

Diagnosis and Management of Immune Mediated Polyneuropathies: A lecture from the Neuromuscular Review Course

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Acute Immune Mediated Polyneuropathies

Acute polyneuropathies are best thought of as a group rather than focusing solely on Guillain-Barré syndrome.

These conditions tend to come on acutely and are monophasic, meaning they begin, reach a plateau, and then resolve (Figure 1). They are often preceded by an infection, though not always. Most cases fall under Guillain-Barré syndrome (GBS) with a characteristic demyelinating pattern, but not all do. GBS is also referred to as acute inflammatory demyelinating polyneuropathy (AIDP). Progression typically occurs over days to a couple of weeks.

GBS classically presents with ascending weakness and large-fiber sensory loss, with motor involvement usually more pronounced than sensory involvement.

It is generally symmetric (Figure 2). Clinical severity varies widely. Some patients may present with relatively mild symptoms, reporting weakness that developed weeks earlier without major progression, while others deteriorate rapidly

and require intensive care within 24 hours (Dimachkie & Barohn, 2013).

There are numerous variant presentations that still follow an acute monophasic pattern.

Not all cases are ascending (Figure 3). First symptoms may be ocular, pharyngeal or in the arms and then they descend. These have been labeled the oculopharyngeal and brachio-pharyngeal variants. Some patients initially experience radicular pain resembling sciatic or cervical pain for several days before weakness appears. Other presentations include facial weakness or paraparesis that can mimic spinal cord pathology. The classic works by Allan Ropper in the 1980s and 1990s helped define these atypical forms (Ropper 1986; Ropper 1994).

There are also “no-weakness” presentations, most notably Miller Fisher syndrome, first described in the 1950s (Fisher 1956). This syndrome is characterized by acute ophthalmoplegia and ataxia with preserved reflexes. These cases are usually straightforward to recognize and tend to resolve spontaneously within six to eight weeks. Evidence suggests intravenous immunoglobulin (IVIg) does not significantly alter outcomes in this subtype.

Another related condition is Bickerstaff brainstem encephalitis, considered a central nervous system variant in which immune attack targets structures emerging from the brainstem. Patients may develop ophthalmoplegia, ataxia, confusion, and increased reflexes.

Additional variants include acute autonomic neuropathy, sensory ganglionopathy, and pure sensory neuropathy. Axonal forms, such as acute motor axonal neuropathy (AMAN) and acute motor and sensory axonal neuropathy (AMSAN), are often described as having faster progression. They may be labeled as AMSAN because the most rapidly progressive cases are the ones that come to attention earliest. In other words, it can be confused with typical cases of GBS where nerve conduction studies are done too early and do not show demyelinating changes yet, but this is probably an improper use of the term AMSAN which refers to only cases that have axonal loss in addition to an absence of demyelination.

Diagnostic evaluation typically begins when a neurologist is consulted for acute weakness.

Figure 1

The Acute Immune Mediated Polyneuropathies

- Acute, monophasic, immune-mediated
- Preceding infection reported in 70% of cases
- 80% with “characteristic” demyelinating pattern
- Progression typically days to two weeks

Figure 2

The Phenotype of Classic AIDP (The Guillain Barre Syndrome)

- Acral paresthesia or dysesthesia
- Objective sensory loss often mild or delayed
- Symmetric ascending weakness
- Severity spectrum from very mild to complete paralysis

Dimachkie, Barohn. Guillain-Barre Syndrome and Variants. Neurol Clin. 2013 May;31(2):491-510

Figure 3

Variant presentations

Atypical patterns of weakness

- Oculopharyngeal, Brachiocephalic
- Radicular pain
- Facial weakness
- Paraparesis resembling spinal cord lesion

No weakness (5%):

- Miller-Fisher Syndrome: acute ophthalmoplegia ataxia (AOA)

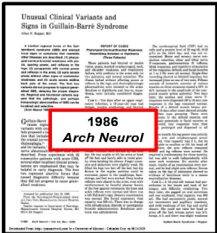
N Engl J Med. 1956 Jul 12;255(2):57-65. doi: 10.1056/NEJM195607122550201.

An unusual variant of acute idiopathic polyneuritis (syndrome of ophthalmoplegia, ataxia and areflexia)

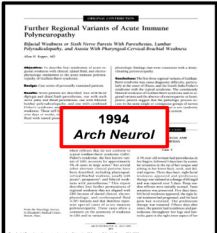
M FISHER

PMID: 13334797 DOI: 10.1056/NEJM195607122550201

- Bickerstaff's: ophthalmoplegia, confusion, DTR ↑
- Acute autonomic neuropathy, sensory ganglionopathy
- Acute pure sensory neuropathy



1986
Arch Neurol



1994
Arch Neurol

1986 *Arch Neurol*
Ropper AH. Unusual clinical variants and signs in Guillain-Barré syndrome. *Arch Neurol*. 1986;43(11):1150-1152.

1994 *Arch Neurol*
Ropper AH. Further Regional Variants of Acute Immune Polyneuropathy. *Arch Neurol*. 1994;51(7):671-675.

Figure 4

Acute Inflammatory Neuropathy Work Up

- Lumbar puncture
 - WBC count is typically 0 to 5, but can be up to 10-30
 - If WBC count is over 15 consider wider differential: HIV, Lyme, sarcoid, West Nile, leptomeningeal carcinomatosis
 - Protein may be normal early on
 - Elevated in 90% after first week
- NCS:
 - Also have relatively poor sensitivity early after presentation (about 22%)
 - Mildly prolonged F-waves or distal latencies may be only finding
 - By 2 to 3 weeks post onset:
 - Temporal dispersion, conduction block, then slowing
 - Sensitivity of NCS is 87% at 5 weeks

Two primary tests support the diagnosis: lumbar puncture and nerve conduction studies (Figure 4). Lumbar puncture is often performed first. The key finding is cytoalbuminologic dissociation, elevated protein with minimal cells. Lymphocytic pleocytosis (up to 50-60 cells per cubic millimeter) can occur and does not exclude the diagnosis but prompts consideration of alternative causes such as HIV, Lyme disease, sarcoidosis, or West Nile virus. CSF protein may be normal or have minimal elevation early on. Normal CSF protein early on does not rule out the diagnosis of GBS.

Similarly, nerve conduction studies may show only minor abnormalities early in the disease course. Slightly prolonged distal latencies or F-waves are usually the earliest electrophysiologic sign of the condition. More definitive demyelinating findings (temporal dispersion, conduction block, slowing) can take up to several weeks to appear.

Treatment

Treatment focuses primarily on IVIg, typically initiated when patients lose independent ambulation. Figure 5

summarizes recommendations from the AAN practice parameters.

Very mild ambulatory cases may not require intervention. Plasmapheresis is an alternative but is usually more logistically complex. Sequential IVIg and plasmapheresis are avoided because plasmapheresis removes therapeutic immunoglobulin. Both IVIg and plasmapheresis are giving the patient a better long-term prognosis. One should not expect rapid improvements after IVIg or plasmapheresis has been administered. In fact, the goal of the treatment is to improve long-term outcome such as decreasing time in the intensive care unit and shortening the time to ambulation. If progression continues after a completed IVIg course, supportive management is usually preferred over repeat treatment (Hughes 2003; Cortese 2011; Walgaard 2021). IVIg has a half-life of about three weeks.

A key transition point is distinguishing AIDP from chronic inflammatory demyelinating polyneuropathy (CIDP) (Figure 6).

Figure 5

PE & IVIg for GBS AAN Practice Parameters

- PLEX
 - Nonambulatory patients, 4 weeks since onset (Level A)
 - Ambulatory patients within 2 weeks of onset (Level B)
- IVIg:
 - Nonambulatory patients within 2 weeks (Level A)
 - Nonambulatory patients, 4 weeks of onset (Level B)
 - Corticosteroids NOT recommended in GBS (Level A)
 - Second course IVIg/severe GBS/not recommended (Level A)

Hughes RA, et. al. *Neurology*. 2003;61:736-74
Cortese I, et. al. *Neurology*. 2011;76(3):294-300
Walgaard C, et al. *The Lancet*. 2021; 20(4):275-283

Figure 6

Temporal Aspects of AIDP/CIDP

KEY POINT:

- Temporal evolution or speed of onset?
 - acute (days to 4 weeks)- GBS
 - subacute (4 to 8 weeks)- SIDP
 - chronic (> 8 weeks)- CIDP

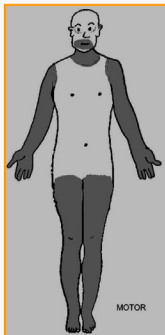
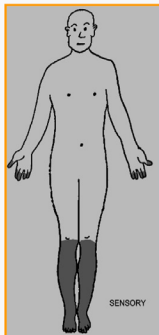



Figure 7

CIDP: Community Bias Slants Towards Over-diagnosis

- Allen and Lewis
 - 50% of CIDP cases referred to tertiary center do not meet disease criteria
 - Based on comparison to disease criteria

Muscle Nerve. 2018 Apr;57(4):542-549

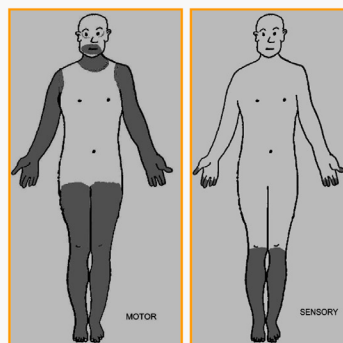
Neurology. 2015 Aug 11;85(6):498-504
- Levine et al.
 - Nearly 70% of immune neuropathies cases where IVIG is approved by insurance do not have CIDP
 - Based on expert review of submitted charts

Neurol Clin Pract. 2018 Oct;8(5):429-436
- Diagnoses that may be confused with CIDP/MADSAM/MMN
 - Subacute combined degeneration, POEMS, amyloid, CMT, Diabetic neuropathy, CSPN, primary muscular atrophy, DADS-M, GBS with poor recovery

Figure 8

Early Descriptions of CIDP (Typical CIDP)

- “Tendency towards symmetric proximal and distal weakness”
- Of all FOUR extremities
- Large fiber modalities
 - Large fiber sensory loss
 - Weakness
 - Loss of reflexes



Barohn RJ, Kissel JT, Warmolts JR, Mendell JR. Chronic inflammatory demyelinating polyradiculoneuropathy. Clinical characteristics, Course and recommendations for diagnostic criteria. Arch Neurol 1989;46:878 -884.

Gorson KC, Katz J. Chronic inflammatory demyelinating polyneuropathy. Neurol Clin. 2013 May;31(2):511-32.

The time it takes to present is generally used to differentiate acute (GBS/AIDP), subacute (SIDP), and chronic (CIDP) cases. A patient may present acutely yet continue progressing for months, ultimately meeting criteria for chronic disease. Therefore, this is a fluid diagnosis. Approximately 15% of patients initially diagnosed with Guillain-Barré will continue to progress and later demonstrate CIDP. Conversely, some cases that appear chronic may still be monophasic. Observation over time is essential before making definitive classification.

Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)

Typical CIDP presents with symmetric, proximal, and distal weakness, large-fiber sensory loss, and reflex reduction (NP1) (Barohn, Kissel, et al 1989; Barohn, Dimachkie, et al 2024; Barohn, Wolfe, et al 2025; Gorson & Katz 2013; Saperstein, et al 2001).

CIDP carries a high community misdiagnosis rate (Figure 7). Studies by Jeffrey Allen and Richard Lewis (Allen & Lewis 2015; Allen, Ney, Lewis 2018) demonstrated that roughly half of referred CIDP cases referred to an expert clinic failed to meet strict criteria, even when patients seemingly reported objective improvement with therapy.

Figure 9

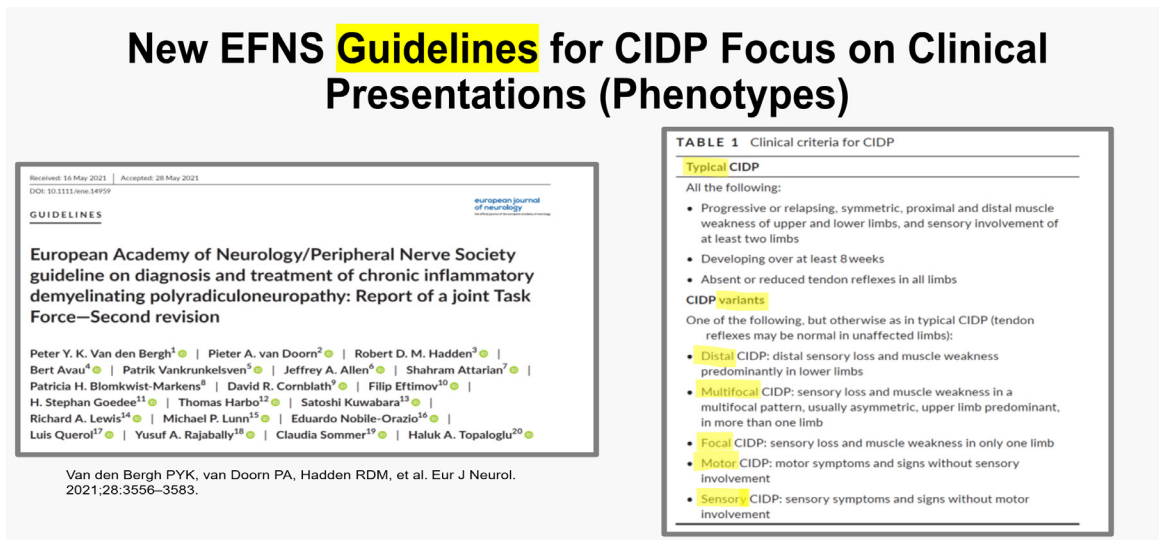
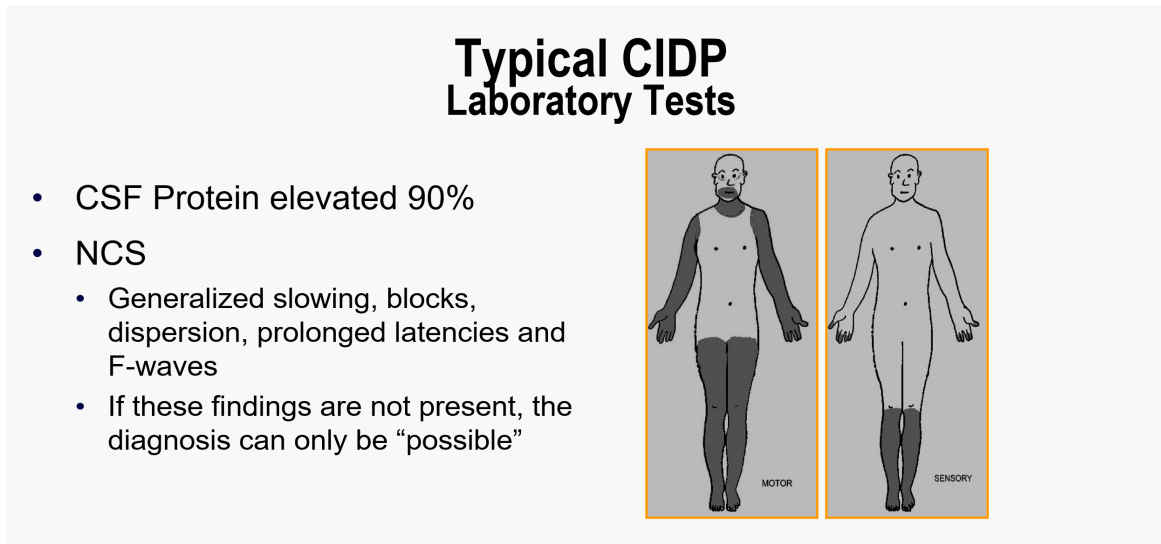


Figure 10



Additional work by Todd Levine found that most insurance-approved IVIG cases lacked convincing diagnostic evidence (Levine, et al 2018).

Early descriptions of CIDP emphasize a tendency towards symmetric proximal and distal weakness of all four extremities (Figure 8). Therefore this is consistent with the neuropathy pattern 1 (NP1) emphasized in the pattern recognition approach to neuropathy (Barohn, Dimachkie, et al 2024; Barohn, Wolfe, et al 2025).

Figure 9 shows the 2021 European Academy of Neurology/Peripheral Nerve Society guidelines which are the most commonly cited criteria (Van den Bergh, et al 2021). The guidelines separate phenotypes and electrodiagnostic findings, considering them each independently. Typical CIDP remains the same condition it was when first described over 50 years ago. In addition, there are five variant forms

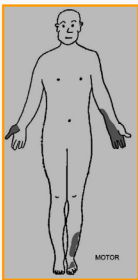
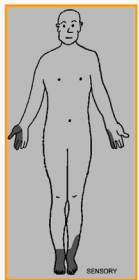
of the disease. Electrodiagnostic criteria that are “strongly supportive of CIDP” are used to confirm the diagnosis. When electrodiagnostic studies are only weakly supportive, the cases are categorized as possible CIDP. These designations relate to how many different specific nerve conduction abnormalities are found in a study such as conduction block, temporal dispersion, conduction slowing, prolonged distal latencies, and prolonged F-waves. Laboratory testing and response to treatment can be used to upgrade diagnostic certainty when electrodiagnostic testing is only weakly supportive. These guidelines are sensitive and specific for CIDP and were developed to maximize the chance of making a diagnosis. It should be noted that there is no single diagnostic test that can confirm or exclude a diagnosis of CIDP.

Typical CIDP is supported by marked demyelination on nerve conduction studies and elevated CSF protein (Figure 10).

Figure 11

Multifocal Acquired Demyelinating Sensory and Motor (MADSAM) Neuropathy “Multifocal Atypical CIDP”

- Sensory and Motor, Asymmetric, Distal, Upper extremity predominant
- Individual Nerves
- Stepwise
- Focal conduction abnormalities
- CSF can be abnormal (50-80%)
- Prednisone or IVIg (50%)

Dimachkie, Barohn, Katz. Multifocal motor neuropathy, multifocal acquired demyelinating sensory and motor neuropathy, and other chronic acquired demyelinating polyneuropathy variants. *Neural Clin.* 2013 May;31(2):533-55

Saperstein DS, et al. Multifocal acquired demyelinating sensory and motor neuropathy: the Lewis-Sumner syndrome. *Muscle Nerve* 1999;22:560-566

Lewis RA, Sumner AJ, Brown MJ, et. al. Multifocal demyelinating neuropathy with persistent conduction block. *Neurology* 1982;32:958-64.

Figure 12

Motor CIDP

- Motor by phenotype
 - Sensory NCS usually normal
- “Relatively Symmetric”
- Where to draw the line versus MMN?
- Only treat with IVIG

Part of 2021 EFNS Criteria

Katz J, et al. Neurology 1997;48:700-707

The variant phenotypes include distal, multifocal, focal, pure motor, and sensory presentations, each with different diagnostic challenges.

Asymmetric Phenotypes

Multifocal CIDP, historically called Lewis-Sumner syndrome or multifocal acquired demyelinating sensory and motor neuropathy (MADSAM), involves patchy asymmetric nerve involvement resembling multiple focal lesions (Lewis & Sumner 1982; Saperstein, et al 1999; Saperstein, et al 2001; Dimachkie, Barohn, Katz 2013).

Motor CIDP is rare and presents with symmetric

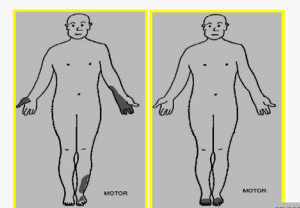
generalized weakness usually involving proximal and distal muscles in the upper and lower extremities (Figure 12).

In contrast to typical CIDP, there is no sensory involvement. These patients may have normal sensory nerve conduction studies, but if sensory nerve conduction studies are abnormal in a case with a motor CIDP phenotype, the condition is called predominantly motor CIDP. Motor CIDP must be differentiated from multifocal motor neuropathy (MMN). The EAN guidelines use the term “relatively symmetric” for motor CIDP while MMN characteristically presents as a clearly asymmetric condition (Figure 13). In our view, the two conditions present on a spectrum (Katz 1997;

Figure 13

Multifocal Motor Neuropathy (MMN) NOT CIDP

- Motor only
- Main Differential is ALS
- Usually Hands
- Stepwise
 - NOT PROGRESSIVE
- Focal conduction abnormalities
- CSF usually normal
- Only responds to IVIG-FDA approved

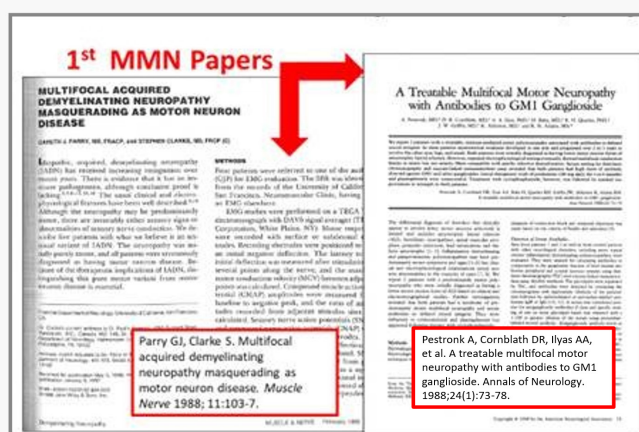


Dimachkie, Barohn, Katz. Multifocal motor neuropathy, multifocal acquired demyelinating sensory and motor neuropathy, and other chronic acquired demyelinating polyneuropathy variants. *Neurol Clin.* 2013 May;31(2):533-55.

Katz J, et al. *Neurology* 1997;48:700-707

Figure 14

Early MMN Publications



Saperstein, et al 2001). However, the authors of the 2021 EAN guidelines treat MMN as a completely distinct condition from CIDP. Figure 14 shows the two earliest publications on MMN (Figure 14).

Early reports of MMN came from ALS clinics. Before the disease was understood, these patients presented with asymmetric distal motor weakness and were often diagnosed with ALS. As a result, they tended to be patients that sat in ALS clinics for years without progression. It was eventually discovered that many of these patients had conduction block and conduction slowing in motor nerves and later that the patients were responsive to IVIg. The autoimmune nature of this condition also became recognized because of the discovery of autoantibodies against GM1 ganglioside in a percentage of these patients. Unlike other autoimmune peripheral nerve diseases, MMN does not respond to steroids and in fact to date no new treatment has been discovered besides IVIg (Katz 1997; Saperstein, et al 2001; Dimachkie,

Barohn, Katz 2013).

Distal presentations of chronic inflammatory demyelinating polyneuropathy (CIDP) are particularly challenging to diagnose. In our prior work, we emphasized the difficulty of recognizing these relatively rare cases among several more common conditions that also present with predominantly distal sensory or both sensory and motor signs.

A paper by Shin Oh in 1992 (Oh 1992) reported on a series of patients who presented with numb feet or numb feet accompanied by weak ankles yet demonstrated profound demyelinating abnormalities on nerve conduction studies indistinguishable from typical CIDP. These patients correspond to the distal CIDP variant in the current EAN criteria and show marked demyelinating abnormalities. They can respond to either IVIG or prednisone, but the response rate is probably much lower than other disease variants. In an early publication, we refer to these cases as distal acquired

Figure 15

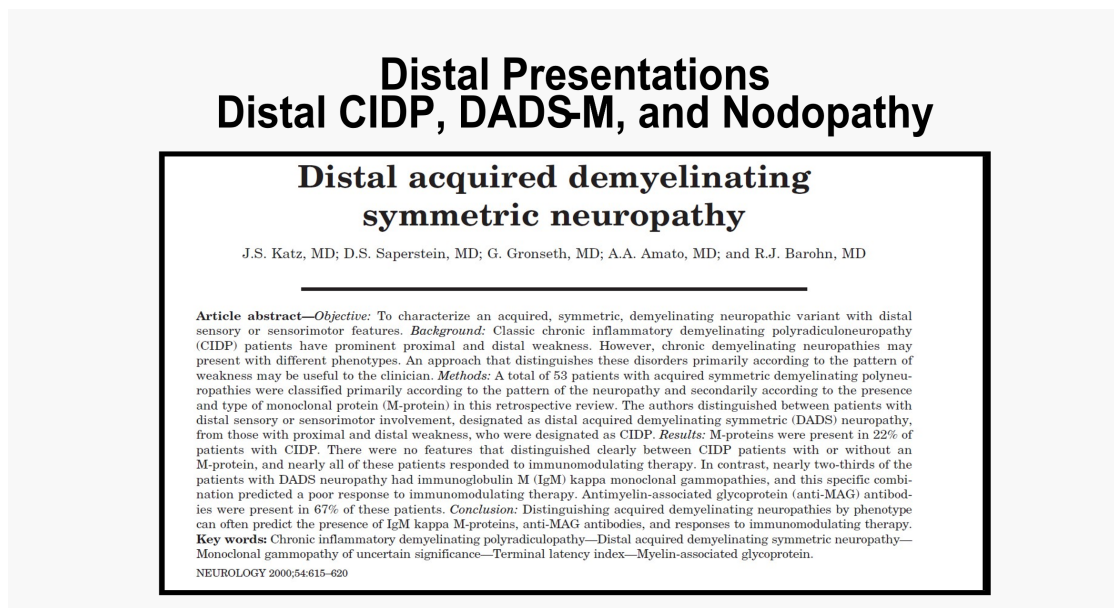
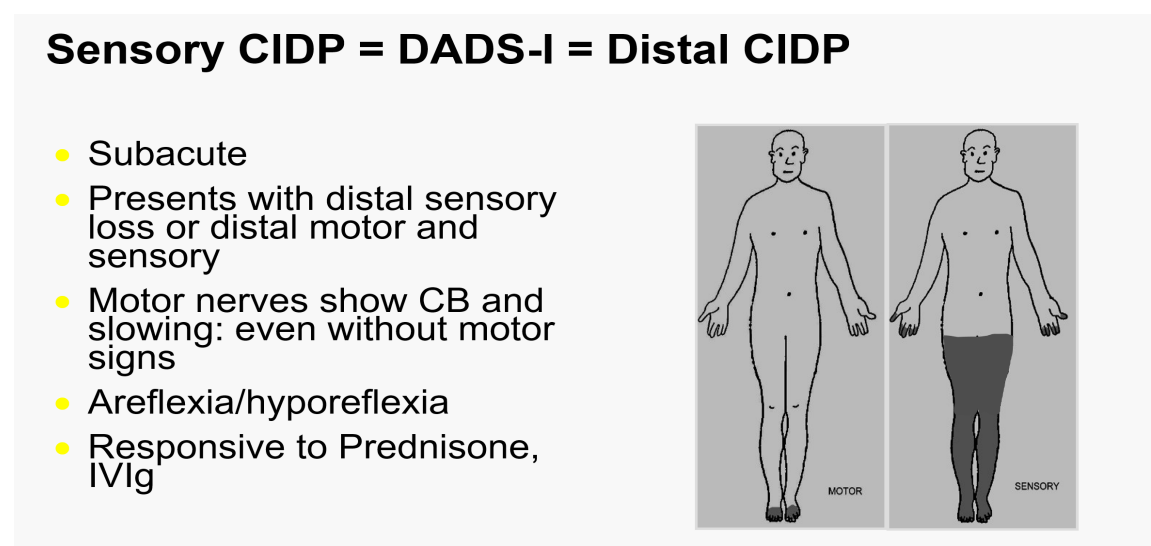


Figure 16



demyelinating symmetric neuropathy without an IgM monoclonal protein or DADS-I (Figures 15 & 16) (Katz, et al 2000). Our goal at the time was to distinguish these cases from DADS-M neuropathy with a monoclonal protein. We also wanted to distinguish it from diabetic neuropathy and CSPN, which sometimes has more than minor degrees of demyelination on nerve conduction studies.

Although nodopathies are not strictly distal and may resemble typical CIDP, they represent a distinct subset of disease and are not considered part of the CIDP spectrum according to the EAN criteria (Querol, et al 2014; Querol, et al 2015; Querol, et al 2017; Doppler, et al 2015; Doppler, et al 2016; Doppler, et al 2017). In these cases, patients have measurable antibodies directed against components of the nodes of Ranvier, which interfere with saltatory conduction. These target proteins include neurofascin and contactin. Clinically, patients are usually younger, present with

severe weakness and sometimes tremor. Most importantly, nodopathies are notoriously difficult to treat.

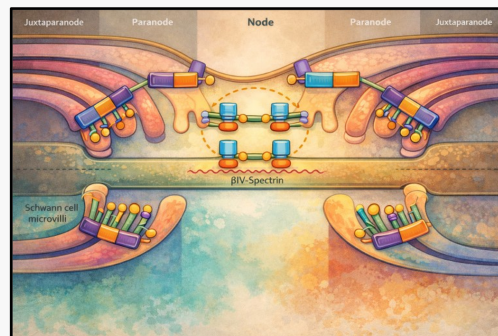
Before we get to DADS-M, it is important to interpret antibody results in the appropriate clinical context. A patient with otherwise typical CIDP who responds well to therapy may have positive anti-nerve antibodies, but in such cases the antibodies may not provide meaningful diagnostic insight. By contrast, a younger patient with a distal-predominant presentation, tremor, and treatment-refractory disease who tests positive for nodal antibodies more closely fits the syndrome of interest.

A recurring issue in the antibody literature is the risk of false-positive results. Many antibody studies originate in laboratory settings, where samples are submitted from a broad range of neuropathy cases. While a small number of samples may represent true disease with positive antibodies, a larger number may reflect unrelated neuropathies in which

Figure 17

Nodopathies are not CIDP

- Acute Onset/Chronic progression
- Younger
- Distal predominant sensorimotor phenotype
 - NP2
- Multifocal conduction blocks
- Difficult to treat
- No monoclonal
- Neurofascin or Contactin Polyclonal IgG Antibodies

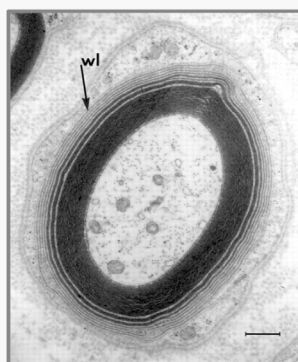


Querol L, et al. *Nat Rev Neurol*. 2017;13:533-547.
 Querol L, et al. *Neurology* 2014;82:879-86
 Querol L, et al. *Neurol Neuroimmunol Neuroinflamm* 2015; 2:e149
 Doppler K, et al. *Brain*. 2016;139:2617-2630
 Doppler K, et al. *J Neurol Neurosurg Psychiatry* 2015; 86:720-728
 Delmont E, et al. *Brain*. 2017;140:1851-1858

Figure 18

DADS-M is a Unique Disorder

IgM or Anti-Mag Neuropathy



DADS-M with monoclonal

- Mostly older men
- Ataxia /tremor
- Distal slowing on NCS
- Responds poorly to therapies
- IgM paraprotein against nerve antigens
- Most are MAG+

false positives occur. Because true nodopathies represent such a small percentage of cases, false positives within the population of all other neuropathies may outnumber true positives in laboratory datasets. Distinguishing true-positive from false-positive results is essential and we recommend first focusing on the clinical context and making sure that the antibodies are representative of a distinct clinical syndrome. In contrast to conditions such as myasthenia gravis, where antibody positivity closely correlates with clinical disease, antibody interpretation in neuropathy requires considerable caution. This complexity contributes to the diagnostic difficulty of these disorders.

The third distal demyelinating presentation, and the one that is probably the most common in clinical practice, is distal acquired demyelinating symmetric neuropathy with IgM monoclonal gammopathy (DADS-M) (Figure 18).

DADS-M is a distinct disease entity. It affects older men, produces distal slowing on nerve conduction studies, and responds poorly to therapy. Many patients exhibit anti-MAG antibodies. Aggressive treatment has shown minimal long-term benefit and carries risk. Electron microscopy demonstrates a characteristic unraveling of myelin, in which the myelin sheath separates from the axon. As the axon loses trophic support from the myelin, secondary axonal degeneration develops. Over time, the neuropathy may resemble a primary axonopathy despite its demyelinating origin.

DADS-M is characterized by distal sensory symptoms—typically numb feet—in association with an IgM paraprotein (the “M” in DADS-M). DADS-M is not considered part of the CIDP spectrum according to the EAN criteria. These cases have also been labeled “IgM neuropathy” or “anti-MAG neuropathy,” but we discourage these terms.

Figure 19

DADS-M Versus Sides of the Elephant

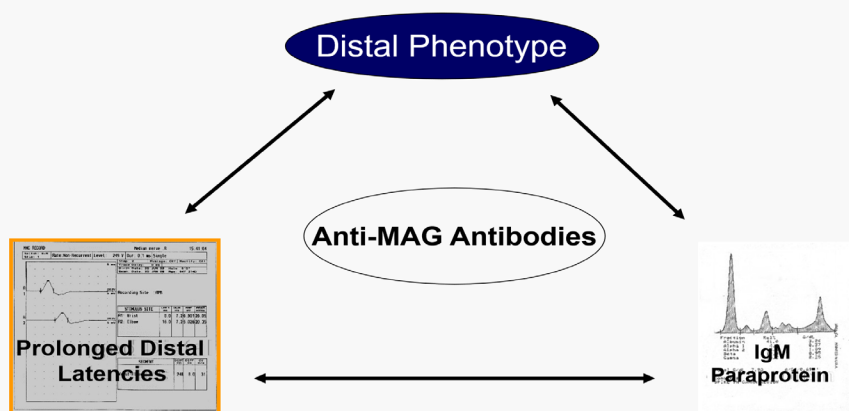
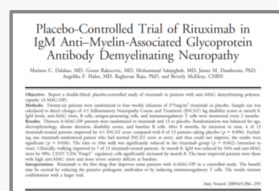
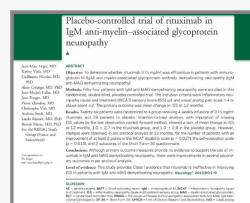


Figure 20

Placebo-Controlled Trials of Rituximab in IgM Anti-Myelin-Associated Glycoprotein Neuropathy



Annals of Neurology 2009;65(3):286-293.



Variable	Placebo group (n = 28)	Rituximab group (n = 28)	p Value
Intention-to-treat population			
Between day 0 and month 1.2	Mean change in ISS $\pm$ SD	1.0 $\pm$ 2.8	1.0 $\pm$ 2.7
	Mean percent change in ISS $\pm$ SD	10.0 $\pm$ 33.7	11.3 $\pm$ 38.3
	ISS improvement $\geq 20\%$ with respect to baseline, n (%)	12 (42.9)	11 (42.9)
	ISS improvement ≥ 4 , n (%)	6 (21.4)	4 (15.4)
	ISS improvement ≥ 2 , n (%)	11 (39.3)	8 (34.6)
	Median change in ISS for the lower limbs (IQR)	0.0 (-1.0, 1.0)	0.0 (-1.0, 2.0)
Per protocol population			
Between day 0 and month 1.2	Mean change in ISS $\pm$ SD	1.0 $\pm$ 2.8	1.3 $\pm$ 3.0
	Mean percent change in ISS $\pm$ SD	10.4 $\pm$ 34.3	15.5 $\pm$ 42.2
	ISS improvement $\geq 20\%$ with respect to baseline, n (%)	12 (44.4)	10 (50.0)
	ISS improvement ≥ 4 , n (%)	6 (22.2)	4 (20.0)
	ISS improvement ≥ 2 , n (%)	11 (40.7)	8 (40.0)
	Median change in ISS for the lower limbs (IQR)	0 (-1.0, 1.0)	1.0 (-0.5, 3.0)

Neurology 2013;80:2217-2225

The term “IgM neuropathy” is imprecise. IgM paraproteins may be present in other clinical syndromes. When the typical features of DADS-M are not present, the IgM may represent a monoclonal gammopathy of uncertain significance (MGUS) or be related to another disease process. Similarly, anti-myelin-associated glycoprotein (MAG) antibodies may yield false-positive results, particularly when ordered indiscriminately as part of broad panels. However, when the clinical syndrome is recognized first and anti-MAG antibodies are subsequently identified, the finding supports the diagnosis.

Clinically, DADS-M most commonly affects older men and may be associated with tremor. Nerve conduction studies reveal a distinctive pattern of uniform, distal-predominant slowing, reflected primarily in prolonged distal latencies. Conduction block is typically absent. The condition responds

poorly to therapy. Approximately 80% of patients who exhibit the characteristic triad—distal phenotype, prolonged distal latencies, and IgM paraprotein—also have anti-MAG antibodies, although some do not.

Most patients described in the literature as having “IgM neuropathy” or “anti-MAG neuropathy” in fact have DADS-M. Studies, including one from France and another from the National Institutes of Health, demonstrate that these cases are largely refractory to therapy, likely because of substantial secondary axonal involvement. Both studies evaluated rituximab (Rituxan), and outcomes after one year showed no meaningful difference between treatment and control groups, with p-values approximating 0.9 (Figure 20) (Dalakas, et al 2009; Léger, et al 2013).

Shortly after our DADS paper was published, a subsequent report from Italy described 19 patients with IgM

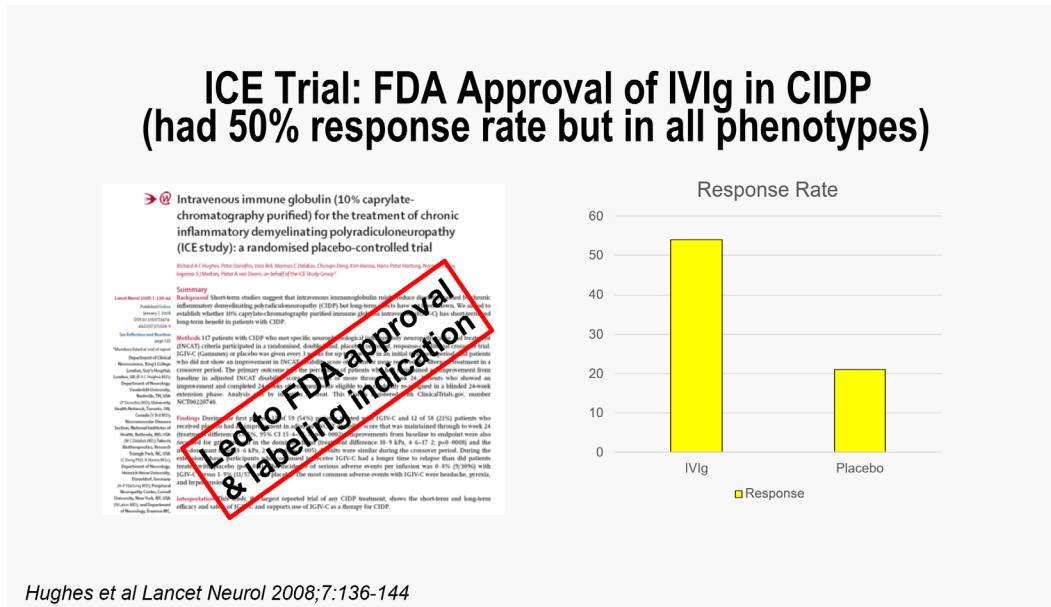
Figure 21

Retrospective Outcomes in IgM Neuropathy

19 patients

- 1 sustained response
- No hematological deaths
- 3 treatment deaths
- 7 others treatment-related morbidity

Figure 22



paraproteins who, like our patients with DADS, had been treated aggressively for a presumed diagnosis of CIDP over the years before DADS-M was distinguished as a separate disorder (Figure 21) (Nobile-Orazio, et al 2000).

The paper showed these patients did not have overt malignancy, and the IgM was not indicative of blood cancer. Nonetheless, several patients experienced treatment-related morbidities, and only one achieved a sustained response. In our view, the responder could represent a patient with otherwise typical CIDP who happened to have an incidental IgM paraprotein. Overall, the clinical reality remains that most patients with DADS-M do not experience meaningful improvement with available therapies. Our practice has been to avoid treatment as long as the condition remains low grade and chronic, which it usually does.

In summary, distal neuropathic presentations demand careful clinical assessment. Antibody testing can be

informative but must be interpreted within a well-defined clinical syndrome. Without this context, there is substantial risk of misclassification and inappropriate treatment.

Treatment of CIDP and its Variants

Prior to the introduction of IVIg for CIDP, the two primary modes of therapy were prednisone and plasmapheresis. An investigator initiated a clinical trial that demonstrated that IVIg was more effective than placebo in improving the neurologic status of CIDP patients (Mendell, et al 2001). Subsequently, the pharmaceutical industry has been heavily involved in establishing trials in order to get medications FDA approved for CIDP. The first industry-initiated trial that led to FDA drug approval for CIDP was the ICE trial (Figure 22) (Hughes, et al 2008). That study demonstrated that approximately half of patients respond to IVIg. 20% of patients also improved during placebo therapy

Figure 23

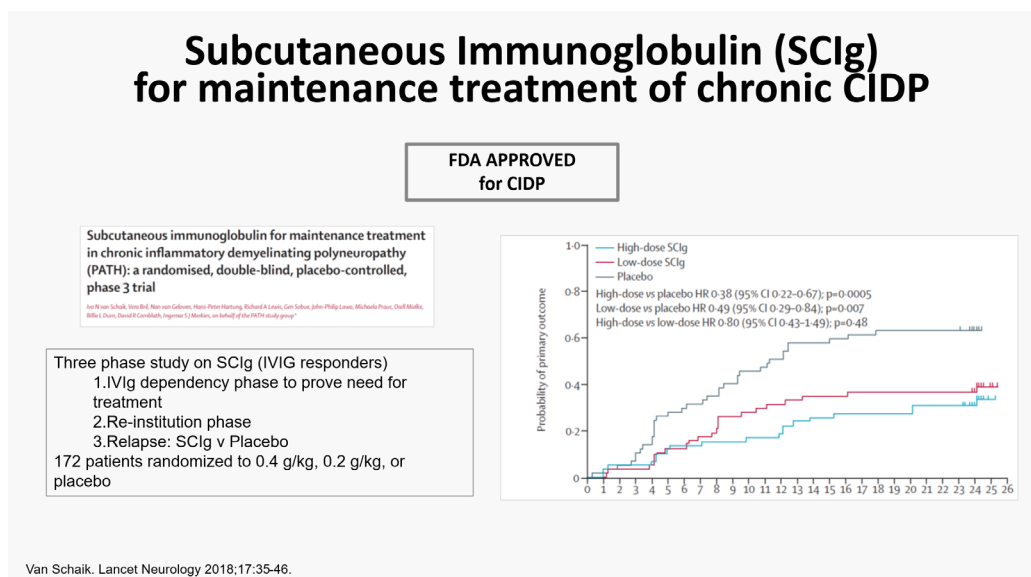


Figure 24

ADHERE in CIDP Design

- Adjudication process
- Run-In: Must re
- lapse or progress within 12 weeks
 - (> 90% relapsed when drugs stopped)
- Phase A: Must respond to drug
 - (66% improved)
- Phase B: Enter double-blind phase if respond in Phase A
 - Rate of relapse by 24-weeks greater in Placebo than drug
 - Rate of relapse in Placebo Group was only 40% by 12 weeks
- Open Label Extension (over 90% entered)

Allen, et al. Lancet Neurology. 2024;23:1013-1024.

reflecting diagnostic complexity. Most studies use 2 grams per kilogram induction dose followed by 1 gram per kilogram every three weeks.

Subsequently, subcutaneous immunoglobulin was shown to be effective for CIDP in the PATH study (Figure 23) (van Schaik, et al 2018). In this study, patients that were stable on intravenous immunoglobulin were randomized to placebo or to different doses of subcutaneous immunoglobulin and patients randomized to subcutaneous immunoglobulin had a lower relapse rate than patients randomized to placebo. This led to FDA approval of subcutaneous preparation. Keeping up with the theme of diagnostic complexity, not all of the patients randomized to placebo relapsed despite having been stable on IVIg prior to the study. Patients can be converted to subcutaneous immunoglobulin after they have been on a stable dose of IVIg. The usual conversion dose from IVIg is 1:1.

The next new class of drugs approved for CIDP were Fc receptor blockers and thus decreases levels of endogenous immunoglobulin. Figure 24 describes the ADHERE study that led to FDA approval of efgartigimod for CIDP (Allen, et al 2024). The ADHERE trial found that 70% of patients who had been withdrawn from their standard of care treatment and subsequently relapsed, improved when they received open label efgartigimod. The patients who responded to efgartigimod were subsequently placed in a double-blind withdrawal phase where patients treated with efgartigimod relapsed less frequently than those in the placebo arm. The data from this withdrawal phase led to FDA approval.

While the results seem to be encouraging at first glance, the trial data is worth discussing. First, the trial started with an open withdrawal of standard of care therapy. The goal was to determine which patients had treatment-dependent CIDP. Unfortunately, nearly all patients relapsed, suggesting

Figure 25

Same Motif: Design No Longer Appears Parallel

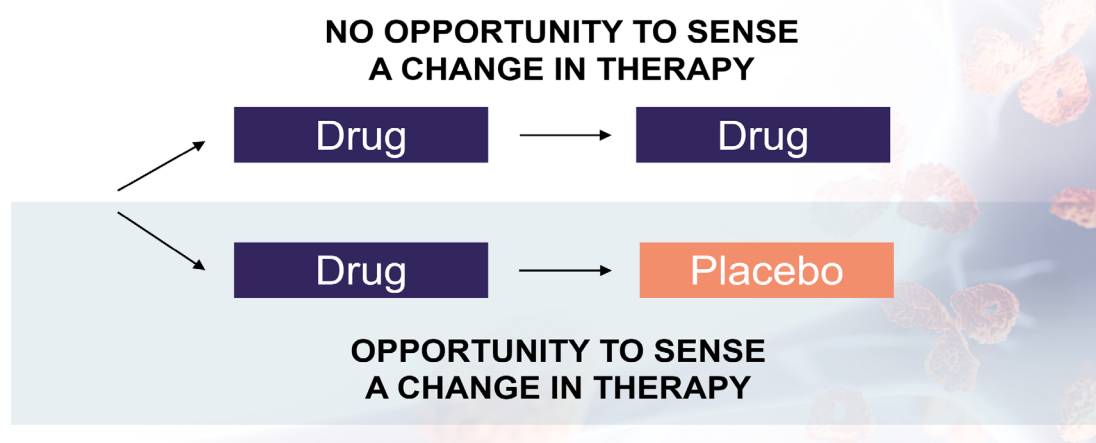


Figure 26

Recommendations in 2021 EAN Criteria (Our interpretation)

Diagnose	Level of Certainty	Treat	Reiterate
• Typical • Atypical • Not sure	• Electrodiagnostic • High CSF Protein • Scans/Biopsies	• Respond • Chronically Stable • No response	• Reconsider • Taper the dose • Continue

in den Bergh PYK, et al. Eur J Neurol. 2021;28:3556–3583.

that those who were susceptible to placebo response reacted to the discontinuation of their treatment as well as those who truly withdrew from biologically consistent pathology. The trial used patient reported outcome measures so there was no objective way to control adverse reported outcomes. Similarly, high relapse rates have been seen in previous CIDP trials (Cornblath, et al 2023). The next phase was open label treatment with efgartigimod in patients that were already relapsing from discontinuation of their standard of care therapy. In this phase, approximately 30% of patients left the trial, presumably because they went back on standard of care therapy. We don't know what percentage of the 70% of patients that were rescued by efgartigimod were potentially placebo responders. These responders entered the double-blind withdrawal phase which had two problems. One, as mentioned above, is that the trial may have had a significant number of patients who were prone to placebo responses.

The second was that patients had just been exposed to efgartigimod and could have recognized if they were no longer on treatment, particularly if there were any adverse effects that changed. In contrast, the group that remained on treatment had no opportunity to sense any change (Figure 25). In a disease like CIDP where we know that there is a prominent placebo effect, the potential of unblinding could potentially lead to discrepancies in outcomes. After the FDA approved the drug, there were immediate reports of severe worsening in patients that were transitioned from IVIg to Fc inhibitor therapy (Levine & Muley 2025).

Clinically, diagnosis should proceed with structured skepticism. If CIDP is suspected clinically, confirmatory electrodiagnostic findings, CSF abnormalities, and even therapeutic responses are all key diagnostic tools. Lack of improvement should prompt reassessment, taper trials, and reconsideration of the diagnosis. Confidence in the diagnosis

increases when there are reproducible treatment responses and relapse patterns.

Because of the known problem with misdiagnosis and the additional possibility that correctly diagnosed patients may no longer require therapy, the EAN criteria recommend a cautious approach to therapy with detailed diagnostic criteria. In essence, the criteria break down the disease into typical CIDP and variants and encourage the clinician to keep close tabs on outcomes long after the original clinical encounter (Figure 26) (Van den Bergh, et al 2021). The criteria go on to say that when treatments do not lead to clear and objective responses to therapy, the diagnostician should consider stopping therapy, readdressing the diagnosis, and even referring the case to expert centers for confirmation. In other words, they are recommending a Bayesian approach where one should have a probabilistic assumption about the diagnosis before ever starting treatment and to update that probability (either more likely or less likely) after observing the response to treatment. This means that when the diagnosis is highly likely at the start because it is typical and many supporting features are present, a poor response to therapy would suggest that the diagnosis is still likely and other therapies might be considered. On the other hand, if the initial findings are more in line with the variant phenotype, electrodiagnostic findings are weak, or other supporting features are not present, the clinician should be cautious and a negative response to therapy would lead to consideration of other conditions.

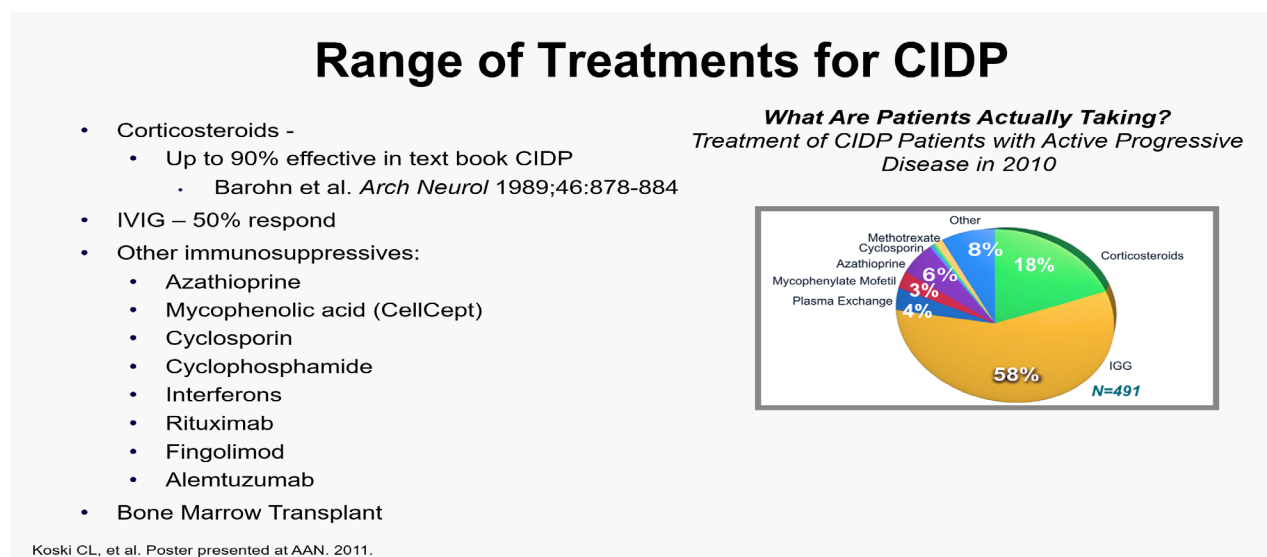
Figure 27 summarizes the range of different therapies that CIDP patients reported taking in a 2010 survey (Koski, et al 2011). Most were on IVIg, or prednisone and a number of patients ended up on other less commonly used therapies. We wonder if the new EAN criteria had been developed at that time, how many of the patients on therapy would have

been reconsidered as possibly having a different diagnosis. There were probably many patients that did not have active CIDP in that survey.

References

- Allen JA, Lewis RA. CIDP diagnostic pitfalls and perception of treatment benefit. *Neurology*. 2015;85(6):498–504.
- Allen JA, Ney J, Lewis RA. Electrodiagnostic errors contribute to chronic inflammatory demyelinating polyneuropathy misdiagnosis. *Muscle Nerve*. 2018;57(4):542–549.
- Allen JA, Lin J, Basta I, et al. 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. *Lancet Neurol*. 2024;23:1013–1024.
- Barohn RJ, Kissel JT, Warmolts JR, Mendell JR. Chronic inflammatory demyelinating polyradiculoneuropathy: clinical characteristics, course and recommendations for diagnostic criteria. *Arch Neurol*. 1989;46:878–884.
- Barohn RJ, Dimachkie MM, Levine TD, Saperstein DS, Katz JS. Pattern recognition of neuropathy and neuronopathy. *RRNMF Neuromuscular Journal*. 2024;5(1):44–74.
- Barohn RJ, Wolfe GI, Saperstein DS, Dimachkie MM. Pattern recognition approach to neuropathy and neuronopathy. *Neurol Clin*. 2025;43(4):617–635.
- Cornblath DR, van Doorn PA, Hartung HP, Merkies ISJ, Katzberg HD, Hinterberger D, Clodi E; ProCID Investigators. Safety and Tolerability of Intravenous Immunoglobulin in Chronic Inflammatory Demyelinating Polyneuropathy: Results of the ProCID Study. *Drug Saf*. 2023;46(9):835–845.
- Cortese I, Chaudhry V, So YT, Cantor F, Cornblath DR, Rae-Grant A. Evidence-based guideline update:

Figure 27



- plasmapheresis in neurologic disorders [retired]. *Neurology*. 2011;76(3):294–300.
- Dalakas MC, Roakocevic G, Salajegheh M, et al. Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein antibody demyelinating neuropathy. *Annals of Neurology*. 2009;65(3):286–293.
- Delmont E, Manso C, Querol L, et al. Autoantibodies to nodal isoforms of neurofascin in chronic inflammatory demyelinating polyneuropathy. *Brain*. 2017;140:1851–1858.
- Dimachkie MM, Barohn RJ. Guillain-Barré syndrome and variants. *Neurol Clin*. 2013;31(2):491–510.
- Dimachkie MM, Barohn RJ, Katz J. Multifocal motor neuropathy, multifocal acquired demyelinating sensory and motor neuropathy, and other chronic acquired demyelinating polyneuropathy variants. *Neurol Clin*. 2013;31(2):533–555.
- Doppler K, Appeltshauser L, Villmann C, et al. Autoantibodies to contactin-associated protein 1 (Caspr) in two patients with painful inflammatory neuropathy. *Brain*. 2016;139:2617–2630.
- Doppler K, Appeltshauser L, Wilhelmi K, et al. Destruction of paranodal architecture in inflammatory neuropathy with anti-contactin-1 autoantibodies. *J Neurol Neurosurg Psychiatry*. 2015;86:720–728.
- Fisher M. An Unusual Variant of Acute Idiopathic Polyneuritis (Syndrome of Ophthalmoplegia, Ataxia and Areflexia). *N Engl J Med* 1956;255:57–65.
- Gorson KC, Katz J. Chronic inflammatory demyelinating polyneuropathy. *Neurol Clin*. 2013;31(2):511–532.
- Hughes RA, Wijdicks EF, Barohn RJ, et al. Practice parameter: immunotherapy for Guillain-Barré syndrome. *Neurology*. 2003;61:736–744.
- Hughes RAC, et al. Intravenous immunoglobulin for chronic inflammatory demyelinating polyradiculoneuropathy. *Lancet Neurol*. 2008;7:136–144.
- Katz JS, Wolfe GI, Bryan WW, Jackson CE, Amato AA, Barohn RJ. Electrophysiologic findings in multifocal motor neuropathy. *Neurology*. 1997;48(3):700–707.
- Katz JS, Saperstein DS, Gronseth G, Amato AA, Barohn RJ. Distal acquired demyelinating symmetric neuropathy. *Neurology*. 2000;54(3):615–620.
- Koski CL et al. Treatment patterns in CIDP patients in the United States (2010 survey). Poster presented at: American Academy of Neurology Annual Meeting; 2011.
- Léger JM, Viala K, Nicolas G, Créange A, Vallat JM, Pouget J, Clavelou P, Vial C, Steck A, Musset L, Marin B; RIMAG Study Group (France and Switzerland). Placebo-controlled trial of rituximab in IgM anti-myelin-associated glycoprotein neuropathy. *Neurology*. 2013;80(24):2217–25.
- Levine TD, Katz JS, Barohn RJ, et al. Review process for IVIg treatment: lessons learned from INSIGHTS neuropathy study. *Neurol Clin Pract*. 2018;8(5):429–436.
- Levine TD, Muley S. Early deterioration of CIDP following transition from IVIG to FcRn inhibitor treatment. *Journal of the Neurological Sciences*. 2025;468:123–313.
- Lewis RA, Sumner AJ, Brown MJ, et al. Multifocal demyelinating neuropathy with persistent conduction block. *Neurology*. 1982;32:958–964.
- Mendell JR, Barohn RJ, Freimer ML, et al. Randomized controlled trial of IVIg in untreated chronic inflammatory demyelinating polyradiculoneuropathy. 2001;56(4):445–449.
- Nobile-Orazio E, Meucci N, Baldini L, Di Troia A, Scarlato G. Long-term prognosis of neuropathy associated with anti-MAG IgM M-proteins and its relationship to immune therapies. *Brain*. 2000;123(4):710–717.
- Oh SJ. A case of chronic sensory demyelinating neuropathy responding to immunotherapies. *Muscle & Nerve*. 1992;15(2):255–256.
- Parry GJ, Clarke S. Multifocal acquired demyelinating neuropathy masquerading as motor neuron disease. *Muscle Nerve*. 1988;11:103–107.
- Pestronk A, Cornblath DR, Ilyas AA, et al. A treatable multifocal motor neuropathy with antibodies to GM1 ganglioside. *Annals of Neurology*. 1988;24(1):73–78.
- Querol L, Devaux J, Rojas-Garcia R, et al. Autoantibodies in chronic inflammatory neuropathies: diagnostic and therapeutic implications. *Nat Rev Neurol*. 2017;13:533–547.
- Querol L, Nogales-Gadea G, Rojas-Garcia R, et al. Neurofascin IgG4 antibodies in CIDP associate with disabling tremor and poor response to IVIg. *Neurology*. 2014;82(10):879–886.
- Querol L, Rojas-García R, Díaz-Manera J, et al. Rituximab in treatment-resistant CIDP with antibodies against paranodal proteins. *Neurol Neuroimmunol Neuroinflamm*. 2015;2(5):e149.
- Ropper AH. Unusual clinical variants and signs in Guillain-Barré syndrome. *Arch Neurol*. 1986;43(11):1150–1152.
- Ropper AH. Further regional variants of acute immune polyneuropathy. *Arch Neurol*. 1994;51(7):671–675.
- Saperstein DS, et al. Multifocal acquired demyelinating sensory and motor neuropathy (Lewis-Sumner syndrome). *Muscle Nerve*. 1999;22:560–566.
- Saperstein DS, Katz JS, Amato AA, Barohn RJ. Clinical spectrum of chronic acquired demyelinating polyneuropathies. *Muscle & Nerve*. 2001;24(3):311–324.
- Van den Bergh PYK, van Doorn PA, Hadden RDM, et al. European Academy of Neurology/Peripheral Nerve Society guideline on diagnosis and treatment of chronic inflammatory demyelinating polyradiculoneuropathy: second revision. *Eur J Neurol*. 2021;28:3556–3583.
- van Schaik IN, Bril V, van Geloven N, et al. Subcutaneous immunoglobulin for maintenance treatment in chronic inflammatory demyelinating polyneuropathy (PATH): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2018;17:35–46.

Walgaard C, Jacobs BC, Lingsma HF. Second intravenous immunoglobulin dose in patients with Guillain-Barré syndrome with poor prognosis (SID-GBS): a double-blind, randomised, placebo-controlled trial. *Lancet*. 2021;20(4):275–283.