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Understanding CIDP: Disease Heterogeneity and Diagnostic Challenges

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Today's guest, Dr. Allison Crowell, is a paid speaker for argenx. And now, here's your host, Dr. Jennifer Caudle.

Dr. Caudle:
This is *NeuroFrontiers* on ReachMD, and I'm your host, Dr. Jennifer Caudle. Today, we're talking about chronic inflammatory demyelinating polyradiculoneuropathy, or CIDP for short, and its clinical heterogeneity, challenges with diagnosis, and underlying complex immune pathophysiology.

Joining me is Dr. Allison Crowell, who's a neurologist with Penn Medicine Lancaster General Health in Pennsylvania. Dr. Crowell, welcome to the program.

Dr. Crowell:
Thanks, I'm looking forward to our discussion.

Dr. Caudle:
Thanks. I am as well. So let's start off with the basics. What is CIDP, and how common is it?

Dr. Crowell:
Absolutely. So at its core, CIDP is a rare and severe, immune-mediated polyradiculoneuropathy characterized predominantly by inflammatory demyelination of motor and sensory nerve fibers, that can potentially lead to irreversible nerve damage.[1,2] CIDP isn't a single, uniform condition— but a heterogenous syndrome. This is reflected in the 2021 European Academy of Neurology and Peripheral Nerve Society, or EAN/PNS, guidelines, which provide distinction between typical CIDP and CIDP variants within the disease spectrum.[3]

Clinically, CIDP is characterized by a motor-predominant peripheral neuropathy causing proximal and/or distal weakness, reduced or absent reflexes, and possible sensory deficits. In typical CIDP, this presentation is symmetric and proximal, but CIDP variants can differ in distribution, symmetry, and whether motor or sensory nerves predominate.[3]

It primarily affects heavily myelinated peripheral nerves and that's where we see the most impact.[1] Symptom onset is gradual, typically worsening over a period of eight weeks or more. This eight-week mark is an important metric because it can help us distinguish CIDP from neuropathies like Guillain-Barré syndrome, or GBS,[1] which typically reaches its peak within four weeks.[4] Additionally, symptoms in CIDP can follow a progressive, relapsing-remitting, or monophasic course.[2] The overall prevalence is estimated at 8.9 cases per 100,000 persons.[5]

CIDP is twice as common in men as it is in women, and while onset can occur at any age, it is most common between the ages of 40 and 60.[2] We do see considerable variability across these estimates, likely due to differences in how diagnostic criteria are applied, challenges in recognizing CIDP variants, and broader disparities in access to diagnostic testing.[6]

Dr. Caudle:
Now, you mentioned CIDP variants and the challenges in recognizing them. Can you elaborate on how CIDP variants can present in patients?

Dr. Crowell:
Sure. Several studies have reported that typical CIDP accounts for approximately 50 to 60 percent of cases, whereas CIDP variants comprise the remaining 40 to 50 percent.[7] Indeed, a real-world global survey conducted between 2022 to 2023 across five countries reported typical CIDP diagnosed in about 68 percent of patients, and CIDP variants diagnosed in about 32 percent of patients.[8] Typical CIDP is the form most clinicians are familiar with—a symmetric proximal more than distal weakness along with sensory involvement. In the CIDP variants, the presentation shifts—either in terms of distribution or the type of nerve fibers involved.[3]

For example, distal CIDP tends to affect the distal extremities more prominently, while multifocal forms can present in an asymmetric manner. There are also sensory-predominant and motor-predominant variants, where one modality is more affected than the other.[3]

What's important is that both typical and CIDP variants of CIDP follow a progressive course over at least eight weeks.[3] Where things get more complicated is with acute-onset CIDP, which is seen in up to 18 percent of patients.[9] These patients can initially present very similarly to GBS, with symptoms that develop acutely and progress rapidly within the first four weeks.[3]

Because of that overlap, many are initially diagnosed with GBS, and the distinction often only becomes apparent over time. Guillain-Barré typically has a monophasic course, whereas patients with acute-onset CIDP continue to progress beyond eight weeks or may experience three or more relapses after initial improvement.[3]

Dr. Caudle:
Before we go further into those clinical differences, let's take a step back. What do we know about the underlying pathophysiology of CIDP?

Dr. Crowell:

Certainly. CIDP has been associated with various underlying pathophysiological mechanisms that aren't fully understood and likely vary across different patient subsets. It's been proposed that there's an interplay between multiple immune pathways—including cellular, humoral, and complement-mediated processes—which contribute to peripheral nerve damage.[10,11]

A hallmark in many patients is macrophage-mediated demyelination. In addition to directly contributing to myelin damage through phagocytosis, macrophages also release inflammatory mediators that amplify tissue injury.[10,12,13] T cells have been identified in affected peripheral nerves, where they release proinflammatory cytokines that help propagate the immune response and promote recruitment of other immune cells.[10,11]

On the humoral side, with B-cells, autoantibodies may contribute based on immunoglobulin G and M deposited on Schwann cells and myelin in peripheral nerves. These autoantibodies can promote macrophage-mediated demyelination through interactions with the Fc receptor. However, the target antigens triggering the immune response remain unidentified.[10-12]

And finally, complement activation further amplifies antibody-mediated inflammation as a bridge between innate and adaptive immunity. Through activation of the classical, lectin, and potentially other pathways, complement can promote macrophage recruitment and contribute to downstream tissue injury.[10,11]

So overall, it's the interaction between these diverse pathophysiological mechanisms—rather than a single pathway—that underlies the demyelination and nerve dysfunction we see in CIDP. And this immune complexity gives us a much-needed framework for understanding the disease's clinical variability.[10,12]

Dr. Caudle:
Given those underlying immune mechanisms, how does that translate into the way CIDP presents clinically–and how we actually diagnose it in practice?

Dr. Crowell:
It creates quite a bit of overlap with other neurologic conditions, which is where things get tricky.

For instance, distal CIDP can resemble more common length-dependent axonal neuropathies or even inherited neuropathies. And multifocal CIDP may look like a mononeuropathy multiplex. Motor-predominant CIDP can be difficult to distinguish from conditions like multifocal motor neuropathy or motor neuron disease, while sensory-predominant CIDP can overlap with a wide range of disorders that

affect sensation.[14]

Another layer of complexity is that as the disease progresses, many patients initially diagnosed with a variant phenotype will later evolve into a typical CIDP phenotype.[14] So, when you put together the clinical heterogeneity of CIDP with its overlapping features with other neuropathies, it often leads to misdiagnosis and significant diagnostic delays.[14]

In fact, a real-world global survey that linked 542 patients with their physicians, conducted between September 2022 and April 2023, reported a median delay of 7 months from symptom onset to diagnosis.[8] Which matters, because early and accurate diagnosis and initiating appropriate treatment, are critical to preventing irreversible axonal loss and long-term disability in these patients.[15,16] So when you combine that clinical variability with overlapping features, it makes establishing a diagnosis in practice especially challenging.

Currently, a widely used framework in clinical practice is the 2021 EAN/PNS guidelines.[3,8] Diagnosis relies on a careful integration of the clinical course, and nerve conduction evidence of demyelination.[3] If a patient's nerve conduction studies clearly meet the guideline-defined demyelinating criteria in multiple nerves, a CIDP diagnosis can be made.[3]

When these findings are incomplete or only partly meet these criteria, which is often the case, supportive evidence is used to strengthen diagnostic confidence. This may include nerve imaging with ultrasound or MRI, cerebrospinal fluid analysis for elevated protein, and in select cases, nerve biopsy.[3] An important supportive factor for the diagnosis of CIDP is an objective response to treatment. If a patient improves after starting immunotherapy—and we measure that improvement using standardized scales of strength or disability, like the INCAT disability score or an MRC sum score for muscle strength—it increases our confidence of a CIDP diagnosis.[3] No single test or even a positive treatment response is conclusive and should be interpreted with the entire diagnostic picture.[3]

It's also important to recognize that the diagnosis may need to be re-evaluated over time—especially in cases where patients do not respond as expected to treatment. At the same time, clinicians should keep in mind that it may take up to three months to fully assess treatment effectiveness, so careful monitoring is essential before reconsidering the diagnosis.[3] And importantly, we don't yet have a specific biomarker for CIDP.[8,11,12] Biomarkers are an exciting area under active investigation for CIDP, but for now, we rely on clinical features and test results.[17-20]

Dr. Caudle:
Building on that, Dr. Crowell, how does CIDP impact our patients' daily lives and the healthcare system as a whole?

Dr. Crowell:
I'm glad you asked because the burden can be substantial for patients. Even with traditional therapies, many patients continue to experience chronic disability from residual neurological symptoms.[9,21-23] The most prominent impacts they face are disability, muscle weakness, sensory issues, fatigue, and pain.[14,21,22] Fatigue is indeed the most common non-sensorimotor symptom, contributing to disease burden.[22,24] Based on findings from a US multicenter study conducted in 85 patients from 2015 to 2017, it is present both in patients with active disease and in those in remission.[25] One longitudinal, prospective study conducted in 50 patients with CIDP from February 2017 to January 2019 reported that over a course of one year, higher levels of fatigue correlated with more disability and worse quality of life.[26]

And beyond what we see clinically, CIDP can have a profound impact on patients' day-to-day functioning. Patients can experience limitations in mobility, which can make basic activities difficult without assistance or adaptive support.[21,27,28]

These physical limitations may often extend into broader aspects of life. Patients may be unable to continue working, and they may reduce participation in social or recreational activities.[27]

In addition, there's growing recognition of less visible symptoms, including cognitive changes, sleep dysfunction, and depression, all of which can further compound overall disease burden.[27,29]

Now, when we look at the impact on the healthcare system, a retrospective case-controlled study based on adjudicated claims in the US found that compared to patients without CIDP, patients with CIDP utilized incrementally greater healthcare resources and carried substantial clinical and economic burden—for example, they were three times more likely to be hospitalized and twice as likely to visit the ER. They also required more physician office visits and physical therapy visits. So, the data really paints a picture of CIDP as a rare disease associated with substantial patient and economic burden.[30]

Dr. Caudle:

Now, once we do make the diagnosis, what are the traditional treatments available for these patients?

Dr. Crowell:
Well, if we look at the 2021 EAN/PNS guidelines, the treatment strategy is generally initial induction and long-term maintenance therapy.[3]

For initial treatment, the guidelines strongly recommend intravenous immunoglobulin, or IVIg, or corticosteroids. Plasma exchange, or PLEX is recommended if IVIg or corticosteroids are ineffective. And then for maintenance, we continue initial treatments that worked such as ongoing IVIg, or subcutaneous immunoglobulin, or SCIg, or tailored doses of corticosteroid.[3] In patients requiring high doses of these single agents during maintenance, we can then consider combination therapies or the addition of an immunosuppressant agent.[3]

Although the majority of patients respond well to traditional therapies, 20 to 30 percent do not respond well, and approximately 15 percent remain refractory to treatment modalities.[12] It's thought that the pathophysiological diversity of CIDP is likely responsible for the variable responses to different therapies.[11]

Dr. Caudle:
With that in mind, can you share where we are today in terms of emerging treatment strategies for CIDP?

Dr. Crowell:
Right, understanding the pathophysiological diversity provides the context for identifying new targeted therapeutic approaches. This is where the field is getting exciting for those of us who treat patients with CIDP. As underlying immunopathologic mechanisms are being investigated, we're starting to see the emergence of targeted treatment approaches that reflect where the field is heading.[11]

New therapies for managing CIDP include targeted approaches such as FcRn blockers. Complement inhibitors are an emerging therapeutic class, and other therapies on the horizon include Bruton's Tyrosine Kinase, or BTK, inhibitors.[11,31]

One approach is targeting FcRn to reduce circulating IgG, which includes the autoantibodies that are thought to drive disease. The idea is that this can lower pathogenic IgG antibody levels more selectively, without broadly affecting other parts of the immune system.[11,31] Complement inhibitors selectively block downstream complement activation, which may play a role in the inflammatory processes that lead to demyelinating damage.[11,31] And, BTK-inhibitors inhibit B-cell activation and proliferation, reducing pathogenic IgG autoantibody production while also modulating macrophage activity.[32]

In clinical practice, oral immunosuppressive agents such as azathioprine or mycophenylate are often used in an attempt to reduce corticosteroid or IVIG burden, though the data here is limited. B-cell depleting therapies, such as rituximab, have reported variable results but may be considered in refractory CIDP cases.[11] Taken together, based on recent developments in the understanding of CIDP pathophysiology, the field is moving towards therapeutic advances and identification of biomarkers.

Dr. Caudle:
Now, as we wrap up our conversation today, Dr. Crowell, what are your closing thoughts on the future outlook for CIDP management? Where do we go from here?

Dr. Crowell:
From my perspective, the landscape is definitely moving in a positive direction. We're transitioning away from a one-size-fits-all and heading towards more targeted approaches, driven by a better understanding of the underlying immunopathologic mechanisms. So, we're looking towards developing new approaches that target specific mechanisms of disease pathways in CIDP.[11]

In parallel, the focus moving forward is on addressing the unmet needs we discussed, such as a reliable biomarker to help refine the diagnostic criteria so that we can diagnose and treat patients earlier.[11] And ultimately, timely diagnosis, prompt initiation of treatment, and careful monitoring of treatment response are essential for the prevention of long-term disability in CIDP.[15,16]

Dr. Caudle:
Well, this has been an incredibly informative discussion. And as those final insights bring us to the end of today's program, I'd like to thank my guest, Dr. Allison Crowell, for sharing this valuable overview of CIDP and for helping us navigate this complex landscape. Dr. Crowell, it was great speaking with you today.

Dr. Crowell:
Thanks for having me.

Announcer:

This medical industry feature was sponsored by argenx. If you missed any part of this discussion or to find others in this series, visit *NeuroFrontiers* on ReachMD.com, where you can Be Part of the Knowledge.

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