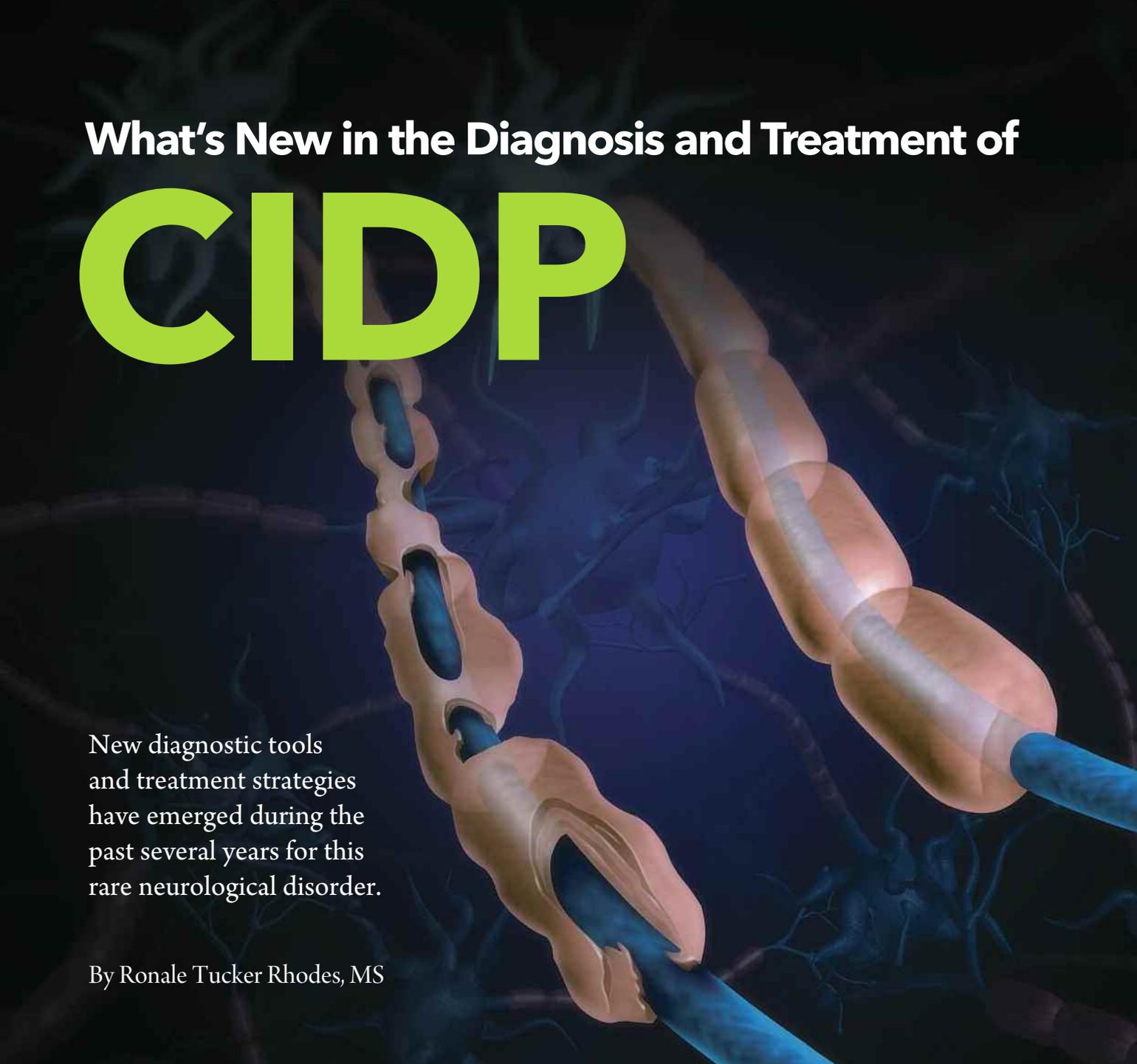


What's New in the Diagnosis and Treatment of

CIDP



New diagnostic tools and treatment strategies have emerged during the past several years for this rare neurological disorder.

By Ronale Tucker Rhodes, MS

THE FIRST probable cases of chronic inflammatory demyelinating polyneuropathy (CIDP) were described by J.H. Austin, MD, in 1958 as a “fluctuating motor-predominant neuropathy that produced severe weakness that would either improve spontaneously or in response to corticosteroids” with “focal areas of segmental demyelination rather than axonal degeneration” likely the pathological cause. It wasn’t until 1975 that the name chronic inflammatory polyradiculoneuropathy was coined by Peter James Dyck, MD, and colleagues after conducting a historical study of 53 personally evaluated patients with these symptoms. Later, the term

demyelinating was subsequently added, which defined CIDP as a separate disease entity.¹ (The terms polyradiculoneuropathy and polyneuropathy are used interchangeably.)

CIDP is rare, affecting approximately 40,000 people in the U.S. Its estimated incidence is 0.7 cases to 1.6 cases per 100,000 persons per year, and its overall prevalence is estimated to be 5 cases to 9 cases per 100,000 individuals, with an estimated prevalence in children to be 0.5 cases per 100,000. The disease can affect any age group, and onset can begin during any decade in life. However, CIDP affects twice as many males as females, and the average age of onset is 50 years.^{2,3}

Since its distinction as a separate disease from similar neuropathies, advances have continued to be made in understanding this debilitating disorder. In fact, the past several years have produced some significant new diagnostic tools and treatment strategies.

What Is CIDP?

CIDP is the most common chronic immune-mediated polyneuropathy, and is sometimes called chronic relapsing polyneuropathy or chronic inflammatory demyelinating polyradiculoneuropathy because it involves the nerve roots. It is a progressive autoimmune disease that destroys the myelin sheath (the fatty covering that wraps around and protects nerve fibers and assists in nerve signal transmission) of peripheral nerves.⁴ The result is a slowing of the nerve signals and subsequent weakness in the muscles they control. CIDP has a variable course that can be relapsing-remitting (relapses and periods of stability in between relapses), stepwise progressive or gradually progressive.²

There are two categories of CIDP: typical and atypical. Typical CIDP is the most common subtype and accounts for at least 50 percent to 60 percent of all cases. It is a fairly symmetric sensorimotor polyneuropathy in which proximal and distal motor involvement exceeds sensory involvement. It presents with gradually progressive symptoms over the course of several months or longer. Some patients present with more rapidly progressive symptoms, which have been termed “acute-onset CIDP.” However, the diagnosis of CIDP is dependent on progression or relapse of the disease over greater than eight weeks.

Atypical variants of CIDP are distinguished by their clinical presentation and/or pathogenic (organism causing disease) mechanism. These include:⁵

- Lewis-Sumner syndrome, also known as multifocal acquired demyelinating sensory and motor neuropathy, a well-described atypical variant that accounts for 5 percent to 10 percent of CIDP cases;
- The sensory-predominant form of CIDP characterized by symptoms and signs consistent with large fiber sensory dysfunction, including balance problems, pain, paresthesias (pins and needles) and dysesthesias (abnormal sensation);
- Distal acquired demyelinating symmetric neuropathy, a distal and sensory-predominant variant of CIDP, which is usually more slowly progressive than typical CIDP;

- A proximal variant of CIDP in which inflammatory demyelination is confined to dorsal (sensory) nerve roots;
- A pure motor variant of CIDP reported in a small number of cases;
- Neurofascin (NF) antibody-mediated CIDP with autoantibodies to NF155 that appear to be younger and more likely to have sensory ataxia (lack of muscle control or coordination) and prominent tremor, which can cause severe dysfunction; and
- Contactin 1 (CNTN1) antibody-mediated CIDP caused by autoantibodies of the IgG4 class to CNTN1 or CNTN-associated protein 1, which is found in a small subset of patients.

Symptoms of CIDP

CIDP symptoms usually begin in the feet and move slowly over time up the legs and arms, typically affecting both sides of the body (Table 1). Both proximal and distal muscles can be involved. Symptoms reported include:⁶

- Initial limb weakness, both proximal and distal
- Sensory symptoms (e.g., tingling and numbness of hands and feet)
- Motor symptoms (usually predominant)
- Symptoms of autonomic system dysfunction (e.g., orthostatic dizziness)
- Preceding infection (infrequent)
- A relatively acute or subacute onset of symptoms in about 16 percent of patients
- Usually a more precipitous onset of symptoms in children

Table 1. Common Manifestations of CIDP

- Gradually worsening paresthesia (pins and needles feeling) and numbness
- Muscle weakness in the legs and arms
- Areflexia (absent tendon reflexes) without wasting
- Preferential loss of vibration of joint position sense
- Foot drop and difficulty getting out of a chair
- Difficulty with fine finger control
- Sensory ataxia
- Fatigue

Sources: Ryan, M and Ryan, SJ. Chronic Inflammatory Demyelinating Polyneuropathy: Considerations for Diagnosis, Management, and Population Health. *American Journal of Managed Care*, Sept. 25, 2018. Accessed at www.ajmc.com/journals/supplement/2018/examining-therapies-cidp/chronic-inflammatory-demyelinating-polyneuropathy-considerations-for-diagnosis-management-and-population-health?p=4.

When the condition is associated with other diseases, symptoms may include:⁶

- Signs of cranial nerve involvement (e.g., facial muscle paralysis or diplopia)
- Gait abnormalities
- Motor deficits (e.g., symmetric weakness of both proximal and distal muscles in upper and lower extremities)
- Diminished or absent deep tendon reflexes
- Sensory deficits (typically in stocking-glove distribution)
- Impaired coordination

The rate and severity of progression of weakness varies from person to person; however, CIDP usually presents slowly over several months and has ongoing symptoms for more than eight weeks and usually does not improve unless ongoing treatment is given. This is in contrast to the acute form of demyelinating neuropathy known as Guillain-Barré syndrome (GBS). GBS presents with a rapid progression of symptoms occurring over days or weeks that usually warrants hospitalization due to involvement of the breathing muscles. Respiratory involvement does not occur in CIDP.³

Causes of CIDP

While it is unknown what causes CIDP, it is believed to be an autoimmune disorder. Autoimmune disorders occur when the body's natural defenses (antibodies and lymphocytes) against invading organisms suddenly begin to attack healthy tissue.³ With CIDP, the autoimmune disorder causes the immune system to attack the myelin cover of the nerves causing inflammation of nerves and nerve roots.⁷

Table 2. CIDP-Related Disorders

- Lewis-Sumner syndrome: A rare neurological disorder characterized by asymmetric or multifocal weakness and sensory dysfunction affecting the arms and legs.
- Multifocal motor neuropathy: A rare disorder characterized by asymmetric or multifocal weakness of the arms and legs without sensory signs or symptoms.
- Charcot-Marie-Tooth disease: A group of inherited neurological disorders that progressively affect movement.
- Multiple sclerosis: A chronic disease of the brain and spinal cord that may be progressive, relapsing, remitting or stable.

Source: National Organization for Rare Disorders. Chronic Inflammatory Demyelinating Polyneuropathy. Accessed at rarediseases.org/rare-diseases/chronic-inflammatory-demyelinating-polyneuropathy.

In addition, CIDP may occur in association with other conditions such as diabetes (more than half of people with diabetes develop some type of neuropathy), infections, medications (especially those used to treat cancer), bone marrow disorders (including an abnormal protein in the blood, a form of bone cancer, lymphoma and amyloidosis), other diseases (including kidney disease, liver disease, connective tissue disorders and hypothyroidism) and alcoholism.⁸ However, it should be noted that the vast majority of patients with CIDP cannot identify a specific cause.³

While previously there did not seem to be a genetic link to CIDP, one study did suggest a possible genetic cause. In that study, patients with CIDP had a high frequency of perforin gene variations that impair the function of cytotoxic T and natural killer cells, which may influence the development and course of CIDP.⁹

Diagnosing CIDP

Not only is CIDP difficult to diagnose, it can go undiagnosed for months or years either because symptoms aren't prominent enough or because nondebilitating symptoms in the early stages make it difficult to make a definitive diagnosis.¹⁰ In addition, according to recent studies, CIDP is misdiagnosed in up to 50 percent of cases, with alternative diagnoses given such as motor neuron disease, diabetic and inherited polyneuropathy, and even conditions clinically distinguishable from CIDP such as fibromyalgia or multiple sclerosis.¹¹ Notably, there are some related disorders that can be useful in a differential diagnosis of CIDP (Table 2).³

While many sets of diagnostic criteria have been developed for CIDP, the one used most often in current clinical practice was developed by the European Federation of Neurological Societies and the Peripheral Nerve Society (EFNS/PNS). This is mainly due to the high specificity and lack of sensitivity of other diagnostic criteria that can lead to underdiagnosis. For instance, a study of 151 CIDP patients and 162 control patients found the EFNS/PNS criteria had a sensitivity of 81.3 percent and specificity of 96.2 percent for definite or probable CIDP, whereas sensitivity of other diagnostic criteria in the study ranged from 45.7 percent to 79.5 percent.²

According to the EFNS/PNS criteria, "CIDP should be considered in any patient with a progressive symmetrical or asymmetrical polyradiculoneuropathy in whom the clinical course is relapsing and remitting or progresses for more than two months, especially if there are positive sensory symptoms, proximal weakness, areflexia (no muscle response to stimuli)

without wasting, or preferential loss of vibration or joint position sense.”¹² EFNS/PNS criteria also state electrophysiologic tests are mandatory.² These tests can help determine whether an individual has CIDP by looking at the demyelination process. Other features that support a diagnosis include elevated cerebrospinal fluid protein without an increased leukocyte (white blood cell) count; MRI evidence of gadolinium enhancement or nerve root plexus hypertrophy; nerve biopsy finding of primary demyelination; and improvement following immunotherapy.¹⁰

Most recently, it has been found a small subset of patients harbor one of two autoantibodies: isoforms of NF155 and NF186, as well as anti-CNTN1 antibodies, which target a specific portion of peripheral nerves and may have important treatment implications.¹³ Anti-CNTN1 antibodies are found in between 2.2 percent and 8.7 percent of patients, and NF155 and NF186 have been detected in between 4 percent and 18 percent of CIDP patients. Anti-CNTN1 antibody-positive patients are clinically distinct with predominant involvement of motor fibers and axonal (the appendage of the neuron that transmits impulses away from the cell body) damage. Clinical features associated with NF155 seropositivity are younger onset, tremor and sensory ataxia. Patients with NF186 (and NF140 found in less than 2 percent of patients) have associated autoimmune disorders, are severely affected and present with sensory ataxia but not tremor.¹¹

Treating and Managing CIDP

Treatment of CIDP is complex and has to be individualized for each patient. The goal of treatment is to block immune processes to stop inflammation and demyelination, as well as to prevent secondary axonal degeneration. Secondary goals of treatment are to reduce symptoms such as weakness and pain and to improve overall functional status, as well as to reduce the frequency of relapses and slow disease progression.¹⁰

First-line treatments include corticosteroids to suppress the immune system, intravenous immune globulin (IVIG) to infuse antibodies into the blood, and plasmapheresis to remove harmful antibodies.¹⁴ Research shows 60 percent to 80 percent of individuals treated with first-line treatments show improvements in their condition; however, long-term prognosis varies according to when therapy is initiated and the degree of associated axonal loss.¹⁰ The determinations to use one first-line treatment versus another include disease severity, comorbid disorders, venous access, potential adverse

effects, availability and cost. According to the EFNS/PNS guidelines, corticosteroids and IG therapy are recommended for patients with moderate to severe CIDP, IG therapy should be considered instead of corticosteroids for patients with pure motor CIDP, and PE (plasma exchange) should be considered when patients don't respond to IVIG or corticosteroids, or for severe CIDP when a rapid response is needed.²

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Corticosteroids have been used to treat patients for more than 40 years, yet there remains no consensus about the optimal regimen.² There was a retrospective study that compared regimens (daily oral prednisolone, pulsed oral dexamethasone or pulsed intravenous methylprednisolone) in 125 CIDP patients, 60 percent of whom responded to them with no significant difference in safety and efficacy between the three regimens.¹¹ The main benefit of corticosteroids is their low acquisition cost. The downside, however, is adverse effects from long-term use, which can include osteoporosis and fractures, adrenal suppression and Cushing syndrome, hyperglycemia, hypertension, psychiatric disturbances, cataracts, weight gain and immunosuppression. Studies have shown dexamethasone and pulsed intravenous methylprednisolone have a lower risk of adverse effects than prednisolone.²

The benefit of IG therapy is attributed to anti-inflammatory activity.² Currently, there are three U.S. Food and Drug Administration (FDA)-approved IVIG products to treat CIDP: Gamunex-C (Grifols), Gammaked (Kedrion) and

Privigen (CSL Behring). The standard maintenance treatment regimen is 1.0 g/kg every three weeks, with studies showing high response rates. One study showed a response rate of almost 70 percent after 52 weeks at this maintenance regimen.¹¹

It should be noted that both anti-CNTN1-positive and NF155-positive patients show a poor response to IVIG. However, some case studies suggest these patients may benefit from treatment with rituximab (a monoclonal antibody discussed below). NF140 and NF186-positive patients do respond well to IVIG or corticosteroids.¹¹

In 2018, FDA approved Hizentra (CSL Behring) as the first subcutaneous IG (SCIG) therapy to prevent relapse of neuromuscular disability and impairment. It is the only SCIG approved for this indication based on data from the Phase III PATH (Polyneuropathy And Treatment with Hizentra) study, the largest controlled clinical study in CIDP patients to date. In the PATH trial, patients taking Hizentra relapsed or withdrew less often than those taking placebo. Patients in the study also maintained their grip strength, as well as upper- and lower-body strength.¹⁵ Another study found both SCIG and IVIG are equally effective. That study compared CIDP patients who received SCIG for five weeks to patients who received IVIG for five days after 10 weeks of opposite treatment, and found both treatments had similar effects on muscle strength.¹¹ However, there are three differences between IVIG and SCIG. SCIG offers improved quality of life since patients can self-administer at home and a lower relative risk of systemic adverse effects (fever, headache, nausea).² SCIG is also a therapeutic alternative for patients who suffer wear-off phenomena (loss of benefit) before the start of their next cyclical IVIG infusion.¹¹

PE, although used less frequently, is a method for removing unwanted substances (toxins, metabolic substances and plasma parts) from the blood. With PE, blood is removed from the individual, blood cells are separated from the plasma, the plasma is replaced with other human plasma and the patient's blood cells are transfused back into the individual, thus removing only the plasma and its constituents. PE is similar to IVIG since it is only effective for a few weeks, so it requires chronic intermittent treatments.³

In cases where first-line treatments fail, other immunosuppressants can be tried. These include azathioprine, mycophenolate mofetil and methotrexate. Monoclonal therapies that have been found to be effective in multiple sclerosis are also being studied to treat CIDP. Rituximab, a monoclonal antibody that targets

Table 3. CIDP Outcome Measures

- Inflammatory neuropathy cause and treatment (INCAT) disability scale and sensory subscore: Measures upper and lower limb dysfunction
- Overall disability sum score (ODSS): Measures the function of the upper and lower limbs
- Overall neuropathy limitations scale (ONLS): Modified ODSS; ODSS item "Does the patient have difficulty walking?" was changed to "Does the patient have difficulty walking, running or climbing stairs?" The remaining scoring criteria are not different from ODSS
- Rasch-built overall disability scale (RODS): Measures upper and lower limb disability
- GAITrite: Measures gait parameters (velocity, cadence, swing phase, double support time, stance phase)
- Timed up and go test (TUG): Time taken to stand up from a chair, walk a short distance, turn around, return and sit down again
- 10-meter walk test (10MWT): Measures walking speed
- Dynamometer or vigorimeter: Measures grip strength
- Manual muscle strength testing and isokinetic strength testing: Muscle strength testing
- Fatigue severity scale (FSS): Measures fatigue
- SF-36: Quality-of-life measure (physical functioning, role functioning, social functioning, body pain, mental health, vitality, general health perception and change in health)
- Chronic acquired polyneuropathy patient reported index (CAP-PRI): Quality-of-life measure (physical function, social function, pain and emotional well-being)

Source: Physiopedia. Chronic Inflammatory Demyelinating Polyneuropathy (CIDP). Accessed at [www.physio-pedia.com/Chronic_Inflammatory_Demyelinating_Polyneuropathy_\(CIDP\)](http://www.physio-pedia.com/Chronic_Inflammatory_Demyelinating_Polyneuropathy_(CIDP)).

a certain portion of B cells, including those that play a role in the immune response thought to occur in autoimmune conditions, has shown to be beneficial particularly in those positive for anti-CNTN1 and anti-F155 antibodies.¹¹ And, alemtuzumab, which targets B cells and T cells, could provide a broader attack on the immune system. However, one that has not shown to be effective is fingolimod, a drug that affects the ability of lymphocytes to contribute to immune function.³

After treatment is started, it must be continued in those who respond to it until the condition is stabilized or greatly improved. Response to treatment is measured by improvements in sensation, strength and the performance of activities of daily living.¹⁰ Assessment tools to monitor response to therapy include the Rasch-Built Overall Disability Scale to measure disability and the Martin Vigorimeter to measure grip strength,² among others (Table 3).

Lastly, physiotherapy plays an important role in treatment. Physiotherapists prescribe gait aids to assist with balance and ambulation, manual therapy to prevent joint contractures and maintain available range of motion, and exercises to promote muscle strengthening and aerobic conditioning.¹⁰

A Costly Disease

While rare, CIDP poses a substantial clinical and economic burden among the thousands of patients affected by this neurological disorder of the peripheral nervous system. In a recent retrospective case-control analysis using data from the IQVIA Real-World Data Adjudicated Claims, adults newly diagnosed with CIDP between July 1, 2010, and June 30, 2014, were identified and direct matched to controls without CIDP. The researchers assessed and compared baseline characteristics over a six-month pre-index period; healthcare resource use, costs and clinical characteristics over a two-year follow-up; and total cost differences over the two-year follow-up between matched cohorts. They found that compared to controls, more CIDP patients had greater than or equal to one hospitalization (26.2 percent versus 9.0 percent), and a higher mean number of outpatient prescription fills (62.8 versus 32.0) and physician office visits (34.7 versus 13.0). In addition, CIDP patients had 7.5-times higher mean total costs (\$116,330 vs. \$15,586). Important cost drivers were costs for outpatient ancillary, radiology and HCPCS drugs (mean \$76,366 versus \$4,292) and costs for inpatient care (mean \$16,357 versus \$2,862). CIDP therapy (inclusive of both outpatient pharmacy and medical claims) accounted for 51.2 percent of mean total costs.¹⁶ In an earlier study conducted in 2011 that analyzed insurance claims data for 73 CIDP patients, the annual health plan cost per patient was almost \$57,000. Pharmacy claims were the primary cost driver (57 percent), with IVIG therapy accounting for 90 percent of those costs.²

Fortunately, a lot has been learned over the last few years. According to Jeffrey A. Allen, MD, a member of the GBS/CIDP Foundation Global Medical Advisory Board, there are currently a multitude of studies around the world exploring ways to get more out of current CIDP treatments. And, he says, equal to this is identification of new treatment options.¹³

Yet, while much progress is being made, there remains an unmet need to improve diagnostic criteria and find clinical

or biological variables that can predict treatment response. But, it is believed these issues can be uncovered through collecting and analyzing data from patients with CIDP in large registries and biobanks. According to the GBS/CIDP International website, a multidisciplinary group at the European Neuromuscular Center workshop recently compared eight currently ongoing international CIDP registries that included a total of more than 1,300 patients to assess infrastructure and collect clinical data, diagnostic data and biomaterials. The outcome was a decision to set up a central database, known as INCbase, to upload data from current registries and databases while these registries continue to exist. The global database is expected to be operational in mid-2020 and will collect data from thousands of CIDP patients to enable solving some of the important challenges in diagnosing and treating CIDP.¹⁷ ■

RONALE TUCKER RHODES is the editor of *IG Living* magazine.

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