

Senior Editor

Vera Bril, FRCPC, MD

Professor, Division of Neurology
Department of Medicine
University of Toronto
Division Director, Neurology
University Health Network and Mount Sinai Hospital
Krembil Family Chair, Neurology
University Health Network
Toronto, Ontario, Canada

Pharmacy Reviewer

Sachin Shah, PharmD, BCOP

Associate Professor
Texas Tech University Health Sciences Center
School of Pharmacy
Dallas, Texas

Target Audience

Physicians, nurses, and pharmacists who are involved in the care of patients receiving IGIV therapy.

Activity Goal

To familiarize physicians, nurses, and pharmacists with the latest developments in the field of immune globulin intravenous (IGIV) therapy and the relevance to patient care—specifically, key strategies for diagnosing and managing chronic inflammatory demyelinating polyneuropathy (CIDP).

This issue is part of a series of 4 continuing education newsletters.

Learning Objectives

After completing this activity, participants should be better able to:

- Describe the clinical presentation patterns of typical and atypical CIDP.
- Use clinical findings, laboratory testing, and electrodiagnostic procedures to differentiate CIDP from Guillain-Barré syndrome, diabetic neuropathy, and other peripheral neuropathies.
- Evaluate the relative benefits and drawbacks of IGIV, plasma exchange, corticosteroids, and immunosuppressants as initial treatment and maintenance therapy for CIDP.

Accreditation

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of New York Medical College (NYMC) and Continuing Education Alliance. NYMC is accredited by the ACCME to provide continuing medical education for physicians. NYMC designates this educational activity for a maximum of 1.0 *AMA PRA Category 1 Credit™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.



Continuing Education Alliance is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. This program is approved for 1.0 contact hour (0.10 CEUs). Universal Program Number 270-999-08-003-H01-P.

The providers of this program have waived the processing fees.



This program is supported by an unrestricted educational grant from Talecris Biotherapeutics, Center for Science and Education.

Managing Chronic Inflammatory Demyelinating Polyneuropathy: A Case-Based Approach

Chronic inflammatory demyelinating polyneuropathy (CIDP) is an immune-mediated peripheral neuropathy with an estimated prevalence of 1 to 2 per 100,000 adults and 0.5 per 100,000 children.¹ It can occur at all ages but has a peak incidence at 40 to 60 years of age with a slight male preponderance.² The pathogenesis of CIDP is not well defined, but molecular mimicry, antiglycolipid antibodies, and T-cell involvement are possible immunopathologic features of the disease.³ CIDP is a potentially treatable disease, and patients may improve with immunosuppressive and immunomodulatory treatments.⁴ However, underdiagnosis is common, highlighting the need for improved disease recognition.

This issue of IGIV: Achieving Improved Patient Outcomes is the fourth in a series of 4 continuing education newsletters on current trends in immune globulin intravenous (IGIV) therapy. The clinical presentation patterns, diagnostic tools, and treatment options for effectively managing CIDP are discussed using a case-based approach.

Faculty Disclosures

All faculty and planners participating in continuing medical education activities sponsored by New York Medical College are expected to disclose to the audience any significant support or substantial relationship(s) with providers of commercial products and/or devices discussed in this activity and/or with any commercial supporters of the activity. In addition, all faculty are expected to openly disclose any off-label, experimental, or investigational use of drugs or devices discussed in this activity. The faculty and planning committee have been advised that this activity must be free from commercial bias, and based upon all the available scientifically rigorous data from research that conforms to accepted standards of experimental design, data collection, and analysis.

Dr Bril: consultant/research: Talecris Biotherapeutics, Inc.

Dr Shah: has no significant relationships to disclose.

The Planning Committee for this activity included Kathy Johnston-Kavanagh and Margaret Astrologo of New York Medical College, and Ruth Cohen and Christine M. Olsen, PhD, of Continuing Education Alliance. The members of the Planning Committee have no significant relationships to disclose.

Disclaimer

The opinions or views expressed in this CE activity do not necessarily reflect the opinions or recommendations of Continuing Education Alliance, New York Medical College, or Talecris Biotherapeutics, Center for Science and Education.

How to Receive Credit

To receive continuing education credit, the target audience must:

1. Study the newsletter.
2. Relate the content material to the learning objectives.

Physicians and nurses may take the self-assessment test by accessing the Web site www.cealliance.org, printing the self-assessment test and evaluation form, completing the evaluation form, and returning it to New York Medical College as indicated on the form. Nurses must answer at least 70% of the questions correctly.

Pharmacists may take the self-assessment test by accessing the Web site www.cealliance.org and submitting the evaluation form online. Pharmacists must answer at least 70% of the questions correctly.

If Internet access is unavailable, please fax a request to 203.487.0406 (please include return fax number) or e-mail inquiries@cealliance.org to obtain a self-assessment test and evaluation form.

The estimated time to complete this activity is 1 hour. Upon successful completion of the above requirements, CME/CE certificates will be mailed within 6 weeks of receipt of the evaluation form. CPE certificates will be generated online.

Release date: November 30, 2008

Expiration: Credit will be awarded for required materials received no later than November 30, 2009.

Case: Paul, A 65-Year-Old Man With Difficulty Walking and Increasing Leg Weakness

History

- 6-month history of difficulty walking and progressively increasing weakness in his legs; experienced 2 falls during the previous month, described as legs “giving way”; no weakness in his upper limb, ocular, or bulbar muscles
- Occasional numbness in his feet, but no other sensory symptoms; pain and stiffness in his knees exacerbated by activity, but no pain in hands, feet, neck, or lower back
- No difficulties with bowel, bladder, or erectile function; no cognitive changes, dizziness, orthostatic light-headedness, blackouts, or other neurologic symptoms; no weight loss, fevers, night sweats, or other systemic symptoms
- Comorbidities: type 2 diabetes mellitus (3 years), controlled on diet and oral antihyperglycemic therapy (metformin), A1C 7% 1 month ago, no diabetic retinopathy or nephropathy; hypercholesterolemia (3 years), treated with atorvastatin; osteoarthritis in hips and knees (about 5 years), treated with extra-strength acetaminophen; no history of hypertension, cardiac disease, or thyroid disease
- Does not smoke or consume alcohol; no known toxic or chemical exposures; no family history of neuromuscular disorders

Physical Findings

- Appearance: alert and cooperative; blood pressure: 150/85 mm Hg; osteoarthritic changes in knees and hips
- Cranial nerves: normal; speech: normal; motor tone: normal, no involuntary movements; muscle bulk: preserved
- Muscle strength: neck and upper limbs (normal); hip flexors (grade 3/5); quadriceps, hamstrings, dorsiflexors, and toes (grade 4); plantar flexors (grade 4+); other lower-limb groups (grade 5)
- Deep tendon reflexes: sluggish in upper limbs (1/4) and absent at knees and ankles (0/4); plantar responses: flexor
- Sensory testing: glove-and-stocking loss of light touch; pin-prick and thermal sensitivity to the wrists and mid-calves; loss of vibration to the knees
- Position sense: normal; gait: slightly unsteady, unable to perform a tandem gait well or to walk on heels or toes; Romberg test: normal findings
- Other physical findings: unremarkable

Why should CIDP be suspected in Paul?

Clinical Features

Typical CIDP: Most patients with CIDP typically present with symmetric muscle weakness (with or without sensory loss), involving the upper and lower limbs, with deterioration in symptoms during at least 2 months.^{1,2,4,5} The motor deficit usually follows a proximal to distal distribution. Deep tendon reflexes usually are absent or diminished in all 4 limbs. Many patients have impaired balance because of proprioceptive deficits.² Facial and neck muscles also may be affected, but bulbar involvement is rare.² If present, sensory symptoms follow a distal to proximal distribution and usually manifest as numbness and tingling, although painful dysesthesia may occur.⁵ Cranial nerves are affected in 10% to 20% of patients.⁵ Constipation and urinary retention are rare in CIDP and seldom appear early in the disease.

Atypical CIDP: Several clinical variants of CIDP have been recognized, including distal acquired demyelinating sensory disease, marked by mainly distal weakness; Lewis-Sumner syndrome or multifocal acquired demyelinating sensory and motor disease, marked by asymmetric weakness with a multifocal distribution; purely motor deficits; and purely sensory deficits.^{4,6} Although CIDP variants

have some unique characteristics and may respond differently to therapeutic interventions, the variants share electrophysiologic and laboratory features.^{2,4,6}

Clinical course: In most patients with CIDP, the clinical course of the disease is slowly progressive. However, in about one third of patients, usually younger patients, the course is relapsing-remitting.^{2,5}

Differential diagnosis: CIDP can be distinguished from other chronic peripheral neuropathies by the more global muscle weakness of upper and lower extremities, the general decrease or absence of deep tendon reflexes, and the more aggressive course of the disease.⁵ These features point to CIDP’s multifocal or generalized nature, even at early stages. The differential diagnosis includes Guillain-Barré syndrome (GBS), diabetic neuropathy, mononeuritis multiplex, and genetic disorders of peripheral nerve myelin such as Charcot-Marie-Tooth (CMT) disease.⁵

Case Commentary: Why Should CIDP Be Suspected in Paul?

Symmetrical motor weakness that begins early in the course of the disease, progresses slowly, and persists for at least 2 months is typical of CIDP. Although

diabetic neuropathy should be considered in Paul, early motor weakness is not typical of this disorder. The slowly progressive and chronic nature of his symptoms rules out GBS, an acute disorder in which motor weakness does not progress beyond 8 weeks. Mononeuritis multiplex affects scattered nerves and typically is not symmetric, whereas CIDP is a diffuse neuropathy that starts in the legs with a symmetric presentation. Based on his presenting symptoms and the absence of a family history of neuropathy, CIDP should be suspected in Paul. Electrodiagnostic testing is warranted, as are laboratory tests to rule out other common causes of neuropathy in patients with diabetes, including vitamin B₁₂ deficiency, hypothyroidism, and uremia.⁷

Diagnostic Evaluation

When CIDP is suspected, electrodiagnostic testing is mandatory to confirm demyelination, the cardinal symptom of CIDP. The diagnostic workup also may include laboratory studies, nerve biopsy, and imaging tests to confirm or exclude other disorders.

Electrodiagnostic testing: Nerve conduction studies (NCS) are used to detect demyelination. A prolongation of distal motor latency, reduction of motor conduction velocity, delay or absence of F waves, and presence of conduction block and/or an abnormal temporal dispersion on motor NCS

are strongly suggestive of a demyelinating neuropathy.^{2,4}

Laboratory studies: Cerebrospinal fluid (CSF) analysis usually is not necessary, but can be helpful to confirm a diagnosis of CIDP when NCS is inconclusive. An elevated CSF protein concentration (>45 mg/dL) without an elevated CSF white blood cell count (<10/mm³) is present in >90% of patients with typical CIDP.²

Normal CSF study results, however, do not exclude the diagnosis.⁴ In some patients, additional laboratory tests may be used to screen for other causes of demyelinating neuropathy (eg, CMT) or for coexisting diseases (eg, diabetes, HIV infection, hepatitis B/C, cancer, and sarcoidosis).⁴ These

tests could include measures of serum glucose and glycated hemoglobin, thyroid function studies, hepatitis profiles, HIV screening, and serum immunofixation electrophoresis to detect lymphoproliferative disorder (osteosclerotic myeloma or lymphoma).^{2,5}

Nerve biopsy: Nerve biopsy to demonstrate signs of demyelination, axonal degeneration/regeneration, and inflammation is not indicated for most patients presenting with neuropathy. However, it may be helpful in excluding other etiologies, such as amyloidosis, vasculitic neuropathy (often presenting with mononeuritis multiplex), and toxic neuropathies. Nerve biopsy also may

be helpful when patients present with symptoms resembling CIDP but NCS and CSF analyses do not support the diagnosis.²

Imaging: Evidence of abnormalities of nerve roots, plexuses, and peripheral nerves on magnetic resonance imaging (MRI) may be useful in supporting the diagnosis.⁴ In patients with degenerative joint disease, MRI of the cervical and lumbar spine can rule out spinal stenosis. Radiography and computed tomography (CT) may be considered to detect concomitant diseases. Chest radiographs may be ordered to exclude neoplasias, for example, and CT scans of the chest and abdomen may be considered if lymphoma is suspected.

Case: Paul, A 65-Year-Old Man With Difficulty Walking and Increasing Leg Weakness

Laboratory/Imaging/Electrodiagnostic Findings

- Vitamin B₁₂ and folate levels: normal; thyroid, liver, and renal function: normal; A1C level: 6.5%; complete blood cell count and erythrocyte sedimentation rate: normal; serum immunoelectrophoresis: normal; syphilis serology: negative
- Chest radiograph: normal; CT scans of chest and abdomen: normal; MRI of cervical and lumbar spines: normal
- NCS: Sensory NCS of upper limbs: normal; sensory NCS of lower limbs: mild decrease in sensory nerve action potential amplitude and slowed sensory conduction velocity; motor NCS of upper and lower limbs: prolonged distal motor and F-wave latencies, slowed motor nerve conduction velocities, and motor conduction block

What is the diagnosis? What should be done next?

Case Commentary: What Is the Diagnosis?

Because Paul has type 2 diabetes mellitus, the possibility of diabetic neuropathy must be considered. However, the early motor involvement, the marked motor changes on NCS (prolonged motor distal latency, prolonged F-wave latency, slowed motor nerve conduction velocity, and motor conduction block), and the A1C of 6.5% (indicating excellent glycemic control) point to a diagnosis of CIDP, not diabetic neuropathy.

Treatment Approaches

Treatment of CIDP aims at blocking immune processes to arrest inflammation and demyelination and to prevent secondary axonal degeneration.¹ Treatment response is measured by improvements in strength, sensation, and ability to perform daily activities.¹ After the initial response, therapy should be continued until improvement is maximized or the disease is stabilized. Maintenance therapy may be needed to prevent or reduce relapse

or disease progression. IGIV, plasma exchange (PE), and corticosteroids have been the mainstays of therapy for CIDP.^{1,2,6} Because of its better long-term safety profile (compared with corticosteroids, which can have adverse effects on bone, blood pressure, blood sugar, and electrolytes) and greater ease of administration (compared with PE), IGIV has been considered the preferred first-line treatment.^{2,6}

In September 2008, the US Food and Drug Administration designated IGIV-10% caprylate/chromatography purified (IGIV-C) as an orphan drug for CIDP and approved it for treatment of CIDP to improve neuromuscular disability and impairment and for maintenance therapy to prevent relapse.⁸ The approval was based on the results of the IGIV-C CIDP Efficacy (ICE) study.⁹ This randomized, placebo-controlled trial demonstrated a significant improvement in disability with IGIV-C (2 g/kg over

2-4 days, followed by 1 g/kg over 1-2 days every 3 weeks) compared with placebo over 24 weeks (treatment difference 33.5%; $P = .0002$), as well as a significantly longer time to relapse ($P = .011$) among initial IGIV-C responders during a 24-week extension phase.⁹

The most recent evidence-based guidelines on CIDP management were published by the European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society (PNS) in 2006.⁶ For motor and sensory CIDP, EFNS/PNS recommends IGIV or corticosteroids as first-line therapy and PE as second-line therapy. For pure motor CIDP, it recommends IGIV as first-line and PE as second-line therapy; corticosteroids have no benefit in pure motor CIDP. Between 15% and 30% of patients whose CIDP responds to IGIV do not need additional treatment; if maintenance therapy is required, it

should be individualized to each patient's needs and comorbid conditions. Some patients may require combination therapy with corticosteroids or immunosuppressants.⁶

Case Commentary: What Should Be Done Next?

The next step is a trial of IGIV to assess responsiveness to immunomodulation. In most patients, 2 complete courses of IGIV, separated by a 1-month interval, are required to determine treatment response. Because the clinical diagnosis of CIDP is highly certain in Paul's case, a course of PE would be considered if his CIDP did not

respond to IGIV. In patients with CIDP, coexisting conditions such as multifactorial neuropathy or neurologic dysfunction, spinal stenosis, and diabetic neuropathy may limit treatment response; however, these disorders had been ruled out in Paul. If maintenance therapy is required and response to IGIV had been inadequate, corticosteroids would be an option, but because of Paul's diabetes, an alternative immunosuppressant agent (eg, azathioprine, mycophenolate mofetil, or rituximab) would be considered. Corticosteroids, with vigilant glycemic control, would be an option only if Paul were intolerant to immunosuppressants and his CIDP were

disabling. Rehabilitation services (physiatry, physiotherapy, gait assessment and aids, and appropriate strength-building exercises) also can be helpful for patients with CIDP.

Conclusions

CIDP is a treatable peripheral neuropathy and should not be overlooked as a possible diagnosis in patients who present with neuromuscular symptoms. Long-term intervention is required, and appropriate "buy-in" by patients to the treatments and adjustments that may be necessary to improve their overall health is important.

References

1. Köller H, Kieseier BC, Jander S, Hartung H-P. Chronic inflammatory demyelinating polyneuropathy. *N Engl J Med*. 2005;352:1343-1356.
2. Saperstein DS. Chronic acquired demyelinating polyneuropathies. *Semin Neurol*. 2008;28:168-184.
3. Dalakas MC. Intravenous immunoglobulin in autoimmune neuromuscular diseases. *JAMA*. 2004;291:2367-2375.
4. The French CIDP Study Group. Recommendations on diagnostic strategies for chronic inflammatory demyelinating polyradiculoneuropathy. *J Neurol Neurosurg Psychiatry*. 2008;79:115-118.
5. Lewis RA. Chronic inflammatory demyelinating polyneuropathy. *Neurol Clin*. 2007;25:71-87.
6. Hughes RA, Bouche P, Cornblath DR, et al. European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy: report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. *Eur J Neurol*. 2006;13:326-332.
7. Boulton AJM, Vinik AI, Arezzo JC, et al. Diabetic neuropathies. A statement by the American Diabetes Association. *Diabetes Care*. 2005;28:956-962.
8. US Food and Drug Administration. FDA approves treatment for rare neurologic disease. FDA News, September 12, 2008. Food and Drug Administration Web site. Available at: <http://www.fda.gov/bbs/topics/NEWS/2008/NEW01884.html>. Accessed October 9, 2008.
9. Hughes RA, Donofrio P, Bril V, et al. Intravenous immune globulin (10% caprylate-chromatography purified) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (ICE study): a randomised placebo controlled trial. *Lancet Neurol*. 2008;7:136-144.

IGIV: Achieving Improved Patient Outcomes

Complimentary
CME/CE Activity

PERMIT 1801
LOUISVILLE KY
PAID
US POSTAGE
STANDARD
PRESORTED

Continuing Education Alliance
One Dock Street, Suite 510
Stamford, CT 06902