Diagnosis and Emerging Treatments in Inflammatory and Demyelinating Neuropathies

Norman Latov, MD, PhD
Thomas H. Brannagan III, MD
Marinos C. Dalakas, MD
Michio Hirano, MD

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Diagnosis and Emerging Treatments in Inflammatory and Demyelinating Neuropathies

Faculty

Norman Latov, MD, PhD
Professor
Department of Neurosurgery and Neuroscience
Weill Medical College of Cornell University
New York, New York

Dr. Latov earned his medical degree and his PhD from the University of Pennsylvania, then performed a postdoctoral research fellowship in immunology at Columbia Presbyterian Medical Center in New York. He then joined the department of neurology at Columbia University, where he spent almost two decades before moving to Weill Medical College where he is currently Professor of Neurosurgery and Neuroscience. Dr. Latov’s research interests are in peripheral neuropathy and neuroimmunology, and focus on the mechanisms and treatment of inflammatory neuropathies. He is a member of the American Neurological Association, the American Academy of Neurology, and is the Medical and Research Director, a founding member, and a member of the Board of Directors of the Neuropathy Association.

Thomas H. Brannagan III, MD
Associate Professor
Department of Clinical Neurology
Cornell University
New York, New York

Dr. Brannagan graduated and received his medical degree from the University of Virginia in Charlottesville. He completed his Neurology residency training at the Neurological Institute of Columbia Presbyterian Medical Center. He subsequently performed a neuromuscular EMG fellowship at Columbia, followed by a neuroimmunology fellowship. Dr. Brannagan is currently Associate Director for Clinical Trials at the Peripheral Neuropathy Center at Cornell University. He is a member of the American Academy of Neurology, the American Association of Neuromuscular & Electrodiagnostic Medicine, the Neuropathy Association, and the Peripheral Nerve Society. Dr. Brannagan’s major interest is in the treatment of immune-mediated neuropathies. His publications have focused on new treatments for chronic demyelinating polyneuropathy, painful neuropathies, and the use of IVIg in neurological disorders.

Marinos C. Dalakas, MD
Chief
Neuromuscular Diseases Section
National Institutes of Health
Bethesda, Maryland

Dr. Dalakas is Chief of the Neuromuscular Diseases Section of the National Institute of Neurological Disorders and Stroke at the National Institutes of Health. He was trained in Neurology at the University of Medicine and Dentistry-New Jersey Medical School and in Neuromuscular Diseases at the National Institute of Neurological Disorders and Stroke. He served as a senior staff fellow in neurovirology and neuroimmunology and later became the Chief of Neuromuscular Diseases Section. He is board-certified in neurology, a fellow of the American Academy of Neurology, and a member of the American Neurological Society. Dr. Dalakas serves on the editorial board of several journals and has received a number of awards, including the NIH Director’s Award, the US Public Health Service Special Recognition Award, the Ramsay Medal, and the Gaetano Conti Prize for Clinical Research. His clinical and research interests are neuroimmunology, neurovirology, immunotherapies, and controlled clinical trials in autoimmune neurological disorders.

Michio Hirano, MD
Associate Professor
Department of Neurology
Columbia University
New York, New York

Dr. Hirano is currently an associate professor of neurology at Columbia University and the Co-director of New York-Presbyterian Hospital’s Muscular Dystrophy Association Clinic. Dr. Hirano attended the Albert Einstein College of Medicine, where he earned his medical degree. He is a member of several professional organizations, including the American Academy of Neurology, the American Association of the Advancement of Science, and the American Neurological Association, among others. Dr. Hirano is Board-certified by the American Board of Psychiatry and Neurology.

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Course Chair: Norman Latov, MD, PhD

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### OBJECTIVES

After attending this course, participants will learn (1) how to diagnose inflammatory and demyelinating polyneuropathies, (2) the current treatment of inflammatory and demyelinating neuropathies, (3) the emerging treatment of inflammatory and demyelinating neuropathies, and (4) the diagnosis and treatment of axonal and demyelinating mitochondrial neuropathies.

### PREREQUISITE

This course is designed as an educational opportunity for residents, fellows, and practicing clinical EDX physicians at an early point in their career, or for more senior EDX practitioners who are seeking a pragmatic review of basic clinical and EDX principles. It is open only to persons with an MD, DO, DVM, DDS, or foreign equivalent degree.

### ACCREDITATION STATEMENT

The AANEM is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education (CME) for physicians.

### CME CREDIT

The AANEM designates attendance at this course for a maximum of 3.25 hours in category 1 credit towards the AMA Physician's Recognition Award. This educational event is approved as an Accredited Group Learning Activity under Section 1 of the Framework of Continuing Professional Development (CPD) options for the Maintenance of Certification Program of the Royal College of Physicians and Surgeons of Canada. Each physician should claim only those hours of credit he/she actually spent in the activity. The American Medical Association has determined that non-US licensed physicians who participate in this CME activity are eligible for AMA PMR category 1 credit. **CME for this course is available 9/05 - 9/08.**
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Gary Goldberg, MD
Pittsburgh, Pennsylvania
DEFINING CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY

There is no definitive test for chronic inflammatory demyelinating polyneuropathy (CIDP). A diagnosis is made on the basis of the clinical presentation, evidence for demyelination, absence of another cause for demyelinating neuropathy, and response to immune therapy.

CLINICAL PRESENTATION

The typical clinical presentation is that of progressive, symmetric proximal and distal weakness with large fiber sensory loss. Over 50% of patients, however, have atypical presentations, including: (1) asymmetric CIDP, with asymmetric weakness and large fiber sensory loss; (2) distal CIDP, with symmetric, predominately sensory neuropathy, or with mild distal weakness; or (3) purely sensory CIDP. There is some debate as to whether multifocal motor neuropathy or the Lewis-Sumner syndrome should be lumped in with CIDP, as they have more prominent focal lesions and more severe axonal loss. However, it is important to note that patients with atypical syndromes can progress to generalized involvement and exhibit the typical CIDP phenotype.

The diagnosis is usually straightforward in patients with the typical presentation. However, in patients with asymmetric or distal CIDP, demonstration of demyelination becomes paramount for distinguishing CIDP from other causes of neuropathy.

ELECTRODIAGNOSIS

The diagnosis of CIDP requires a demonstration of demyelinating lesions that cannot be explained by other known causes of neuropathy, such as Charcot-Marie-Tooth type 1 (CMT1). In electrodiagnostic (EDX) studies, demyelinating range abnormalities are defined as those showing more severe abnormalities than can occur as a consequence of primary axonal degeneration, with hereditary axonal neuropathy or motor neuron disease used to define the acceptable ranges. This, however, makes it difficult to diagnose CIDP in early cases where the nerve conduction velocity is only mildly abnormal, or where secondary axonal degeneration is sufficiently severe to mask the effects of demyelination. Demyelinating lesions that are proximal or distal to the areas of investigation, or that are only present in sensory nerves, can also be easily overlooked. In such patients, nerve biopsy studies are often required to prove the diagnosis.

The number, type, and distribution of demyelinating abnormalities required for the diagnosis of CIDP is a matter of dispute. In the author's studies, a significant number of patients with typical CIDP (25-30%) exhibited only one such abnormality, even if eight motor nerves were tested.
Consequently, three limbs, or eight motor nerves may need to be investigated in order to detect the presence of demyelination.

**PATHOLOGICAL DIAGNOSIS**

Pathological changes on nerve biopsy that are indicative of demyelination/remyelination include axons that are denuded or that have abnormally thin myelin sheaths or onion bulbs. These can be seen in semi-thin sections or electron micrographs. Teased fiber analysis, in addition, can demonstrate segmental demyelination, or variation in internodal length as a sign of demyelination/remyelination.

**RESPONSE TO THERAPY AS A CLUE TO DIAGNOSIS**

In earlier studies, patients were defined by their response to corticosteroids, rather than by phenotype or presence of demyelination.1 Given the ambiguities inherent in diagnosing CIDP, one can argue that a patient with a compatible phenotype who responds to immunotherapy, is more likely to have CIDP than idiopathic neuropathy, if no other cause for neuropathy can be identified.

**LABORATORY TESTING**

Laboratory tests are routinely ordered for other causes of demyelinating neuropathy. Deoxyribose nucleic acid tests may reveal the presence of a hereditary demyelinating neuropathy, particularly in patients with a positive family history, compatible phenotype, or that are resistant to immunotherapy. The presence of an immunoglobulin M (IgM) monoclonal gammopathy or IgM autoantibodies to glycoconjugates is routinely detected by immunofixation electrophoresis (IFE), and by testing for antibodies to myelin-associated glycoprotein, sulfatide, and GD1b in the distal CIDP phenotype, or for GM1 and GD1a in the predominantly motor neuropathies. Serum, urine IFE, and a skeletal survey are ordered for the diagnosis of osteosclerotic myeloma or the polyneuropathy, organomegaly, endocrinopathy, M protein, skin changes syndrome. Spinal fluid protein concentration is elevated in over 90% of patients with typical CIDP, but in less than half of the patients with distal or multifocal CIDP16,21

**CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY IN PATIENTS WITH OTHER TYPES OF NEUROPATHIES**

Chronic inflammatory demyelinating polyneuropathy can also occur in patients with other types of neuropathy. When associated with axonal neuropathies, the presence of demyelinating features on EDX testing or nerve biopsy, can confirm the diagnosis. When associated with other types of demyelinating neuropathies such as diabetes19 or CMT1,11 however, the diagnosis can be difficult to make. A typical phenotype, rapid progression, unusually high cerebral spinal fluid protein concentration, or a particular distribution of demyelinating lesions may alert the physician to the diagnosis of CIDP.

**PREVALENCE OF CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY**

According to epidemiologic studies, the incidence of CIDP is 1-7.7 per 100,000 which correlates to 2000-15,000 patients in the United States.13 However, reports from academic centers note an incidence of CIDP in 3–21% of previously undiagnosed patients2,4,10 which correlates to over 100,000 people in the United States. The difference is likely to be due to referral bias and differences in diagnostic criteria.

**RESEARCH VERSUS CLINICAL DIAGNOSTIC GUIDELINES**

In developing diagnostic guidelines for the diagnosis of CIDP it is important to keep in mind that clinical guidelines and research guidelines serve different purposes. Research guidelines that help select patients for clinical trials must be highly specific rather than sensitive and have few confounding variables. Clinical guidelines used in routine practice need to be more sensitive so as not to miss potentially treatable patients, as well as accommodate patients with more atypical features and confounding variables. These guidelines
should help the physician determine what disorder the patient is most likely to have, regardless of whether or not particular criteria are met.

**SHOULD DIAGNOSTIC GUIDELINES BE EVIDENCE-BASED OR BASED ON THE BEST AVAILABLE EVIDENCE**

Evidence-based recommendations can only be based on blinded controlled trials. Since there are no controlled trials to evaluate diagnostic criteria for CIDP, the diagnosis needs to be based on the best available evidence: noncontrolled trials, case series and reports, outcome studies, physician experience, and clinical judgment.

**ECONOMIC CONSIDERATIONS**

Since therapy of CIDP can be expensive, payers denying reimbursement often justify their decision on the basis of diagnosis rather than cost. As such, diagnostic criteria for CIDP have become a contentious issue.

**SUMMARY**

Given the lack of a definitive diagnostic test for CIDP, there is controversy regarding clinical, electrodiagnostic, or pathological diagnostic criteria for research or clinical practice. There are also questions regarding when to use genetic or immunological tests to rule out other causes of demyelinating neuropathy, or the prevalence of the disease in the general population. These issues have important implication for patient care, and are impacted by economic considerations.

**REFERENCES**


INTRODUCTION

This manuscript will discuss the treatment of chronic inflammatory demyelinating polyneuropathies, including chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) and anti-myelin-associated glycoprotein (MAG) associated neuropathy. The following immunomodulatory treatments will be discussed: corticosteroids, intravenous immunoglobulin (IVIg), plasmapheresis, beta-interferon, etanercept, rituximab, and chemotherapeutic agents including cyclophosphamide azathioprine, mycophenolate mofetil, fludarabine, and cyclosporine.

CORTICOSTEROIDS

Glucocorticoids inhibit inflammation by activating the cytosolic glucocorticoid receptor (GR). This complex is then transported to the nucleus and regulates gene expression. The glucocorticoid-GR complex binds to specific regions of deoxyribonucleic acid (DNA), within the regulatory regions of genes, designated as glucocorticoid responsive elements. There are also interactions of the GR that inhibit the proinflammatory transcription factor NF-κB that are important in the antiflammatory effects of glucocorticoids.59,63

A single dose of glucocorticoids leads to a decrease in the number of lymphocytes. Glucocorticoids also suppress inflammation by decreasing the release of proinflammatory cytokines, vasoactive, and chemoattractive factors. Macrophage function is inhibited and there is a decreased release of lipolytic and proteolytic enzymes. They also result in decreased transmigration of leukocytes to areas of injury.63 Corticosteroids increase the apoptosis of autoaggressive T cells in peripheral nerve.160 Despite their widespread effects on cellular immunity, corticosteroids have little effect on B cells or humoral immunity.63

Side effects occur in almost all patients on chronic steroid therapy. These can include hyperglycemia, hypertension, gastritis and gastrointestinal bleeding, osteoporosis, glaucoma, aseptic necrosis of the hip, cataracts, poor wound healing, susceptibility to infection, myopathy, and psychiatric problems.63,162

Some measures can reduce the incidence of adverse effects. Patients who are on chronic daily steroids should take calcium and vitamin supplements (1000 mg of elemental calcium) have bone density monitored and follow a diabetic, low carbohydrate diet with low salt and regular weight-bearing exercise to minimize complications. Potassium should be monitored and supplementation is often needed. Patients who are on 16 mg or more of prednisone a day for 8 or more weeks should receive pneumocystis pneumonia prophylaxis, such as with trimethoprim-sulfamethoxazole (bactrim).138 The dose of prednisone is usually tapered to the lowest effective dose, once a response is seen.
Efficacy

A single placebo controlled study showed benefit for prednisone in CIDP. This study was randomized, though not blinded and not an intention-to-treat study. Despite the lack of randomized, double-blind, placebo-controlled studies, corticosteroids for CIDP are accepted because of the long experience with their use. With an initial high dose of 100 mg of prednisone, the mean time to improvement was 1.9 months, though the range was from several weeks to 5 months.

Prednisone is usually not effective for MMN and may result in worsening of the disease. Corticosteroids have only been effective in patients with anti-MAG neuropathy, when combined with other therapy.

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin (IVIg) is prepared from human plasma derived from 3000-10,000 donors. The immunoglobulin (Ig) product is purified by enzymatic treatment, followed by fractionation and chromatography and usually stabilized with sugars or amino acids such as sucrose, glucose, maltose, glycine, sorbitol, or albumin to avoid aggregation. Most products are treated with solvents and detergents to inactivate hepatitis viruses. More than 95% of IVIg contains IgG and less than 2.5% IgA. Other plasma components such as CD4, CD8, human lymphocyte antibody molecules, and coagulation factors are also present in variable amounts and may play a role in some adverse effects.

Intravenous immunoglobulin has multiple effects on the immune system and affects costimulation and antigen recognition, auto-antibodies, chemokines, and adhesion molecules and their receptors. Intravenous immunoglobulin can neutralize pathogenic cytokines. It inhibits complement activity and limits apoptosis through anti-Fas Ab. By binding to the Fcγ receptor on macrophages, it can modulate phagocytosis.

It is likely that different actions are important in different autoimmune disease. For example, the anti-ideotype action of IVIg as well as the down-regulation of complement activation are important in the benefit seen in MMN with anti-GM1 antibodies. In other autoimmune diseases, such as immune thrombocytopenic purpura (ITP), accelerated elimination of pathogenic antibodies by competitive inhibition of the neonatal Fc receptor (FcRn) may be more important. Rapid infusion rates of up to 800 ml/hr have been employed, though these rates are not recommended for patients with renal or vascular disease. Others recommend limiting the rates to 200 ml/hr to avoid complications. Those with cardiac disease may have an increased risk of complications with rates over 200 ml/hr. A study in children did not show a difference in adverse effects comparing 400 g/kg for 2 days with 1 g/kg for 2 days. Children, however, are not likely to have renal or thrombotic complications. Lower daily doses at slower infusion rates is advisable in older patients with cardiac, vascular or renal disease to minimize complications.

The author’s approach is to continue treatment until benefit is maximized. After an induction dose of 2 g/kg, maintenance doses of 1 g/kg monthly were effective. In another open label study, patients were assessed every 6 weeks and the frequency and dosage required to maintain improvement was noted to be variable from .4 g/kg every other day to .25 gm/kg every 10 days. van Doorn noted in 9 of 21 patients the dose of IVIg could be gradually tapered off to .25g/kg every 2 weeks. The half-life of IVIg is 18-32 days. Therefore, a maintenance dose of 0.2 grams to 2 grams per kilogram per month should be offered to maintain a constant serum drug level.

Treatment is usually given with 2 g/kg divided over 5 days. Treatment with 2/kg in either 1 day or divided over 2 days is also effective. A single dose of 2 g/kg in 1 day has been demonstrated to be more effective than 0.4g/kg for 4 days in children with Kawasaki’s disease. The regimen of .4 g/kg weekly for 3 weeks, followed by .2 g/kg weekly for 3 weeks is also effective. These regimens have not been compared in regards to efficacy and safety. Higher doses (400 mg/kg x 5 days) have been shown to be more effective than lower doses (200 mg/kg x 5 days or 50 mg/kg x 5 days) in a dose-dependent manner.

A maintenance dose of 0.5 grams per kilogram over 2 weeks with adjustments made on an individual basis is this author’s approach.

Infusion-related Symptoms

Infusion-related symptoms consisting of chills, nausea, myalgias, headache, and vasomotor symptoms are frequent. These are typically self-limited and can often be controlled with reducing the infusion or with acetaminophen or diphenhydramine. More severe reactions may be controlled by intravenous hydrocortisone (solucortef) 50-100 mg. These reactions can sometimes be severe and interrupt or even cause patients to discontinue treatment. The cause of these
reactions is uncertain. Similar symptoms have been noted to a lesser degree in patients receiving placebo of albumin or saline.

**Congestive Heart Failure**

Congestive heart failure may occur in patients with preexisting heart disease because of the volume overload with IVIg infusion. Congestive heart failure was seen in 10% of patients receiving rapid infusion (600-800 ml/hour). Rapid infusion should be avoided in patients with cardiac disease.

**Anaphylaxis**

Anaphylaxis has only been described in patients with common variable immunodeficiency and selective IgA deficiency. The incidence of IgA deficiency is 1:1000. Patients with IgA deficiency have safely been given IVIg. Antibodies to IgA may identify those at risk of anaphylaxis. Patients with IgA deficiency and IgG antibodies against IgA have also been given IVIg without incident and IgG anti-IgA antibodies are not associated with adverse reactions to IVIg. IgE antibodies against IgA may predict those that develop anaphylaxis after receiving IVIg.

A National Institute of Health consensus panel recommended that prescreening for IgA levels was not essential, though it may be advisable for treatment of chronic neuropathies and is often a part of the diagnostic evaluation for immune-mediated neuropathies.

An IVIg product that is low in IgA is available, however the risk for anaphylaxis is not eliminated with the use of this product.

**Renal**

Oliguric renal failure may occur as a complication of IVIg. Most, though not all cases of renal failure have occurred in patients with mild pre-existing renal insufficiency and who receive a sucrose containing product. Among the 86 cases reviewed by the Center for Disease Control (CDC) with available data, the majority of patients received products containing sucrose, however 8% received a product with another stabilizing sugar. Renal biopsies have shown swelling and vacuolization of the proximal tubular epithelial cytoplasm typical of damage from a high-solute load, such as sucrose.

The following have been identified as risk factors for renal failure: pre-existing renal disease, diabetes mellitus, hypovolemia, sepsis, concomitant therapy with nephrotoxic agents, and patient age greater than or equal to 65. The CDC recommends checking renal studies prior to initiating treatment and periodically thereafter. Patients who have previously had renal failure associated with IVIg may safely be given IVIg. Slower infusion rates, discontinuing nephrotoxic medications, correcting hypovolemia, and the use of products without sucrose is advised.

**Rash**

Rash was reported in 6% of patients treated with IVIg in two series. There are reports of urticaria, eczema, erythema multiforme, purpuric erythema, maculopapular rash, and alopecia. A nonpruritic petechial rash may occur with normal platelet counts. A pruritic papular facial vasculitic rash has also followed treatment with IVIg treatment.

Recurrent urticarial or localized eruptions, which may be recurrent can be controlled with diphenhydramine or topical corticosteroid ointments. More severe and extensive reactions may require systemic corticosteroids, sometimes for up to 4-6 weeks. In some cases, recurrence of the rash precludes further IVIg treatment, but changing the formulation or batch of IVIg may allow continuing treatment without recurrence.

**Thrombosis**

One of the most concerning complications related to IVIg has been thromboembolic events. A small number have been reported including stroke, myocardial infarction (MI), central retinal vein occlusion, deep vein thrombosis (DVT), and pulmonary embolus. Most patients who have had thrombotic events have had known risk factors including increased age, preexisting vascular disease, or immobility. A preliminary report examining hospital discharge codes in patients receiving IVIg identified 16 thromboembolic events in 295 patients within 1 month (5%), including 9 (3%) within 24 hours. Most case series or clinical trials have noted thromboembolic events in 0-3% of patients.

The etiology of thromboembolic events after IVIg is not clear. The rise in platelets in patients with ITP after treatment with IVIg, accompanied by increased platelet aggregation has been suspected as a cause of coronary thrombosis. Thrombotic events have also been described in many other diseases treated with IVIg other than ITP. Increased viscosity may play a role and measuring serum viscosity prior to treatment has been suggested. Intravenous immunoglobulin can increase serum viscosity by 0.1 to 1.0 centipoise (mean 0.55 cp), which declines over 1 month. The increase in viscosity is dose dependent. Patients with monoclonal gammopathies and other causes of increased viscosity may be
more susceptible to this affect of IVIg and screening serum viscosity is recommended.37,126

Procoagulant activity of coagulation Factor XIa has been found in some batches of the majority of IVg brands and could contribute to thrombosis.157 Intravenous immunoglobulin's action on endothelial cells may also contribute.155 One patient who had an MI on day three of IVIg was given IVIg again on day 4 and had a stroke158 and another who continued to receive IVIg after suffering from a stroke had worsening.28 Intravenous immunoglobulin has been regiven to a patient who previously had an MI associated with IVIg after angioplasty corrected the coronary stenosis.54 Intravenous immunoglobulin was safely given again after a central retinal vein occlusion at a less frequent dose.120

One patient seen in this author's center developed a DVT after IVIg and was identified to have a prothrombin gene mutation.15 Some patients who have developed thromboembolic events have been tested for anticardioin antibodies, factor V leiden mutation, activated protein C resistance, antiphospholipid antibodies, anti thrombin III, protein C, protein S, heparin cofactor II, and homocysteine after the event. This has been unrevealing.46,57,61,62

Reversible Vasospasm

A reversible encephalopathy has occurred in three patients with Guillain-Barré syndrome, while receiving treatment or within days after IVIg treatment. All patients had visual complaints and disorientation. Aphasia, tremor, and seizures occurred. Magnetic resonance imaging showed occipital white matter changes and cerebral spinal fluid showed a pleocytosis with polymorphonuclear leukocytes in one patient. Electroencephalogram showed diffuse slowing and transcranial dopplers suggesting vasospasm. Total recovery occurred in all patients after stopping IVIg.75,100,152 Doppler studies have revealed vasospasm following IVIg in a patient with a reversible encephalopathy who improved after treatment with nimodipine. In a series of 10 patients receiving IVIg without symptoms of encephalopathy, Doppler studies revealed vasospasm in one patient 3-10 days after the infusion.136

Headache

Headache occurs commonly after IVIg and has been reported in 26-56% of patients in some series.8,17,118,134 Mendel reported 67% of patients receiving IVIg for CIDP had headache, though 44% of the patients receiving albumin as placebo did also. The headache is often mild or moderate, short-lived, and can respond to acetaminophen, nonsteroidal anti-inflammatory medications, or lowering the infusion rate.17,134 Sometimes headaches are more severe and can interrupt treatment. Prophylactic intravenous steroids may be effective.17,118 Migrainous headaches may respond to prophylactic medications such as propranolol.36

Aseptic meningitis has been reported with varying incidence after IVIg. The incidence has been reported as high as 11%134 although less frequently in most other series.8,17,131

Patients develop severe headache with nuchal rigidity, drowsiness, fever, photophobia, painful eye movements, and nausea and vomiting lasting 2-5 days. Cerebral spinal fluid reveals a pleocytosis with white blood counts (WBC) up to 1169 with a polymorphonuclear neutrophils predominance (up to 92%). Patients with a history of migraine are more susceptible. This occurs with different IVIg brands and can reoccur in the same patient using different IVIg preparations and slower infusion rates. Patients without migraine may tolerate a different lot of IVIg product without a recurrence of aseptic meningitis. Pretreatment with corticosteroids is not helpful.109,133,147

Hematologic

After IVIg, the WBC commonly falls, which is transient and usually asymptomatic.17,86 Rarely patients develop reversible neutropenia.7,14,17,96 This is also typically asymptomatic, though one patient developed mouth ulcers during neutropenic episodes.97 The neutropenia is often recurrent and may reoccur with different brands of IVIg suggesting that a host factor is involved in the pathogenesis.14,17 Hemolytic anemia may also occur after IVIg treatment.22,115

Transmission of Infectious Agents

There has not been a confirmed case of human immunodeficiency virus transmission via IVIg.25 Human immunodeficiency virus added to plasma prior to the Cohn fractionation process is successfully eliminated.108 In 1994, hepatitis C transmission was reported associated with Gammagard. The product was replaced by Gammagard-S/D, which includes a solvent/detergent step to inactivate the hepatitis C virus.9,131 There is also a report of parvovirus transmitted by IVIg.76 As with any biologic product, there remains a risk of new or unrecognized blood-borne pathogens.39,112

Other Complications

Immune complex arthritis,94 uveitis,2 cryoglobulinic vasculitis,119 and transfusion-related acute lung injury128 have occurred following IVIg.
Predicting and Preventing Complications

Most serious side effects occur in patients with identifiable risk factors. Vascular disease, immobility, and potential causes of increased serum viscosity such as high chylomicrons, triglycerides, cryoglobulins, and paraproteinemia are risks for thromboembolism.\textsuperscript{17,37} Migraine increased the risk of aseptic meningitis\textsuperscript{134} and IgA deficiency increases the risk of anaphylaxis.\textsuperscript{108} A preparation is available with a low content of IgA and may be used cautiously in those with IgA deficiency.

There are differences in the preparation and content of different brands of IVIg,\textsuperscript{11,12,157} though they are generally considered equal in terms of efficacy and safety.\textsuperscript{39,112} The use of sucrose as a stabilizing sugar has been associated with most, though not all, cases of renal failure associated with IVIg.\textsuperscript{26} Other complications such as neutropenia and aseptic meningitis reoccur in the same patient after receiving different products.\textsuperscript{14,133}

Efficacy

Four randomized controlled studies have demonstrated the benefit of IVIg in patients with CIDP,\textsuperscript{50,73,78,105} though not all patients receiving IVIg for CIDP respond.\textsuperscript{64} The usual dose is 2 g/kg as a single dose or divided over 2-5 days.

The half-life of IVIg is 18-32 days therefore a maintenance dose should be offered to maintain a constant serum drug level. This author recommends a maintenance dose of 0.5 grams per kilogram every 2 weeks with adjustments made on an individual basis.\textsuperscript{15} Treatment is usually continued while patients continue to improve and when patients no longer are improving, an attempt at tapering or stopping treatment is made.\textsuperscript{5,15,84}

Intravenous immunoglobulin is the treatment of choice for MMN and has been demonstrated to be effective in placebo-controlled, randomized, double-blind trials.\textsuperscript{57,144}

Intravenous immunoglobulin has been studied in anti-MAG neuropathy. One double-blind placebo-controlled randomized crossover study was negative. However, approximately 20% of patients did have a substantial benefit.\textsuperscript{42} Another randomized, controlled study did not reveal benefit in disability at 2 weeks, but did show reduced disability at 4 weeks as well as improvement in multiple other secondary outcome measures.\textsuperscript{35}

PLASMPHERESIS

Plasmapheresis is a method to remove pathogenic antibodies by removing the blood, separating the plasma by filtration and centrifugation, and then return the blood cells with a plasma substitute. It requires IV’s or other access. A single plasma exchange of one plasma volume will reduce the total IgG by 60% and the total IgM by 45%.\textsuperscript{105}

Adverse events are seen in 3-17% of procedures.\textsuperscript{105} These include infections from indwelling catheters, hypotension, electrolyte imbalance, citrate-induced hypocalcemia, thrombosis, vessel perforation, and bleeding.

Efficacy

Two randomized placebo-controlled studies have demonstrated benefit of plasmapheresis in CIDP\textsuperscript{48,72} Plasmapheresis has a higher incidence of relapse, as a sole treatment than with IVIg, prednisone, or chemotherapy.\textsuperscript{72} Patients with anti-MAG neuropathy also improve after plasmapheresis.\textsuperscript{13} In MMN, plasmapheresis is usually not effective\textsuperscript{58} and has resulted in worsening of disease.\textsuperscript{24}

CHEMOTHERAPY

Cyclosporin

Cyclosporin and other calcineurin inhibitors including tacrolimus block the activity of the phosphatase calcineurin. This interferes with the movement of nuclear factor of activated T lymphocytes into the nucleus, which is required for the induction of genes for IL-2 and other cytokines.\textsuperscript{63}

Cyclosporin-A has been beneficial in some patients with CIDP\textsuperscript{4,95} and MMN.\textsuperscript{113} One patient has been reported to improve with tacrolimus.\textsuperscript{1} There have been four reports of CIDP developing after the use of tacrolimus.\textsuperscript{53,156}
Cyclophosphamide

Cyclophosphamide is an alkylating agent, which targets rapidly proliferating cells, including B and T cells. For autoimmune diseases it is usually given orally at a dose of 2 mg/kg or intravenously monthly at a dose of 1-3 g/m². Side effects include bone marrow suppression, hemorrhagic cystitis, alopecia, vomiting, infertility, teritogenicity and the delayed development of hematologic and bladder malignancies. The risk of malignancy rises when the total cumulative dose exceeds 80 grams, which is more likely to occur when cyclophosphamide is given orally. Cystitis can be reduced by hydration and the use of 2-mercaptoethane sulfonate.

Patients with CIDP, MMN, and anti-MAG associated neuropathy have been reported to improve in open label studies with cyclophosphamide. One patient with CIDP has been reported with a long-term remission after an autologous stem cell transplant. High dose cyclophosphamide (200 mg/kg) without stem cell rescue can produce a long-term remission—up to 20 years in aplastic anemia—and has been used successfully in other autoimmune diseases.

Patients are usually neutropenic for 7-14 days, but because of the presence of the enzyme aldehyde dehydrogenase in the hematopoietic stem cell, there is no dose of cyclophosphamide that is myeloablative. This therapy does not purge hematopoietic stem cells, which allows for rapid white cell recovery without stem cell rescue. B and T lymphocytes are deficient in this enzyme and have no protection against the cytotoxicity of cyclophosphamide, making this regimen strongly immunosuppressive.

High-dose cyclophosphamide without stem cell rescue resulted in long-term remission for a small group of patients that had been refractory to standard and multiple second line treatment modalities and improved quality of life. One patient with MMN who responded to IVIg, but had continued weakness improved after treatment with high dose cyclophosphamide without stem cell rescue and was able to discontinue IVIg.

Azathioprine

Azathioprine is a purine antimetabolite. Patients taking allopurinol, must reduce the dose of azathioprine. Toxicity includes leukopenia, thrombocytosis, susceptibility to infections, hepatotoxicity, alopecia, increased risk of cancer and pancreatitis.

Benefit in patients with CIDP has been reported with azathioprine. A controlled study of azathioprine 2 mg/kg for 9 months added to steroids did not show a benefit for azathioprine. This study, however, was small and lacked power to detect all but a large treatment effect. Often, larger doses such as 3 mg/kg are used.

Fludarabine

Fludarabine is an anti-metabolite, which inhibits DNA polymerase, DNA primase, ligase, and ribonucleotide reductase and is incorporated into DNA and ribonucleic acid. It may inhibit apoptosis. It is given intravenously at 20-30 mg/m² for 5 days. Fludarabine has been successfully used to treat anti-MAG neuropathy.

Mycophenolate Mofetil

Mycophenolate mofetil is a reversible inhibitor of inosine monophosphate dehydrogenase an enzyme in the guanine nucleotide synthesis pathway. Lymphocytes are particularly reliant on this pathway, whereas other white cells can use other pathways. Mycophenolic acid inhibits lymphocyte proliferation and formation of adhesion molecules and migration.

Mycophenolate is more effective than azathioprine in its use for cardiac transplantation. The usual dose is 1000 mg twice a day (bid), though the dose can be increased to 1500 mg bid—the dose (or higher) used for cardiac transplant tolerance. Toxicity is gastrointestinal, including nausea and diarrhea, and hematologic. There is an increased susceptibility to infections. There is an increased incidence in lymphoma, and central nervous system (CNS) lymphoma has been seen.

Efficacy

In a group of 12 refractory CIDP patients 30% improved by either 1 Rankin grade or were able to reduce their use of IVIg. Some of these patients also were able to reduce their use of prednisone. In a group of eight refractory patients with IgM monoclonal associated neuropathy one patient improved with mycophenolate. He had a 62% reduction in his total IgM.

INTERFERONS

Beta interferons have multiple affects on the immune system. They inhibit T cell proliferation. They increase anti-inflammatory Th-2 cytokines, such as IL-2 and IL-4 and decrease pro-inflammatory Th-1 cytokines, such as IL-2, TNF-α and interferon-γ. Suppressor T-cell function is enhanced and there is downregulation of major histocompatibility complex class II molecules, chemokines, and their receptors. Several preparations are available and the medication is given subcu-
Patients with CIDP have improved with alpha interferon and beta interferon in several small studies, although a small, randomized controlled study did not demonstrate benefit. A large multicenter randomized controlled trial of rituximab with beta interferon has also been reported for MMN.

**ETANERCEPT**

Etanercept is a recombinant human TNF-receptor fused to the Fc fragment of human IgG1, which binds to TNF-α, a pro-inflammatory cytokine. The typical dose is 25 mg, given subcutaneously, twice a week.

Side effects can include infection, both site reactions, and a susceptibility to infection. Serious infections may occur, and the medication should be discontinued during infections. Mortality may be increased in patients with congestive heart failure.Central nervous system demyelination has been reported to follow the use of etanercept. Patients should be screened for tuberculosis, prior to use and should be avoided in patients with CNS demyelination and congestive heart failure. An open label study of 10 patients with CIDP noted improvement in 30% and possible improvement or stabilization in another 30%.

**RITUXIMAB**

Rituximab, a human mouse chimeric monoclonal antibody (IgG1 kappa isotype), binds to the lymphocyte molecule CD-20. The exclusive presence of this antigen on B cells from the pre-B cell developmental phase until differentiation into the plasma cell accounts for the drug's specificity. It induces both complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity. Rituximab treatment was initially approved for the treatment of non-Hodgkin's B-cell lymphoma. Recently, its use has been expanded to nonmalignant disorders.

The usual dose is 375 mg/m² given in four weekly intravenous infusions. Rituximab is usually well-tolerated. Side effects include mucocutaneous reactions or more commonly “cytokine release syndrome.” Fever, chills, hypotension, and dyspnea during the first infusion were not observed.

Rituximab has been beneficial for patients with anti-MAG neuropathy and MMN associated with GM1 antibodies. Benefit is noted from 2-6 months. In three trials of rituximab there was an average of a 31%, 58%, and 55% reduction in total IgM levels. Rituximab depletes mature B-lymphocytes for 6-9 months. It does not affect stem or plasma cells, which do not express the CD 20 antigen. The therapeutic benefit for lymphoma patients averages 1 year. In one study of rituximab for polyneuropathy, 50% of patients reported loss of benefit at 1 year, with deterioration having started as soon as 3 months. Retreatment of lymphoma and polyneuropathy patients in both populations has been found safe and effective in small studies.

**COMPARATIVE STUDIES AND GENERAL CONSIDERATIONS**

There is class I evidence (from randomized double-blind placebo-controlled trials) that IVIg and plasmapheresis are beneficial in the treatment of CIDP. The spectra of early and late side-effects of IVIg, plasmapheresis, and corticosteroids need to be taken into account when choosing treatment modalities for patients. For patients with chronic progressive CIDP requiring treatment, IVIg is the usual first line treatment and is started to determine the level of benefit. Further treatment with IVIg or another modality depends on the level of efficacy of IVIg in this initial trial of IVIg. For many patients, IVIg provides adequate monotherapy.

Using a treatment response as defined by a 1-grade improvement on the modified Rankin scale, not all patients respond to IVIg, corticosteroids, and plasmapheresis. Some patients who did not respond to one of these three initial treatments, would respond to a trial of a second or third of these three treatments. Response to at least one of these three main therapies was seen in 66% of patients.

Several small studies have noted no statistical difference in the short-term efficacy of corticosteroids, IVIg, or plasmapheresis. In a study comparing prednisone to IVIg, despite no difference in short-term efficacy over 6 weeks, quality-of-life improved in patients receiving IVIg, but not in those receiving prednisone. Similar studies are not available for periods of greater than 6 weeks; however CIDP is a chronic disease and the well-known, long-term side effects of using IVIg would likely impact outcome if these were conducted. The long-term costs related to treatment of side-effects of chronic steroid use, such as diabetes, avascular necrosis of the hip, hypertension, fractures, and cataracts have been shown to be substantial in other diseases.

Some investigators have designated regional variants of CIDP including the Lewis-Sumner syndrome or multifocal acquired demyelinating sensory and motor neuropathy, distal acquired demyelinating symmetric neuropathy, and sensory CIDP. These regional variants of CIDP respond to treatment in a similar manner to CIDP in its classic presentation, although the ability to measure improvement is impacted by the clinical presentation. Sensory findings may
be more difficult to assess objectively. Scales of gait and posturography may be helpful.\textsuperscript{10} One small retrospective series suggested that a larger number of patients with Lewis-Sumner syndrome may respond to IVIg than prednisone.\textsuperscript{158}

Benefit in patients with anti-Mag neuropathy is seen when the total IgM is reduced by 25%.\textsuperscript{68} Some patients with anti-Mag neuropathy have a relatively benign course and the risks of treatment may outweigh the benefit.\textsuperscript{116} However, new treatments such as rituximab are better tolerated.

**Maintenance Treatment**

Less than one-third of patients with CIDP remain in remission without therapy.\textsuperscript{5,64} Ongoing maintenance treatment is required in the majority of patients. Treatment should be continued, until the benefit is maximized.\textsuperscript{5,15,84}

Some patients, including those with severe axonal loss may require additional treatment before seeing a response.\textsuperscript{66,106} Axonal loss and motor neuron loss of up to 50\% can occur in CIDP, correlating with the severity and duration of the disease, which likely results in some functional decline that is irreversible.\textsuperscript{111} Therefore early treatment to prevent neuronal and axonal loss should be a goal. Intravenous immunoglobulin given as maintenance for up to 51 months was successful in 64\% of patients and plasmapheresis given for up to 60 months was successful in 70\% of patients.\textsuperscript{32}

With all immune peripheral neuropathies, it is likely best to provide regular maintenance in order to prevent a relapse, rather than waiting for a decline in strength before repeating an infusion since functional recovery in CIDP is likely impaired by secondary loss of axons and motor neurons.\textsuperscript{112}

In MMN, some studies have shown axonal loss after long term IVIg.\textsuperscript{145} A recent study suggests that higher maintenance doses approaching the induction dose of 2 g/kg and tailored to the clinical response, prevents axonal degeneration.\textsuperscript{156}

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Emerging Treatment of Inflammatory and Demyelinating Neuropathies

Marinos C. Dalakas, MD
Chief
Neuromuscular Diseases Section
National Institutes of Health
Bethesda, Maryland

INTRODUCTION

Autoimmune peripheral neuropathies (APNs) are potentially treatable or amenable to immunomodulating and immunosuppressive therapies, hence the need for early recognition and accurate diagnosis. Understanding the mechanisms of APNs provides the opportunity to explore how best to suppress the sensitized T cells, antimyelin antibody activity or the molecules associated with T cell transmigration and design target-specific immunotherapies. The most common APNs are listed in Table 1.

This manuscript reviews the rationale for immunotherapies based on T cell or humoral-mediated immunity and describes the most current therapeutic approach.

IMMUNOPATHOLOGY

Autoimmune peripheral neuropathies occur when immunologic tolerance to peripheral nerve components (myelin, Schwann cell, axon, and motor or ganglionic neurons) is lost. In some of these neuropathies there is direct evidence for autoimmune reactivity mediated by specific antibodies or autoreactive T lymphocytes against the peripheral nerve. In others, the underlying immune-mediated mechanism is secondary or indirect, and an autoimmune cause is suspected when the neuropathy coexists with another systemic autoimmune disease or viral infection.

Normally, a network of immune cells and soluble factors meticulously regulates the immune system and maintains a balanced immuno-activity within the local tissue compartment with the ultimate goal to protect its integrity. A key requisite is the maintenance of self-tolerance, i.e., the prevention of immune responses to host/self-antigens. In autoimmune diseases self-tolerance breaks down, autoreactive T and B cells that are part of the normal immune repertoire are unleashed and can engender organ-specific damage. How autoreactivity escapes the regulatory mechanisms is critical, yet still largely unresolved. One theory of special relevance to autoimmune neuropathies is “molecular mimicry.” This term refers to a process in which the host generates an immune response to an inciting factor, most usually an infectious organism, that shares epitopic determinants with the host’s affected tissue. In Guillain-Barré syndrome (GBS), at least in some of its forms, shared epitopes between the bacterial species campylobacter jejuni and haemophilus influenzae, or cytomegalovirus (CMV) and nerve fibers have been identified as targets for aberrant cross-reactive immune responses. How autoreactivity escapes the regulatory mechanisms is critical, yet still largely unresolved. One theory of special relevance to autoimmune neuropathies is “molecular mimicry.” This term refers to a process in which the host generates an immune response to an inciting factor, most usually an infectious organism, that shares epitopic determinants with the host’s affected tissue. In Guillain-Barré syndrome (GBS), at least in some of its forms, shared epitopes between the bacterial species campylobacter jejuni and haemophilus influenzae, or cytomegalovirus (CMV) and nerve fibers have been identified as targets for aberrant cross-reactive immune responses.

Another element of cellular mimicry is based on the association of certain neuropathies, such as chronic inflammatory demyelinating polyneuropathy (CIDP) or paraneoplastic sensory neuropathies, with tumors. Although CIDP is rarely associated with carcinomas, there is a special connection with melanoma. This is of great interest because both melanoma and Schwann cells derive from neural crest tissues.
and share common antigens. A number of carbohydrate epitopes expressed on human melanoma or melanomatous cell lines, including gangliosides GM3, GM2, GD3, GD2, have been implicated in human neuropathies. Some patients with melanoma, after therapy by vaccination with melanoma lysates, develop CIDP. The serum from one of this author’s CIDP patients immunoreacted with and contained high titer antibodies against GM2, while her melanomatous tumor was rich in GM2-positive cells. In paraneoplastic sensory neuropathies with anti-Hu antibodies, the Hu protein is also present in the small-cell lung cancer, suggesting an autoimmune reaction against antigens shared by both the tumor cells and the dorsal root ganglionic neurons. The molecular mimicry hypothesis cannot, however, explain the entire clinical spectrum and laboratory findings of autoimmune neuropathies. It appears that these neuropathies emerge from a synergistic interaction of cell-mediated and humoral immune responses to still incompletely characterized peripheral nerve antigens.

The nerves of GBS patients possess two prominent histologic features: (1) perivascular and endoneurial inflammatory infiltrates consisting of lymphocytes and macrophages and (2) segmental demyelination in areas associated with the lymphoid infiltrates. Although among the infiltrates CD4+ cells appear to predominate over CD8+ cells and macrophages, if one takes into account that 70% of tissue macrophages express CD4, macrophages are a dominant cell population. Macrophages break through the basement membrane of healthy Schwann cells and make direct contact with the outermost myelin lamellae, leading finally to lysis of the superficial myelin sheath. Macrophages may exert their myelinolytic activity via lymphokines, especially interleukin (IL)-1. Interferon-g released by the activated T cells, or complement activation, may also serve as chemotactic factors increasing the capillary permeability and enhancing recruitment of additional macrophages. When the demyelination is extensive, it is associated with axonal degeneration. The degree and effectiveness of remyelination and axonal regeneration dictate the degree of clinical recovery. Other studies indicate that activated T cells play a role in GBS. Further, levels of IL-2 and soluble IL-2 receptors are increased in the serum during the acute phase of GBS and decline during recovery, suggesting ongoing T cell proliferation.

Although CIDP is defined as an inflammatory polyneuropathy, there are only minimal signs of inflammation. The predominant endoneurial mononuclear cell in CIDP is the macrophage and not the lymphocyte. Electronmicroscopic observations have clearly shown that in CIDP the demyelinating process is associated with the presence of macrophages, which sequentially penetrate the basement membrane of the Schwann cell, displace the cytoplasm, and finally disrupt the myelin by focal lysis of the superficial myelin lamellae. A macrophage Fc receptor and complement CR1-receptor-mediated phagocytosis may, therefore, be an important mechanism of myelin destruction.

HUMORAL FACTORS IN GUILLAIN-BARRÉ SYNDROME, CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY, PARAPROTEINEMIAS, AND MULTIFOCAL MOTOR NEUROPATHY

There is much stronger evidence that circulating serum factors are responsible for the cause of GBS and other chronic demyelinating neuropathies. On clinical grounds, this is supported by the beneficial effect of plasmapheresis for GBS and CIDP, presumably by removing putative antibodies. On laboratory grounds, this is supported by the variety of autoantibodies or their effects detected in the patients’ serum based on the following observations: (a) serum from the acute phase of GBS can demyelinate rodent dorsal root ganglionic extracts in a complement-dependent manner; (b) GBS serum

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<th>Table 1 Common autoimmune neuropathies</th>
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<tr>
<td>1. Guillain-Barré syndrome and clinical variants (Miller-Fisher syndrome, pharyngeal-cervical branchial plexopathy, lumbar polyradiculopathy and plexopathy, pure sensory ataxic neuropathy, acute axonal motor neuropathy)</td>
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<td>2. Chronic inflammatory demyelinating polyneuropathy (CIDP) and its newly recognized variants</td>
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<td>a. IgG and IgA monoclonal gammopathy</td>
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<td>b. Polyneuropathy, organomegaly, endocrinopathy, myeloma, and skin changes (POEMS) syndrome</td>
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<td>c. Polyneuropathy with IgM monoclonal gammopathies (demyelinating-anti- myelin-associated glycoprotein, sensorimotor, ataxic, and pure motor with GM1 antibodies)</td>
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<td>d. Cryoglobulinemic polyneuropathy</td>
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<td>4. Multifocal motor neuropathy with conduction block, often associated with GM1 antibodies</td>
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<td>5. Paraneoplastic neuropathies associated with anti-Hu antibodies</td>
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<td>6. Vasculitic neuropathies</td>
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injected into rat sciatic nerves causes demyelination and conduction block;\(^5\) (c) IgG, IgM, complement and membranolytic attack complex are deposited in the nerves of both GBS\(^25\) and CIDP\(^11\) implying complement-fixing antibody activity;\(^1,11\) (d) IgG or IgM anti-acidic glycolipid antibodies are seen in up to 68\% of GBS and up to 50\% of CIDP patients;\(^30\) and (e) anti-ganglioside antibodies are implicated in GBS, CIDP, paraproteinemia, and multifocal motor neuropathy (MMN). Gangliosides are widely distributed within the nervous system and various, such as GM1, are present at the nodes of Ranvier. GM1 antibodies are detected in up to 50\% of patients with MMN\(^43\) but their role in the pathogenesis of the disease remains still unclear. One ganglioside that correlates with a specific clinical syndrome is the GQ1b. Anti-GQ1b IgG antibodies appear to be specifically associated with the Miller-Fisher variant of GBS because they are present in almost 90\% to 100\% of these patients.\(^5\) Such antibodies have also been found in patients with IgM paraproteinemic polyneuropathies\(^31,32\) but in ophthalmologic GBS these antibodies are of the IgG class and do not recognize other polysialogangliosides.

Evidence for a role of antibodies in the pathogenesis of CIDP remains weak. In addition, regarding the glycolipids previously mentioned, up to 20\% of CIDP patients have also anti-P0 antibodies.\(^37\) In IgM paraproteinemic neuropathies, anti-ganglioside or glycolipid antibodies are observed in 75\% of patients with the most common being the myelin-associated glycoprotein (MAG), a 100-kDa glycoprotein of the central and peripheral nerve myelin.\(^35,36\) The anti-MAG IgM paraproteins coreact with an acidic glycolipid in the ganglioside fraction of the human peripheral nerve, the sulfoglucuronyl glycosphingolipid (SGPG).\(^32\) Sera from a number of patients with predominantly sensory demyelinating neuropathy react with various gangliosides, such as those containing a disialo-syl moiety, or with GalNac-GM1b and GalNAc-GD1a, GM1, GD1b or sulfatides.\(^13\)

**Inflammatory Mediators**

Upregulation of cytokines, chemokines, adhesion molecules, and metalloproteinases both at the protein and messenger ribonucleic acid level has been repeatedly noted for GBS and CIDP neuropathies. These molecules allow for the transmigration of T cells to the nerve, activate resident macrophages, and facilitate the continuation of the immune response.\(^26\) These molecules are targets for immunotherapy using the new available agents, as discussed later.

**Concomitant axonal loss**

It is now increasingly recognized that these neuropathies although demyelinating, are invariably associated with a concomitant axonal loss attributed to the primary demyelinating process or to the initial immune attack against both myelin and axonal determinants.\(^7,21,27\) The observation is important because the long term prognosis clearly depends on the magnitude of axonal loss rather than on demyelination. Analogous observations have been made and emphasized in multiple sclerosis to explain the permanent deficits in that disease. Whether the release of neurotoxic cytokines, such as tumor necrosis factor alpha and toxic mediators such as nitric oxide metalloproteinases enhance the axonal destruction remain unclear. The realization that axonal loss is a prognostic factor dictates the necessity for early initiation of therapy.

**TREATMENT**

Autoimmune peripheral neuropathies comprise potentially treatable disorders amenable to various immunosuppressive, immunomodulating, or chemotherapeutic agents. The selection of an effective protocol is based on the results of experimental therapeutic trials, clinical experience, and risk-benefit ratio of available therapies. The author’s approach to the treatment of each one of these disorders follows.

**GUILLAIN-BARRÉ SYNDROME**

**Supportive care**

The dramatic reduction in mortality of GBS is mainly due to availability of intensive care units (ICUs), improvement of respiratory support, antibiotic therapy, and control of autonomic cardiac dysregulation. A GBS patient is best monitored in an ICU, even if respiratory compromise is not evident at the time of admission. When forced vital capacity drops or bulbar weakness is severe, intubation is in order. A team approach provides the best results.

**Plasmapheresis**

In several double-blind studies,\(^38\) plasmapheresis has been shown to be effective, improving the degree and rate of recovery if performed early in the course of the illness. A continuous-flow machine is preferable and a central venous catheter
may be required for some patients. Based on two controlled studies, plasma exchanges should begin within the first week from onset to be effective. A series of five or six exchanges, with one exchange every other day, is sufficient. Early relapses can occur in up to 20% of patients, who may require a second series of plasma exchanges to abort the relapse. Plasmapheresis is effective even in milder cases. Based on controlled studies two exchanges are sufficient for mild GBS, and four exchanges optimal for moderate cases or mild cases that continue to progress.19

High-dose Intravenous Immunoglobulin

On the basis of two controlled studies using intravenous immunoglobulin (IVIg) versus plasmapheresis,44,54 IVIg, given at 2 g/kg in 2-5 days, has been shown to be equally effective to plasmapheresis. A trial of plasma exchange followed by IVIg added mild but not significant benefit.44 The decision as to which treatment to use first—plasmapheresis or IVIg—is governed by circumstances, availability of the treatment modality, experience, age of patients, and consideration of other associated risk factors.9 Early relapses can also occur with IVIg, as often as with plasmapheresis. Because IVIg is easier to use and more readily available, it has become the treatment of choice worldwide.

Steroids are contraindicated in GBS. In a multicenter trial, it was convincingly shown that oral steroids are ineffective and may even increase the incidence of future relapses. The combination of IVIg with IV methylprednisolone did not add significant benefit compared to IVIg alone.55

CHRONIC INFLAMMATORY DEMYE LINATING POLYNEUROPATHY

Prednisone

Chronic inflammatory demyelinating polyneuropathy is a classically steroid-responsive polyneuropathy. The efficacy of steroids was proven in a controlled study.17 A high-dose regimen of 80-100 mg prednisone daily is initiated and then tapered to every other day.10 The starting dose can be a little lower and the tapering faster in patients with coexisting cardiac disease or severe osteoporosis, or the elderly. The goal of therapy is to increase strength, and not to improve nerve conduction studies. As a steroid-sparing agent, azathioprine, cyclosporin, or mycophenolate can be used. This author’s preference now is mycophenolate because it is safer to use for a long-term period. For more effective immunosuppression however, cyclosporine 150 mg twice a day or cyclophosphamide IV every month is preferred. Rituximab IV, 375 mg/m² once a week for 4 weeks, is becoming a promising agent. All these drugs however, have not been tested in controlled studies.

Intravenous Immunoglobulin

In controlled studies23 IVIg 2 g/kg divided in 2-5 days has been effective in the majority of patients with CIDP. The more chronic the disease and the more severe the axonal degeneration that has taken place, the fewer the chances that the recovery will be complete or significant. Intravenous immunoglobulin can be used effectively as a first line therapy to avoid steroid-related side effects and, in spite of its cost, it is now preferable by most practitioners worldwide. Maintenance infusions with 1 or 2 g/kg every 4-8 weeks is often required.

Plasmapheresis

Plasmapheresis has been effective in controlled studies.24 After a series of six plasma exchanges, maintenance therapy, with one exchange at least every 8 weeks, may be required if this therapy is beneficial. Intravenous immunoglobulin has now replaced plasmapheresis although in this author’s experience, some patients may benefit more from steroids, others more from IVIg, and still others more from plasmapheresis.

Combination Therapies

In open-label studies with small numbers of patients or in case reports, other forms of treatment have been tested for difficult cases. Beneficial effects in previously treatment-resistant CIDP patients can be seen with the combination of plasmapheresis followed by IVIg, or IVIg with one of the following: mycophenolate mofetil, cyclosporin A, steroids, etanercept, cyclophosphamide, or stem cell transplantation.34,45 Adding β-interferon offers no significant benefit.45

All evidence stated above concerning the efficacy of plasma exchange, IVIg and corticosteroids comes from short-term studies. Plasma exchange and IVIg are expensive therapies and need to be continued to maintain benefit for the long term. There is clearly a need for controlled studies to assess the long-term efficacy and safety of IVIg, steroids, or plasma exchange in CIDP and perform comparative pharmacoeconomic studies.

Polyneuropathy with Paraproteinemias

Patients with benign IgG or IgA demyelinating polyneuropathies respond similarly to CIDP patients. The patients with malignant paraproteinemias should be treated with chemotherapy as needed for the underlying malignant disease. Sometimes the neuropathy may respond to chemother-
apy. When the neuropathy is axonal, treatments are, in general, disappointing.

Patients with benign monoclonal gammopathy of undetermined significance IgM anti-MAG demyelinating neuropathy may not require therapy if the disability is mild, i.e., minimal gait ataxia. Therapy is however attempted when disabling symptoms develop. There are patients who have responded to prednisone with chlorambucil, plasmapheresis, or IVIg, but the degree and rate of improvement are minimal and quite variable. A controlled study with IVIg showed minimal but not significant benefit in only 3 of 11 patients. Adding interferon shows no significant benefit. Recent open-label studies described improvement with rituximab, a chimeric humanized monoclonal antibody against CD20 antigen which reduces B lymphocyte counts. However, data based on randomized, controlled studies with a sufficient number of patients are not available to allow conclusive treatment recommendations with any of these therapeutic approaches. A controlled study with rituximab has been completed at the National Institute of Health and the data analyzed. (Dalakas MC: Principal Investigator).

Multifocal Motor Neuropathy

Multifocal motor neuropathy is a distinct disease that should be recognized because it is treatable. It affects males more than females, and it is more common in people younger than 50 years of age. Multifocal motor neuropathy had two distinct laboratory criteria, namely, multifocal conduction block in motor nerves, as determined by electrophysiology, and high GM1 antibody titers determined by enzyme-linked immunosorbent assay test that can be seen in up to 50% of patients.

Multifocal motor neuropathy responds to IVIg, which is the treatment of choice. The efficacy of IVIg has been demonstrated in controlled trials. On maintenance therapy, these patients continue to respond up to 10 years after initiation of therapy. Steroids are ineffective in MMN and may worsen the disease. Plasmapheresis is also ineffective. Cyclophosphamide is effective but toxic for long-term use. Aggressive treatment with cyclophosphamide followed by plasmapheresis and then IVIg has also been shown to be of benefit in difficult cases. Rituximab is emerging as an effective agent in difficult cases, based on anecdotal reports in a small series of patients.

Paraneoplastic Neuropathy

Some of these patients have, anecdotally, responded to plasma exchange or IVIg, but overall, this neuropathy is not responding well to available therapies.

Vasculitic Neuropathies

Patients with isolated peripheral nerve vasculitis are treated less aggressively than patients with systemic vasculitis. A combined treatment of prednisone at 1.5 mg/kg/day, and cyclophosphamide is the treatment of choice. Although treatment may vary among patients, the administration of cyclophosphamide may not be necessary for more than 12 months as is the case in systemic vasculitis. Often 6 to 12 months of treatment may suffice. Plasmapheresis and IVIg has been tried with variable and rather disappointing results.

NEW AGENTS AND ONGOING TRIALS

The prospect for semi-specific immunotherapies is heightened by the identification of the following agents currently available or in ongoing trials, directed against the following targets:

1. **Blocking the signal transduction in T lymphocytes.** Three such drugs are now available: (a) humanized monoclonal antibody against IL2-receptor-antagonist which shows promise in patients with multiple sclerosis; (b) a humanized monoclonal antibody called CAMPATH directed against the CD52 molecule associated with T cell activation, causing T cell depletion; and (c) anti-T-lymphocyte globulin;

2. **Agents against co-stimulatory and adhesion molecules.** These include: (a) monoclonal antibodies against LFA-1, and LFA-3, which block the interaction of LFA with ICAM; and (b) anti-integrins and their receptors, such as the monoclonal antibody against 4 integrins, which interferes with transmigration of activated T cells.

SUMMARY

Progress made in the understanding of the immunopathogenesis of autoimmune neuropathies has helped physicians to apply or design more effective therapies. In spite of successes, better therapies and long-term data are still needed. The prospects of target-oriented immunotherapies have now increased.

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REFERENCES


INTRODUCTION

Mitochondria are described as the powerplants of the cell because these organelles are responsible for generating most of the cellular energy. Dysfunctions of mitochondria typically cause encephalomyopathies because brain and muscle are often severely affected due to their high-energy requirements. Nevertheless, peripheral neuropathies are being recognized with increasing frequency in multisystem mitochondrial diseases and can be the presenting or predominant clinical feature of mitochondrial disorders such as neuropathy ataxia retinitis pigmentosa (NARP), or mitochondrial neurogastrointestinal neuropathy (MNGIE). In addition, pure peripheral neuropathy can be caused by mitochondrial dysfunction as exemplified by Charcot-Marie-Tooth (CMT) type 2A which is caused by defects in mitofusin 2, a mitochondrial protein required for fusion of mitochondria.

Although mitochondria perform multiple metabolic functions, by convention, the term “mitochondrial diseases” refers to disorders caused by defects in the respiratory chain enzymes and oxidative-phosphorylation. Energy is derived from the breakdown of carbohydrates and fats that liberate reducing equivalents (electrons) which are transported through four respiratory chain enzymes (complexes I-IV) embedded in the mitochondrial inner membrane and generate a proton gradient which is used by complex V to produce adenosine triphosphate (ATP).

Mitochondria are unique mammalian organelles because they possess their own genetic material, mitochondrial deoxyribose nucleic acid (mtDNA) a small (16.5 kilobases) circular molecule. Each mtDNA encodes 22 transfer ribonucleic acid (tRNA), 13 polypeptides, and two ribosomal RNAs (rRNA). The mtDNA-encoded polypeptides are functionally important, because they are subunits of the respiratory or electron transport chain. The mitochondrial genome has several distinctive features. First, mtDNA is densely packed with genetic information that is required for respiratory chain functions and oxidative phosphorylation. Second, each mitochondrion contains 2-10 copies of mtDNA and, in turn, virtually all cells contain numerous mitochondria, therefore, hundreds to thousands of copies of mtDNA are present in each cell. Third, mtDNA is almost always transmitted maternally. These unusual characteristics of mtDNA lead to the peculiar clinical features of mutations in the mitochondrial genome.

Because mtDNA contains no introns and few noncoding segments, alterations of this genome are often deleterious. Mutations in mtDNA are typically transmitted maternally to both male and female progeny; however, not all individuals
with a mtDNA mutation are equally affected. This is because (1) variable proportions of mutant and normal mtDNA typically co-exist within cells (heteroplasmy), (2) mutation burden usually varies from one organ to another (tissue distribution), and (3) tissues with high-energy requirements are more susceptible to mtDNA mutations (threshold effect).

Although much attention has been focused on mtDNA mutations in human disease, in fact, the vast majority of the mitochondrial proteins are encoded in the nuclear DNA (nDNA). Therefore, it is not surprising that numerous autosomal mitochondrial diseases exist and over the last decade, nDNA mutations have been identified in many mitochondrial encephalomyopathies.6,9

PERIPHERAL NEUROPATHIES IN WELL-DEFINED MITOCHONDRIAL DISEASES

Most mitochondrial patients with peripheral neuropathies have mild and chronically progressive distal sensorimotor dysfunction with stocking-glove sensory loss, distal limb weakness, and less commonly absent tendon reflexes. The neuropathy is typically axonal, but can be demyelinating.4,11,31

Diseases Due to Mitochondrial Deoxyribose Nucleic Acid Mutations

Neuropathy Ataxia Retinitis Pigmentosa/Maternally Inherited Leigh Syndrome

Neuropathy, ataxia, and retinitis pigmentosa are the defining clinical characteristic of NARP15, a maternally inherited disorder. In addition, patients often have developmental delay, dementia, seizures, and ataxia. Patients with NARP may have both proximal and distal neurogenic weakness, loss of vibratory sensation, and absent tendon reflexes.34 Neurophysiological studies are compatible with a sensorimotor axonal polyneuropathy, but muscle biopsies do not show ragged-red fibers (RRF). Most NARP patients have a heteroplasmic missense mutation, T8993G, causing a leucine to arginine substitution in subunit 6 of mitochondrial ATP synthase.15 The mutation affects the proton channel of the F0 segment of complex V and impairs ATP synthesis.39 Three other mutations in ATPase subunit 6 cause NARP: T8993C, T9176G, and T9176C.35

Patients with 70-90% mutant heteroplasmy typically develop NARP. In contrast, individuals with greater than 90% mutation usually present with maternally inherited Leigh syndrome (MILS).33,38 Leigh syndrome is a subacute necrotizing encephalomyelopathy and is clinically characterized by developmental regression, generalized hypotonia, feeding prob-

Mitochondrial Encephalomyopathy Lactic Acidosis and Stroke-like Episodes

Mitochondrial encephalomyopathy lactic acidosis (MELAS) is a multisystem disorder characterized by stroke-like episodes, encephalopathy (evident as seizures or dementia), mitochondrial myopathy, and lactic acidosis.13,26 Other common clinical features include migraine headaches, short stature, hearing loss, diabetes mellitus, and peripheral neuropathy. The prevalence of neuropathy in MELAS has been estimated to be 22%.18 Mitochondrial encephalomyopathy lactic acidosis patients generally have sensory more than motor distal peripheral neuropathies with diminished or absent tendon reflexes and decreased vibration sensation. Electrophysiological studies are consistent with axonal or mixed axonal and demyelinating neuropathy, but pure demyelinating neuropathy has also been observed.18 About 80% of MELAS patients have a heteroplasmic A3243G mtDNA mutation in the tRNALeu(UUR) gene, but at least 14 additional mtDNA mutations have been associated with this phenotype.

Myoclonus Epilepsy Ragged-red Fibers

Myoclonus epilepsy ragged-red fibers (MERRF) is another multisystem mitochondrial disease and is clinically defined by myoclonus, generalized epilepsy, ataxia, and RRF on muscle biopsy. Besides the defining criteria, other common clinical manifestations include impaired hearing, dementia, axonal peripheral neuropathy, short stature, exercise intolerance, and lactic acidosis. In a review of 62 reported MERRF patients, 63% had peripheral neuropathy.3 Although typically a mild sensorimotor peripheral neuropathy, the neuropathy may be symptomatic and occasionally severe.21 Nerve conduction studies show decreased amplitudes of compound motor action potentials (CMAPs), sensory nerve action potentials (SNAPs), or both indicating axonal dysfunction. Sural nerve biopsies have revealed reductions of large myelinated fibers.7

Multiple Symmetric Lipomatosis

Multiple symmetric lipomatosis (MSL) or Madelung disease is characterized by multiple nonencapsulated lipomas around the neck and shoulder-girdle region.22 Most patients also have a predominantly axonal sensorimotor peripheral neu-
### Table 1  Peripheral neuropathies in mitochondrial disorders

<table>
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<td>Maternally inherited Leigh syndrome (MILS)</td>
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<td>Sensory = Motor</td>
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<td>MELAS</td>
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<tr>
<td>KSS</td>
<td>Pigmentary retinopathy, PEO, cardiac conduction block, ataxia</td>
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<td>MSL</td>
<td>Lipomas, ataxia, neuropathy, deafness</td>
<td>Axonal &gt; Demyelinating</td>
<td>Blood DNA test (MERRF mutation), if negative, muscle biopsy for RRF and multiple mtDNA deletions</td>
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<td>MNGIE</td>
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<td>Blood test for thymidine phosphorylase activity and plasma levels of thymidine and deoxyuridine</td>
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<td>Sensory</td>
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DNA = deoxyribose nucleic acid; KSS = Kearns-Sayre syndrome; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERRF = myoclonus epilepsy with ragged-red fibers; MNGIE = mitochondrial neurogastrointestinal encephalomyelopathy; MSL = multiple symmetric lipomas; mtDNA = mitochondrial DNA; NARP = neuropathy, ataxia, and retinitis pigmentosa; NNH = Navajo neurohepatopathy; PEO = progressive external ophthalmoplegia; RRF = ragged-red fiber; SANDO = sensory ataxic neuropathy, dysarthria, and ophthalmoparesis.
ropathy and about 50% have central nervous system dysfunction. In addition, cerebellar ataxia, hearing loss, optic atrophy, pyramidal signs, and myopathy are associated features. The neuropathy is typically mild with decreased vibratory and proprioceptive sensations and decreased or absent tendon reflexes. Nerve conduction studies typically show diminished amplitudes with mildly reduced conduction velocities indicating axonal neuropathy. Needle electromyography (EMG) may show myogenic units in proximal muscles and neurogenic abnormalities in distal muscles. Muscle biopsies usually reveal COX-negative RRF and either the MERRF A8344G mtDNA mutation or multiple deletions of mtDNA. When associated with multiple mtDNA deletions, the disorder is presumably due to a primary nDNA defect.

Leber Hereditary Optic Neuropathy

Leber hereditary optic neuropathy (LHON) typically manifests in young adults as subacute unilateral loss of central vision followed weeks or months later by vision loss in the other eye. Cardiac pre-excitation is a common associated feature and, in one series, peripheral neuropathy was observed in 11%. Biopsies of sural nerve has revealed signs of axonal degeneration and demyelination. Over 90% of LHON patients harbor one of three mutations in mtDNA-encoded subunits of complex I: G11778A in ND4, G3460A in ND1, and T14484C in ND6.

Sporadic Chronic External Ophthalmoplegia and Kearns-Sayre Syndrome

Sporadic chronic external ophthalmoplegia (PEO) is a muscle-specific disorder manifesting with ptosis and extra-ocular muscle weakness; however, facial, oropharyngeal, and proximal limb muscles may also be weak. Kearns-Sayre syndrome (KSS) is a multisystem disease with onset before age 20, PEO, and pigmentary retinopathy, in addition to one of the following triad: cardiac conduction block, cerebellar ataxia, and elevated cerebrospinal fluid protein (above 100mg/dl). Both disorders are typically caused by single large-scale deletions of mtDNA. Peripheral neuropathy is uncommon in these disorders and may be subclinical, although axonal degeneration has been observed in a sural nerve biopsy.

Parkinsonism, Deafness, and Neuropathy

A patient reported with levodopa responsive parkinsonism, deafness, and axonal and predominantly sensory neuropathy who had an mtDNA point mutation, T1095C, in the 12S rRNA gene. Maternal relatives had deafness or parkinsonism. Nerve conduction studies in the proband revealed low or absent sensory amplitudes with normal motor nerve conduction velocities while needle EMG showed abnormalities consistent with chronic denervation.

Diseases Due to Nuclear Deoxyribose Nucleic Acid Defects

Mitochondrial Neurogastrointestinal Encephalomyopathy

Mitochondrial neurogastrointestinal encephalomyopathy is an autosomal recessive disease characterized by PEO, severe gastrointestinal dysmotility leading to cachexia, peripheral neuropathy, and leukoencephalopathy. The disorder is caused by loss-of-function mutations in the gene encoding thymidine phosphorylase and has been associated with multiple deletions, depletion, and point mutations of mtDNA.

Mild to severe sensorimotor peripheral neuropathy has been identified in all MNGIE patients and is the presenting clinical feature in 11%. Nerve conduction studies are typically consistent with demyelinating neuropathy although about one-third also show mixed axonal and demyelinating features. The peripheral neuropathy of MNGIE can mimic acquired demyelinating neuropathies. Bedlock and colleagues described five patients who presented with predominant neuropathies were initially misdiagnosed with chronic inflammatory demyelinating polyneuropathy (CIDP). In addition, MNGIE has been misdiagnosed as CMT. Nerve biopsies have revealed loss of myelinated fibers, segmental demyelination and remyelination, and occasional onion bulb formation. Electron microscopy has revealed morphological abnormal mitochondria in Schwann cells.

SENSORY ATAXIC NEUROPATHY, DYSARTHRIA, AND OPHTHALMOPARESIS

As the acronym implies, sensory ataxic neuropathy, dysarthria, and ophthalmoparesis (SANDO) are the clinical hallmarks of this disease. In addition, ptosis, migraine headaches, depression, and RRF on muscle biopsy are additional associated features. Multiple deletions of mtDNA are detectable in muscle. Autosomal recessive mutations in the mtDNA polymerase catalytic subunit POLG, have been identified in SANDO patients. In addition, German siblings with SANDO and unaffected parents harbored a single
heterozygous mutation in the C10Orf2 gene encoding twinkle, a mitochondrial helicase, suggesting autosomal dominant transmission from germline mosaicism.17

Navajo Neurohepatopathy

Navajo neurohepatopathy (NHH) is an autosomal recessive disorder with an incidence of about 1 in 1600 live births among Navaho Indians in the Southwest of the United States.16 The diagnosis requires the presence of four of the following seven criteria: (1) sensory neuropathy; (2) motor neuropathy; (3) corneal anesthesia, ulcers, or scarring; (4) liver disease; (5) documented metabolic or immunological abnormalities; (6) central nervous system demyelination; and (7) family history of NHH.37 The average age-at-onset is 13 months and most do not live beyond the first decade. Children present with either Reye-like syndrome or severe sensorimotor peripheral neuropathies manifesting as hypotonia, weakness, hyporeflexia, and delayed motor development. Routine laboratory studies reveal elevated liver function tests and lactic acid. Serum CK may be elevated up to 10-fold above the upper limit of normal.41 Sural nerve biopsies show paucity of large and small caliber myelinated fibers with degeneration and regeneration of unmyelinated axons.1 Liver biopsies have demonstrated ultrastructurally abnormal mitochondria with ringed cristae, swelling and loss of cristae, and pleomorphic mitochondria.16 In addition, liver samples have revealed depletion of mtDNA and defects of respiratory chain enzymes leading to the hypothesis that NHH is caused by a nDNA-encoded protein involved in mtDNA maintenance.41

Charcot-Marie-Tooth and Mitochondria

Of the 24 genetically distinct forms of CMT disease,36 mitochondrial abnormalities may contribute to the pathogenesis of some CMT subtypes. The most clear example is CMT 2A-2 an autosomal dominant axonal peripheral neuropathy caused by mutations in MFN2, the gene encoding mitofusin 2.44 Embedded in the mitochondrial outer membranes, mitofusins 1 and 2 are GTPase proteins that control fusion of these dynamic organelles which normally undergo continual cycles of fusion and fission.20 In contrast, CMT 2A-1 is caused by mutations in KIF1Bb, a member of the kinesin family of cellular motor proteins.43 Kinesins are tiny molecular motors that transport organelles and materials along microtubular tracks in cells. KIF1Bb mutations affect anterograde axonal transport and appear to disrupt movement of mitochondria in peripheral nerves.43 In contrast, both retrograde and anterograde axonal transport appear to be impaired by mutations in the neurofilament light chain gene that cause CMT 2E.28 Finally, patients with CMT 4A, a severe infantile-onset peripheral neuropathy, have mutations in the gene encoding ganglioside-induced differentiation-associated protein 1 (GDAP1) which has been localized to mitochondria.27 It is thought that GDAP1 is required for maintenance of the mitochondrial network.27

Therapies of Mitochondrial Peripheral Neuropathies

Since specific treatments for mitochondrial peripheral neuropathies have not yet been developed, currently available therapies are symptomatic. Noxious factors that may contribute to the peripheral neuropathy should be identified and treated. For example, diabetes mellitus is common in mitochondrial disorders and may cause or exacerbate peripheral neuropathies. Drugs that are toxic to peripheral nerves should be avoided in patients with mitochondrial neuropathies as exemplified by a double-blind placebo-controlled study of a lactate lowering agent, dichloroacetate, in patients with MELAS (submitted for publication). Another medication that should be used with caution in mitochondrial patients is linezolid, an oxazolidinone antibiotic that may cause optic and peripheral neuropathy, myelosuppression, and lactic acidosis due to postulated inhibition of mitochondrial protein synthesis.25

Pain and dysesthesias caused by sensory neuropathies may be treated by standard pharmacological agents and proper care to prevent pressure sores. Distal leg weakness should be treated with orthoses if proximal muscle weakness is not prominent.

Because defects of respiratory chain enzymes may lead to increased production of toxic reactive oxygen species, patients with mitochondrial diseases often take antioxidants although clear benefit in double-blind placebo-controlled trials is lacking.

SUMMARY

Ultimately, therapies for the underlying causes of mitochondrial diseases will be developed. Potentially useful therapeutic strategies include: heteroplasmic shifting (lowering the mutation burden in patients with heteroplasmic mtDNA mutations), gene therapy, and removal of noxious agents (elimination of excess thymidine in MNGIE).

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