**Jeff Allen:**

Hi and welcome. I'm Jeff Allen from the University of Minnesota. Welcome to this program, Consider Rare" Suspecting and Diagnosing CIDP. You'll see some continuing education information here. This is a program that was supported by a grant from Santa Fe. You'll see some of my disclosures also included in this slide. Our agenda today is to discuss CIDP. What's the and the diagnostic features of CIDP? What are the common treatment pathways for CIDP? And then what sort of information have we been learning to improve the way we diagnose and treat CIDP? We'll try to cover all of that over the next 30 minutes or so.

CIDP is, of course, a rare disease, but it's one that many of us see in our neuropathy and neurology clinics. It's a disease that has a prevalence of about five per 100,000, ranging from one to nine depending on what study you look at, and that prevalence has been looked at all over the globe. But that means that it affects approximately 40,000 people in the United States. We know that any age can be affected by CIDP. Kids can be affected, adults can be affected, but the peak prevalence tends to happen later in life in the fifth and six decade of life. We know that both genders can get affected, but it has a slight predominance of men over women of about 1.7 to one favoring men over women.

CIDP can be a challenging diagnosis to make. We know that diagnostic delays in CIDP are very common, where if we look at the time from symptom onset to diagnosis, that average range is between 10 and 40 months depending on what study one looks at. So that's a long time for somebody to manifest symptoms and not yet reach that diagnosis. We know the disability in CIDP can be quite substantial, where if you look at the peak disability in patients during their diagnostic and treatment journey, about half of patients reach the point where they're unable to live in independent existence because of their CIDP.

So that can be quite substantial in many patients, and we know that there's several factors that influence prognosis and the disease severity, and those include things like age of onset, the progressive nature of the disease, and how severe the axon loss is in the condition. So why is CIDP such a difficult diagnosis to make? Well, we know there's a number of different factors. Number one, it's rare, and number two, it's heterogeneous. So it can be challenging to diagnose a rare disease, but it's even more difficult to diagnose a rare variant of a rare disease, that makes it really, really tough.

We know that integrating all the different components of the disease can be challenging, from the clinical features, to the electrophysiology, to the supportive diagnostic features. That can be a tough integration process as well. And at the end of the day, there's no single diagnostic test that says for sure you do or you don't have the disease. So that makes it difficult. Then to add on a little more that we know that there's a lot of mimics things that can lead us off track that look like CIDP, but maybe it's not.

So all of those reasons can make it a tough diagnosis to make. So this point, I'd like to hear about Christine's story and what she experienced with CIDP.

**Christine Eleeson:**

My name is Christy Eleeson. I was diagnosed with CIDP in June of 2018. I originally was treated for a pinched nerve and possible diabetes. The pinched nerve was because I had extreme pain in my back. So they thought that those two things... and the numbness and tingling in my exteriors. And then later on the diabetes was the same reasoning, because of the tingling.

Then later on, a friend helped me get into a doctor who was a neurologist that specialized in neurological issues and told me it was going to be one of four things that I had, one of them being

Guillain-Barre and MS. But he was pretty sure at the time of diagnosis that it was Guillain-Barre, which is what I was originally diagnosed with, and then a couple of months later I was diagnosed with CIDP.

**Jeff Allen:**

It's really important to get that diagnosis early and accurately in part because this is a treatable disease. We know that of all the treatments that we use, about 80 to 90% of patients respond to one or more of those treatments. But if we think about the prognostic factors that suggest or may lead to a poor prognosis, delayed diagnosis and axon loss are two of those things, that might mean that you're less likely to have a good response to those treatments.

So if we think about early diagnosis and the importance of early diagnosis and knowing this is a treatable disease, if we miss that opportunity to intervene, then our sort of treatment expectations shifts, where we're not maybe trying to make patients better, but we're trying to manage disability from axon loss that is no longer reversible. So early accurate diagnosis and intervention is really important.

At the same time, we know that misdiagnosis is very common, where if we look at everybody that has that diagnosis of CIDP, most studies would suggest that half or more of those patients that carry that diagnosis of CIDP actually don't have that. We looked at this in an academic setting about 10 years ago. This has been also looked at in different community-based settings, both in the US and in Europe, and all of those studies show similar findings, which is about half the time that diagnosis of CIDP is actually incorrect.

And many of those patients that carry that diagnosis actually are on treatment for CIDP, and that has a number of important implications that we'd like to avoid. Treating patients with a disease they don't have obviously exposes patients to treatments that may be harmful or expensive. It also masks that real condition that is not being treated. So if you're labeled a CIDP, but you have something else, that something else goes untreated, which has important treatments and potentially prognostic implications as well.

So we think that both sides of the coin of this are really, really important. We want to find better ways to improve early accurate diagnosis of CIDP, but also limit those misdiagnostic cases so that we can get people treated with the right drugs for the right reason and know more about prognosis. So when it comes down to really diagnosing CIDP, the clinical features are the place to start.

This is still a clinical diagnosis or largely a clinical diagnosis with some other important supportive characteristics. So we think about CIDP as being a heterogeneous disease. It's a syndrome. It's got a typical phenotype and then also variants that are a little bit different. The typical CIDP phenotype are those patients that have relatively symmetric proximal and distal numbness and weakness that evolves over two months or more in a progressive or relapsing fashion.

And on exam, those patients invariably have reduced or absent deep tendon reflexes. So that's a definition of typical CIDP, which affects about 60% of patients with the disease. We also know that there are other variants of the disease that have different clinical features. And those named other variants include patients with distal CIDP, multifocal CIDP, sensory CIDP, or motor CIDP.

So distal CIDP are patients with numbness and weakness, but just distally usually below the knees and sometimes in the hands. Multifocal CIDP is asymmetric, often follows named nerve or sometimes plexus distributions. It also goes by the name of MADSAM or Lewis-Summer syndrome. Sensory CIDP are patients that have proximal and distal numbness, but no weakness. Should be relatively symmetric, as is the definition of typical CIDP. And motor CIDP are of course those people that have weakness but no

numbness. But the pattern should otherwise look like typical CIDP where it's relatively symmetric, proximal and distal in the upper and lower limbs.

Now, those characteristic clinical features of numbness or weakness are really the features that define the disease. However, we know that other symptoms can affect patients as well. We know that fatigue is very common, affects up to 75% of patients. A third or more have pain, often neuropathic pain. Tremor can be common in some patients, especially those patients with the autoimmune nodopathies that are split off from CIDP now. Even without the nodopathy tremor can still be part of the clinical phenotype.

Autonomic involvement is uncommon, but sometimes subclinical and it can affect minority of patients. Granular dysfunction, typically the seventh nerve facial nerve can be affected in some patients. And respiratory failure, although common in Guillain-Barre syndrome, is distinctly unusual in CIDP. Now, once the disease occurs, it follows a course that can go a couple of different ways. Most patients develop progressive symptoms where they can tend to worsen over time, sometimes with relapses along the way, or a combination of those two things where patients develop relapses in the overall progression of the disease.

Of course, the way we treat the disease may influence some of this progression. The third outcome that sometimes of course that some patients find is more of a monophasic course, where it worsens over a period of many months and then sort of reaches a plateau and that improves or even sometimes even goes into remission. We know about a third of patients enter a prolonged period of drug-free remission at some point. But one of these typical courses is common for the disease.

So let's talk a little bit about an illustrated case that highlights a couple of features that I think are important when we talk about CIDP. So in this illustrative case, that's a 62-year-old gentleman that developed tingling in his hands and feet. And other than hypertension and hyperlipidemia, he was otherwise pretty healthy. His symptoms evolved over several months. By three months, his gait was affected, he needed cane. And at six months he was really having trouble even with the cane when leaving his house.

His examination at six months showed distal sensory deficits, distal weakness and diffusely absent deep tendon reflexes. And the weakness eventually evolved to both include proximal upper and lower limbs as well. So this patient would then meet that definition of typical CIDP, because you've had the weakness that's now involving both proximal in distal areas, arms and legs. It's got sensory deficits throughout. He's got reduced reflexes and he is evolved, in this case, over about six months. So he meets that typical definition of the disease.

Now the second most important thing to make that diagnosis is the electrophysiology. So this is where we define that D in the CIDP. Is there evidence of peripheral nerve demyelination? Demyelination on a nerve conduction study can come from abnormalities that include conduction velocity slowing, conduction block, temporal dispersion, distal latency prolongation or F-wave prolongation.

The degree of abnormality that's required is also filled out in the EAN/PNS guidelines where that takes a deep dive into how much slowing is needed in order to stay confident that you have peripheral nerve demyelination. I won't get into that detail here, but it is really, really a helpful a guide or resource to look at if you've got a nerve conduction study that shows some degree of abnormality and you're wondering how much of a degree of abnormality do I need? I'll often pull out the guideline and say, "Well, slowing in this patient is enough to meet that threshold of 30% reduction in lower limit of normal from conduction velocity, and that meets that supportive criteria for demyelination." Or does the

prolongation, distal latency prolongation is at 50% or more? Same with conduction block of 30% or more in a nerve with an otherwise preserved amplitude or relatively preserved amplitude.

So the EAN/PMS guideline is a really helpful resource in order to say if you've got a nerve conduction abnormality, how much of that abnormality is needed in order to be really be satisfied or confident that you have peripheral nerve demyelination? So when I'm doing the test, I might say, "There's conduction velocity slowing. Is that 30% or more slowing as would be required by the guidelines? Is there a 50% or more distal latency prolongation?" Same for abnormalities and F-waves or durations or conduction block where we're looking for 30% or more.

So if you have abnormalities that meet these requirements in one nerve, you're considered to have evidence of weakly supportive of peripheral nerve demyelination. And if you have two abnormalities, two nerves, you've got strongly supportive peripheral nerve demyelination changes and that would meet the core requirements per the guideline. So in this particular case, we've got changes here that show some minor changes in the sensory studies and the ulnar snap is small.

For the ulnar motor response, we've got a partial conduction block as it goes from 5.1 to 3.3 millivolts. Latency is prolonged as well. And the slowing is 31 meters per second, which meets that guideline requirement. So it was of course not the full nerve conduction type study for this. Particularly this study provides strong evidence of peripheral nerve demyelination in the form of conduction velocity slowing greater than 30% in two nerves, one nerve with conduction block and also sensory abnormalities, so strongly supportive of peripheral nerve demyelination.

We also know that there's supportive criteria that can be helpful to make the diagnosis. And supportive criteria considered supportive of CIDP would be CSF protein elevations, MRIs with nerve root enhancement, ultrasound nerve enlargement, characteristic features in nerve biopsy, and also objective improvement after immunotherapy. All of these can be helpful to increase your confidence that you have CIDP.

However, all of them also come with pitfalls. We know in some situations adding this data can be more confusing than it can be clarifying if it's taken in the wrong context. So, for example, we know that spinal fluid elevations can occur in patients with advancing age, degenerative changes in their back or in diabetes. And so mild to moderate protein elevations are not diagnostic of CIDP. It can sometimes be confusing in the wrong context. Likewise, there are other things that can cause changes in MRI or ultrasound. Hereditary nerve conditions can do that. And also requires some experience of the radiologist or the ultrasonographer in order to really be confident that you have enlargement of a particular nerve or nerve sacrum.

Changes with the improvement after immunotherapy is also a common pitfall, where if we say you're on a drug for a presumed CIDP and you get better and that means you have that disease, it's really important to be objective on what we're saying is getting better if we're using that as evidence that you have that disease type to begin with. So trying to find some structured way to assess improvement is really, really important, rather than relying strictly on a subjective patient experience. So all of these things, although helpful in the right context, can also be misleading in the wrong context.

So to make that diagnosis, core clinical features are required and electrophysiologic evidence as needed. For patients with ambiguous electrophysiologic data, then sometimes the supportive data can be helpful provided that it's interpreted in the right context. However, that supportive data is not needed at all patients where if we've got strong clinical features and strong electrophysiologic features and there's no

clear diagnostic mimic or other red flag, and then the supportive criteria of spinal tap imaging, et cetera, is probably not needed to be confident in the diagnosis of those patients.

So when we start interpreting the criteria, we've got criteria that really allow two classifications of CIDP. You've got CIDP and possible CIDP. CIDP is the highest level of confidence where you've got strong clinical criteria and strong electrophysiologic criteria, no red flags. You can be confident you got CIDP in that case. Possible CIDP are those people with strong clinical criteria, but weak electrophysiologic criteria. For those people, we classify them as possible CIDP. Now, if you fall into that possible category and you have two or more supportive criteria, so your CSF protein is way up, or you've got clear enlarging amount of nerve roots in an MRI, or you've got unequivocal improvement after you start a common treatment for CIDP, then you can bump your confidence up from possible to CIDP, again providing no red flag as their other mimic.

So this is a common diagnostic dilemma, CIDP, we know that of the diagnostic challenges. And one of the big roadblocks that always stands in our way is that there's no diagnostic tests. There's no CIDP diagnostic biomarker. And so recognizing those mimics is really, really important. Recognizing those red flags is important. And the red flags probably different based on which phenotype we're talking about. So a differential diagnosis of distal CIDP is different than a differential diagnosis of motor CIDP, or even a typical CIDP. Recognizing those phenotypes can be really, really helpful.

So for distal CIDP, if that's your phenotype, then thinking about family history, thinking about pain or autonomic involvement, is there a tremor or a taxi or is there monoclonal protein present can really be helpful to think about what are the common mimics? Should we be looking at hereditary neuropathies? Is there autoimmune neuropathy on the table? If there's a lot of tremor, if you've got a lot of pain or autonomics, amyloid is going to come in. TTI amyloid or acquired amyloid. Same for different monoclonal proteins. Are we dealing with an anti-MAG neuropathy or POEMs or amyloid, depending on what protein you might encounter?

So all of these things don't necessarily exclude CIDP, but they would be a red flag that makes you want to dig a little bit deeper. Same for sensory CIDP. There's no clear electrophysiologic evidence of demyelination, really shifting the attention towards axonal causes of that sensory neuropathies is important. There's a family history going down, that hereditary pathway is important. And then if your nerve conductions are normal, maybe we're dealing with something like CISP. Chronic Inflammatory Sensory Polyradiculopathy, which is split up from CIDP in the current guidelines.

If you've got a multifocal variant, one of the common mimics is vasculitis. So is there a lot of pain sensory involvement? Or you have some other laboratory that suggests a vasculitic component, multifocal motor neuropathy enters the differential from multifocal CIDP depending on the presence or absence of sensory abnormalities. And then maybe some other mimics in the form of Parsons-Turner, and maybe patients that have diabetes or other risk factors.

For motor CIDP, looking for Bulbar involvement, family history, symmetry is going to be important. If your CK is high... A little CK may be allowable, but if your CK is very high, then thinking about the muscle diseases is really something to think about. So back to our illustrative case, you've got somebody that's got high confidence from the clinical standpoint and you've got good electrophysiological criteria to be confident of the diagnosis. And we also had two supportive criteria in the form of CSF protein elevation and an MRI that showed a nerve root enlargement enhancement. There was no obvious red flags in this patient. The immunofixation, showed no gammopathy, and so we've got high confidence that this patient has CIDP.

So once we reach this point that it's time to talk about treatment and managing a CIDP, the EAN/PNS guidelines that were published in 2021 provide a very nice algorithm in order to understand how we might work through the treatment options for CIDP. And essentially what they say is it's important to start with evidence-based proven effective therapies. Try those therapies for a reasonable period of time, assess for treatment response. If there is no treatment response, think about reassessing the diagnosis before moving on to a new treatment. The diagnosis is confirmed, then try another evidence-based treatment.

If there is a treatment response, then thinking about how to transition that person to maintenance therapy, trying to find the lowest effective dose of each treatment, and then recognizing that some patients don't need lifelong or long-term treatment. In about a 30% of patients we can get them off. And so taking periodic reductions or changes in treatments to assess treatment need and responses is important. And then folding in drugs that may be helpful to take the place of first-line therapies in individual situations where that might be important.

But talking about our evidence-based therapies. We know that corticosteroids is helpful for CIDP and it's the actually naturally occurring hormones, it decreases inflammation and suppresses the immune system in several days. And they've got a lot of attributes that are desirable for CIDP. They're widely available. They come in oral and IV forms. They're very inexpensive and accessible to many patients.

However, the downsides to chronic steroid use are also well-known. High blood sugars, high blood pressure, bone loss, stomach damage, restlessness, irritability, trouble sleeping, all of those things really steer us away from use of chronic steroids in many of our patients with CIDP. The data that supports their use is actually pretty thin. There was only one small randomized controlled study that compared steroids to not treatment, not placebo. But open label in general experience suggested about 60% of patients respond to treatments. And there are some good studies comparing oral daily steroids to pulse steroids, showing that both protocols are effective for improvement in CIDP. And so consequently, they have an important place in clinical practice.

IVIG and subcutaneous IG immunoglobulins in general are the most widely studied group of treatments for CIDP. We know they work a number of different ways by either competing with pathogenic antibodies or increasing the catabolism of pathogenic antibodies. They interact with complement and other components of the immune system. So the precise mechanism of why immunoglobulins work in CIDP is not known, but it probably comes from a number of different places.

Pros and cons with IVIG and subcutaneous IG are also well known. Efficacy data is really strong. We know that they work very well. Generally, they're well tolerated, they're not immunosuppressive, and they come in either IV or subcutaneous formulations, and they avoid a lot of the side effects, of course, of steroids and plasma exchange. However, the downsides to immunoglobulins are probably the convenience, where they need to be repeated every several weeks, in most instances. Headaches and nausea can sometimes affect patients. Thromboembolic risks are there. And just the dependence on other healthcare professionals to get many of these treatments is also undesirable with some patients.

For IVIG, the quality of data is really, really high. Where there's five randomized placebo-controlled trials, over 200 patients, most of those trials showed that IVIG is helpful to improve strength and disability. And consequently, IVIG is approved for treatment with CIDP. An evidence-based approach would be to use two grams per kilogram loading divided over several days, and then use one gram per kilogram every three weeks for maintenance treatment. Although there's other ways to do that as well. Patients that respond to treatment usually do so within the first couple of months and almost all within

three to six months. If there's no response by six months, probably not the right treatment. So rethinking about what the optimal treatment is for that patient is something to consider.

For subcutaneous IG, we've got two large trials now with subcutaneous IG, one with conventional subcutaneous IG and one with facilitated subcutaneous IG, facilitated meaning subcutaneous IG combined with hyaluronidase. Both of those studies essentially randomized patients on IVIG to either subcutaneous IG or placebo, and looked at a relapse rate over a period of about six months. And both of those studies showed that the relapse rates in patients that were on placebo was much higher than those that were on the subcutaneous IG. Both clinically meaningful and statistically significant differences, showing that both were effective for prevention of relapse.

So subcutaneous IG may be a good option for your patients that need maintenance therapy with immunoglobulin. Typical doses, conventional subcutaneous IG is 0.2 to 0.4 grams per kilogram weekly. And for facilitated IG, you can get much more volume, much more drug into the subcutaneous at one time. So many patients I facilitated, they get about a gram per kilogram once every three or four, four weeks.

Now we've got a number of targeted therapies that are currently either in trials or recently approved of efgartigimod. It's an FcR antagonist that was recently approved by the FDA. Nipocalimab is another drug in clinical trials. And there are several complement inhibitors that are also currently in clinical trials. So thinking about the FcR antagonist and the mechanism of action of these drugs, we know that FcRns are now of course, approved by the FDA for treatment of adults with CIDP. FcRn is a receptor that lives in the endothelial cell, and this receptor is really important in order to cycle or sort through different IgG proteins. So immunoglobulin IgG that's taken up by the endothelial cell tries to bind to the FcRn receptor. If it binds to the receptor, then it's returned to circulation. If it's unbound, it gets destroyed. So this receptor determines which IgGs are destroyed and which ones are spared. And if you've got a pathogenic IgG antibody that happens to bind to this receptor, this also will be returned to circulation.

So the idea with the FcR antagonist is that you block these receptors, the drugs have a high affinity for the receptor. So now IgG and pathogenic IgG antibodies can't bind it, which means they get destroyed. So it kind of tricks the body in order to destroy pathogenic IgG auto-antibodies, and this is where we think that it has its effect.

So when we're thinking about treatment selections for CIDP, there's a number of different factors that of course we want to take into account. What's the age, what's the disease severity, other comorbidities, lifestyle, what an individual's desire is for IV versus subcutaneous therapeutics. All of these are important to balance for individual patients. And of course, if we don't optimize those, then we might have a treatment that works, but it's not successful because it's not well tolerated, or the adherence to the therapy as isn't there for that individual patient.

So all of these things are really, really important. So there's a number of unmet needs in CIDP, and some of them revolved around this issue. How can we find therapeutics that work at least as well as what we have, but maybe are more convenient to tolerated by patients? What can we offer patients maybe that don't have good responses to standard therapies of IVIG or immunoglobulins? Can we improve upon this efficacy? And can we start to think about the immunology of CIDP as a way to develop and utilize rational targeted therapies that maybe go specifically after antibodies or go specifically after complement components in order to find things that work well with maybe less collateral damage?

So finding this optimal treatment is really important. It's got to work. The treatment has to be well tolerated and it also has to be feasible. That burden of getting the treatment ideally is such that it's easy

for patients to get and it's well tolerated, and of course it works. And finding that sweet spot where all three of those things converge is where I hopefully the future is headed for CIDP treatments.

So a few final comments about what we've discussed. We know that CIDP is an acquired immune mediated disease that has key clinical features and also key electrophysiologic abnormalities. We know that the diagnosis can be difficult to make because there's no diagnostic test in order to reach that diagnosis with complete confidence. So there's really a premium on finding that early and accurate diagnosis so we can start treatment before the development of a lot of disability, but also we want to avoid misdiagnosis, so we don't expose patients to treatments that they probably don't need.

We know guidelines can be helpful to sort through all that diagnostic information. We know guidelines can be helpful also to help us understand which treatments make sense for the disease, starting with things that are proven effective and you know work, things like IVIG, subcutaneous IG corticosteroids. And now we know that FcR and antagonists are beneficial for prevention of relapse and improvement of symptoms with CIDP and now have an FDA label. Which of those treatments we should use for an individual patient is a shared decision-making decision where we have to weigh what we know works, what the evidence, that patient's individual preferences, and also side effect profiles in order to find that treatment that works best for that individual patient. But it's nice to be in a place where we have options.

Thank you so much for your attention.