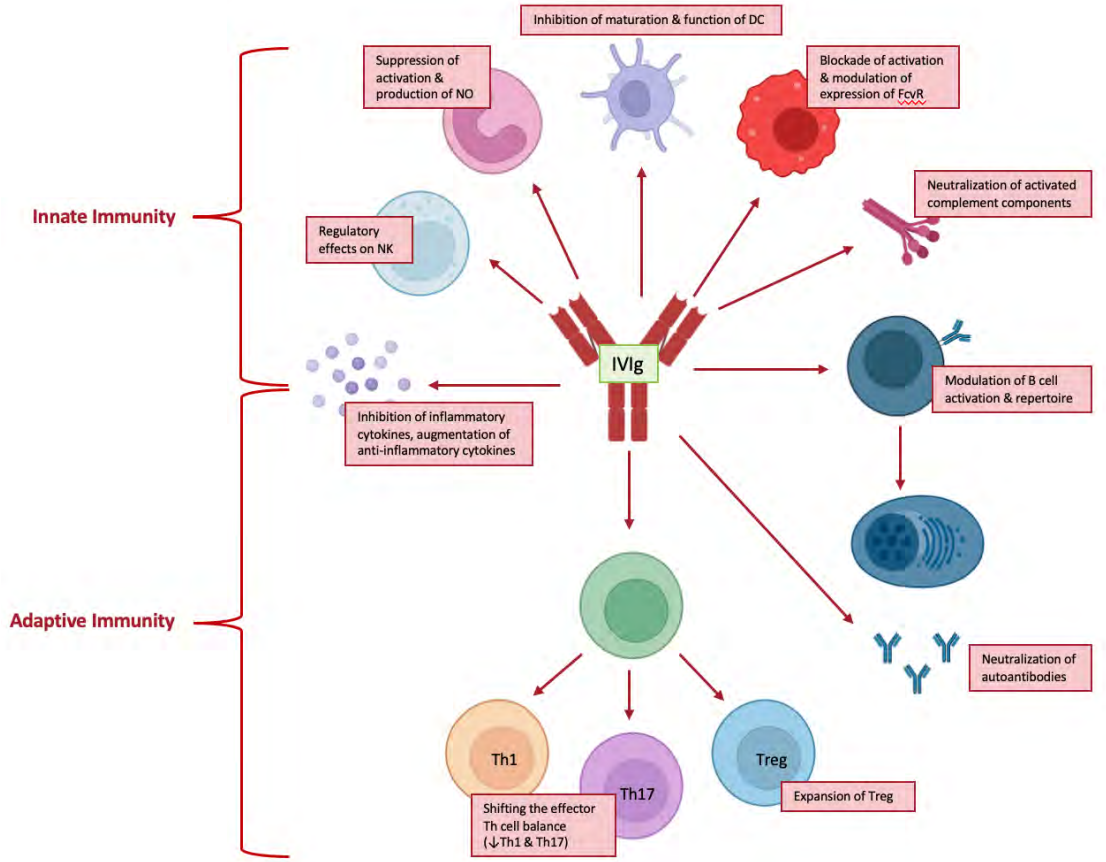


Figure adapted from Galeotti C, *et al.* 2017.[1]

1. Galeotti C, *et al. Int Immunol*. 2017;29(11):491–498; 2. Bayry J, *et al. Transfusion Clinique et Biologique*. 2003;10:165–169.

CIDP treatments

IVIG and SCIG in CIDP

Pros

- ✓ Effective (strongest data)
- ✓ Generally well tolerated
- ✓ Not steroids or PLEx
- ✓ Not immunosuppressive
- ✓ Available IV or SC
- ✓ Relatively fast onset of effect (IVIG)
- ✓ Autonomy (SCIg)

Cons

- ✕ Inconvenient
- ✕ Cost
- ✕ Short-term efficacy
- ✕ Requires IV access (IVIg)
- ✕ Local site reactions (SCIg)
- ✕ Nausea
- ✕ Headaches
- ✕ Thromboembolic risks
- ✕ Others

1. Allen JA, *et al. J Neurol Sci.* 2020;408:116497; 2. Bril V, *et al. J Peripher Nerv Syst*. 2023;28:436–449; 3. Berger M and Allen JA. *Muscle Nerve.* 2015;51(3):315–326.

CIDP treatments

IVIG in CIDP

IVIG: High quality evidence

- 5 randomized placebo-controlled studies with 235 combined participant[1]
- Significantly higher proportion of participants improved disability and strength with IVIg compared to placebo
- Overall response rates vary from 54%[2] to 92%[3]

- Typical induction dose of 2 gm/kg loading and maintenance dose of 1 gm/kg q 3 weeks maintenance[2], although in some patients higher doses may be more beneficial[3]

- Most patients that respond to IVIG do so within 3-6 months[2,3]

1. Etimov F. Cochrane Database Syst Rev. 2013; 2. Hughes R et al. Lancet Neurol. 2008;7:136–144; 3. Cornblath D et al. Brain. 2022 Apr 29;145(3):887-896.

CIDP treatments

SCIG in CIDP

SCIG: High quality evidence

- 2 large randomized placebo-controlled studies for SCIG as a maintenance therapy[1,2]
  - Conventional SCIG[1]
  - Facilitated SCIG combines hyaluronidase with Ig to increase subcutaneous permeability[2]

- Both studies showed SCIG was effective for prevention of relapse
  - SCIG: Relapse rate 33%-39% vs 63% placebo (treatment difference 24%-30%)[1]
  - Facilitated SCIG: Relapse rate 9% vs 31% placebo (treatment difference 22%)[2]

- SCIG: Typical maintenance dose 0.2 and 0.4 gm/kg once weekly[1]
- fSCIG: Mean dose in clinical trial 1.1 gm/kg administered once every 4 weeks, although may vary between 0.4-2.4 gm/kg every 2-4 weeks[2]

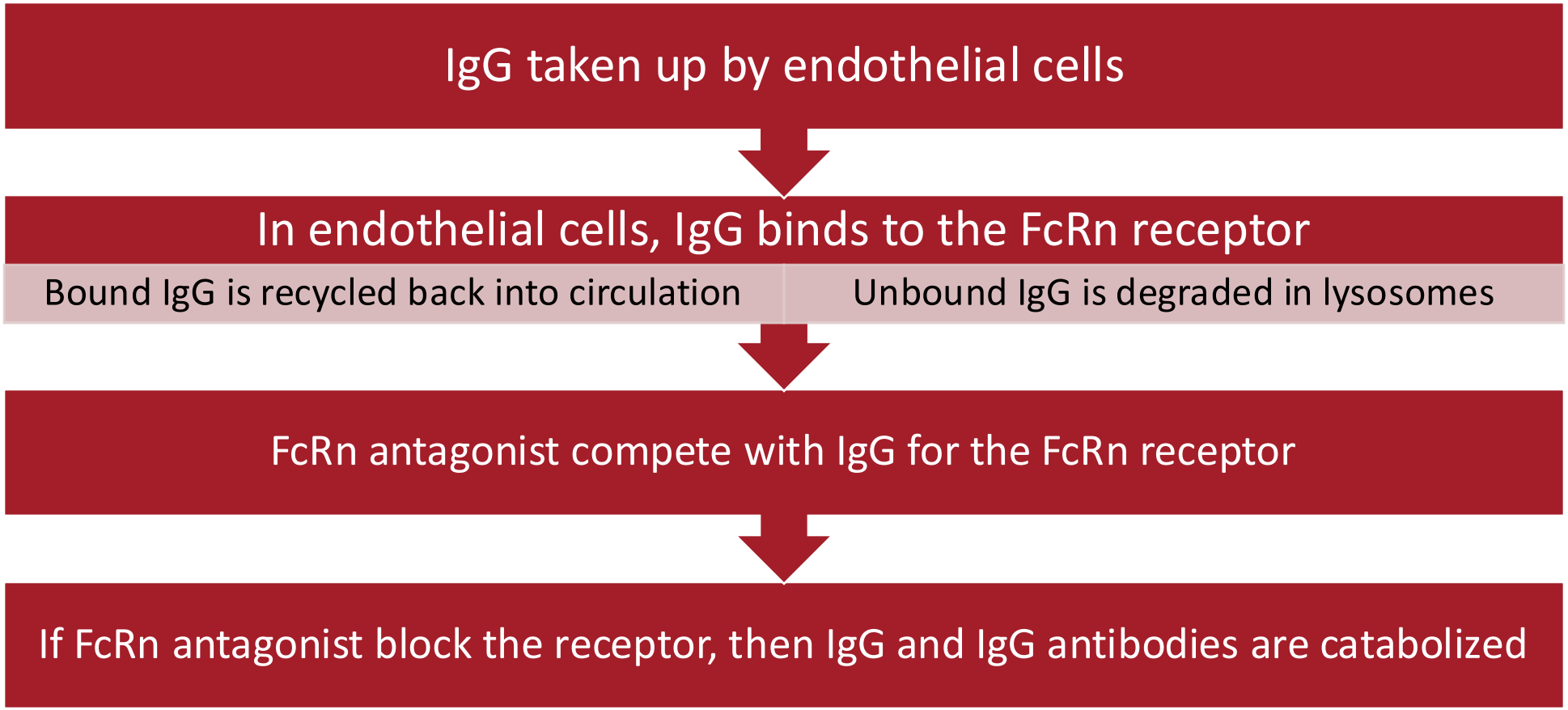
1. Van Schaik IN, et al. Lancet Neurol. 2018;17(1):35–46; 2. Bril V, et al. J Peripher Nerv Syst. 2023;28:436–449

Targeted Therapies

Orphan Drug	Target	Status
Efgartigimod	FcRn	FDA approved (July 2024)
Nipocalimab	FcRn	Phase 3 study (NCT05327114)
Riliprubart	C1	Phase 3 studies (NCT06290141, NCT06290128)
DNTH103	C1	Phase 3 study (NCT06858579)
Empasiprubart	C2	Phase 3 studies (NCT07091630, NCT06920004)

FcRn antagonist

Mechanism of Action



1. Sesarman A. *Cell Mol Life Sci*. 2010;67(15):2533-2550; 2. Patel DD and Bussel JB. *J Allergy Clin Immunol.* 2020;146(3):467–478

Treatment selection in CIDP

Therapeutic decision-making in CIDP requires consideration of factors including[1]

- Age
- Disease severity
- Comorbidities
- Lifestyle
- Access to infusion center
- IV compatibility
- Others

The optimal treatment for one patient is not the optimal choice for every patient

In order to optimize outcomes[2,3]

- Patients like to know about alternative treatments
- Patients want to be involved in decision making

1. Rajabally YA. Neural Regen Res. 2015;10:1399-1400; 2. Hamann J et al. Health Expect. 2007;10:358-363; 3. van den Brink-Muinen A et al. Patient Educ Couns. 2011;84:111-117.

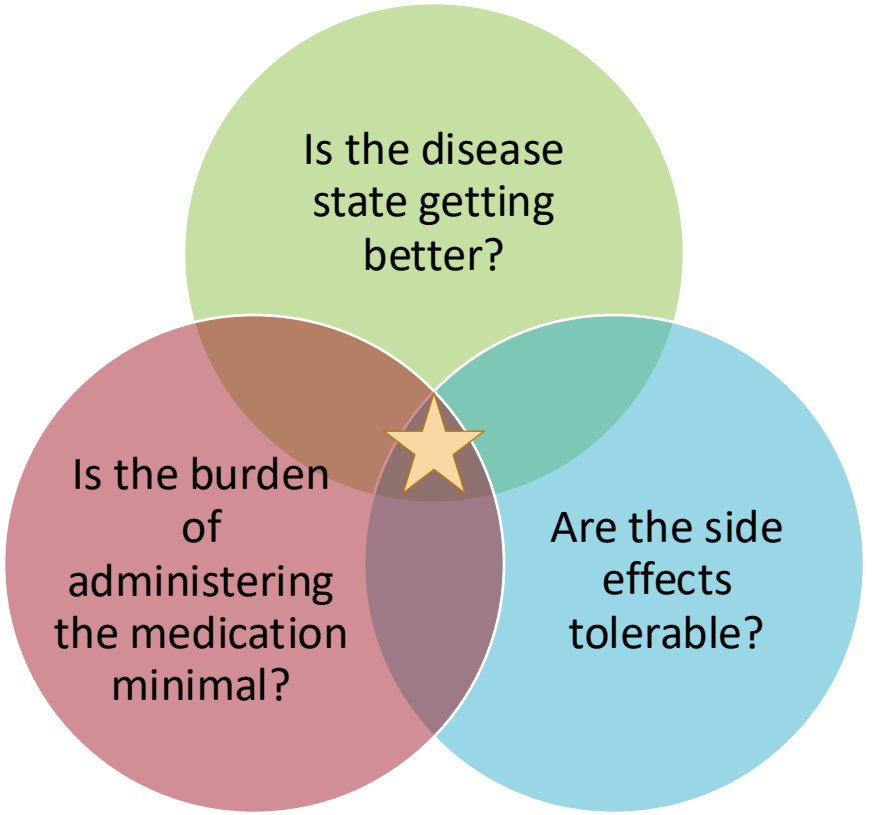
CIDP treatments

Unmet treatment needs in CIDP

- What can we offer patients that do not respond or minimally respond to IVIG or corticosteroids?
- Are there options if IVIG, SCIG or corticosteroids are poorly tolerated?
- How can we maintain or improve upon efficacy of standard treatments, but also find ways to make treatment less burdensome to patients?
- Future therapies should also take into account our current understanding of CIDP immunobiology
  - ✓ Role of antibodies
  - ✓ Role of complement

Treatment selection in CIDP

Considering for finding the optimal treatment



Optimal treatment should be effective, well tolerated, and accessible with minimal burden

Clinical Pearls

Final comments

- CIDP is an acquired immune mediated peripheral nerve disorder characterized by key clinical and electrophysiological findings.
  - Getting the diagnosis right can be challenging!
- EAN/PNS 2021 guidelines are a resource for an evidence-based treatment approach.
  - Data support the use of IVIG, SCIG, corticosteroids and plasma exchange
- FcRn antagonist also effective for the treatment of CIDP.
- Shared decision making is needed to find the best approach that meets the unique values and preferences of individual patients.
  - Consider treatment efficacy, side effects, and administration burden when optimizing treatment.