Peripheral Neuropathy

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Patients who have peripheral neuropathy present in a variety of scenarios to the office, to the emergency department, and at times in the setting of other major medical problems. The majority of patients can be diagnosed, classified, and managed based on history and physical examination.

PATIENT ONE: ACUTE PERIPHERAL NEUROPATHY

Question: How to Approach a Patient who Presents with Symptoms of Acute or Rapidly Developing Peripheral Neuropathy?

Case presentation 1
A 31-year-old farmer presents with 48 hours of progressive difficulty described as initial trouble with getting up out of a chair and going up and down stairs with subsequent trouble walking, decline in balance, and heaviness in the arms. The patient noted several days of a febrile illness with abdominal cramps, loose stools, and malaise before the onset of these symptoms. Past medical and family histories are unremarkable.

Examination shows 4/5 strength involving arms and legs with slightly greater weakness proximally than distally. There is reduced position and vibration sense at the toes and ankles. Muscle stretch reflexes are absent throughout. Cranial nerve function is normal and forced vital capacity (FVC) is 5 L.

Discussion
This patient presented with an acute progressive quadriparesis heralded by a gastrointestinal illness. The examination suggests that the weakness likely was at the level of the motor unit (anterior horn cell, roots, peripheral nerve, neuromuscular junction, or muscle). The presence of somewhat more weakness proximally than distally raised the question of a myopathy but the finding of sensory deficit in the feet pointed toward a localization, including sensory and motor function. Thus the likely localization was the sensory motor peripheral nerve and or the roots. As all neurologists have seen, there are patients who present with an acute myelopathy in whom the examination looks more peripheral than central. Patients who have spinal cord infarction or transverse myelitis and even some who have compressive lesions may present with an
acute progressive quadiparesis, reduced stretch reflexes, reduced muscle tone, and variable form of sensory deficit, and it may be challenging to know with certainty that the problem is peripheral rather than a myelopathy. As a general rule, even if patients are experiencing the phenomenon of acute spinal shock with reduced tone and hypoactive muscle stretch reflexes, the majority of such patients display an extensor toe sign in the early phase of their illness. Also, as a general rule, if clinicians are not completely certain that a problem is peripheral, then it behooves them to obtain immediate MRI of the spine.

The presence of proximal weakness more than distal or, in some patients, arm weakness worse than leg can make the diagnosis of peripheral neuropathy less obvious. Many clinicians consider patients who have distal more than proximal and leg more than arm weakness as reflecting the distribution of peripheral neuropathy, but a significant proportion of patients who have acute peripheral neuropathy may present otherwise.

The differential diagnosis for the patient (discussed in Case Presentation 1) is headlined by acute inflammatory demyelinating polyradiculoneuropathy (acute inflammatory neuropathy or Guillain-Barré syndrome [GBS]). The antecedent illness, time course for presentation, and preponderance of motor involvement all are in favor of GBS.

As such, the patient should be admitted to an ICU setting in which he can have meticulous nursing care and vigilant monitoring for respiratory, bulbar, and autonomic dysfunction. For the patient discussed in Case Presentation 1, I would push for an immediate MRI of the entire spine with gadolinium. Routine laboratory tests should be sent off and supplemented with studies (discussed later) for conditions that may mimic GBS depending on the level of certainty of the diagnosis. Tests that can provide evidence to support the GBS diagnosis include a spinal fluid evaluation. I would obtain a cerebrospinal fluid (CSF) examination after looking at the MRI study. Also, blood for GM1 ganglioside antibodies can be useful especially in patients who have a gastrointestinal prodromal illness when looking for Campylobacter jejuni–related GBS. Often the establishment of Campylobacter-related illness helps with the long-term prognosis and realistic expectations for the time course of recovery.

**What is Known About Guillain-Barré Syndrome and How Should Patient Evaluation and Treatment be Handled?**

GBS is considered the prototype “postinfectious” neurologic disorder. The majority of patients describe an antecedent febrile illness, followed in days or weeks by the development of ascending paralysis, which seems to be on the basis of an acute inflammatory peripheral neuropathy. Although most skilled neurologists recognize GBS when they see it, the disorder is heterogeneous and diverse in its antecedent events, clinical presentations, and natural course. Even the name is diverse, with GBS, Landry-Guillain-Barré-Strohl syndrome, acute inflammatory demyelinating polyradiculoneuropathy, and acute inflammatory neuropathy all synonymous.

**History of Guillain-Barré syndrome**

Octave Landry¹ is credited with the earliest description of what has come to be recognized as GBS. In 1859 Landry reported a condition, which he called acute ascending paralysis, describing a patient who had a febrile illness in the springtime, which was followed by the development of sensory symptoms within 2 months. One month later, the patient developed subacute progressive inability to walk due to leg weakness, respiratory failure, and death. Landry pointed out that bowel and bladder function were spared, sensory involvement was mild, and muscles respond to faradic electrical
stimulation. The patient had an autopsy, but this apparently did not include the peripheral nerves. Landry reviewed four other cases from his own experience and five from the medical literature. He emphasized the absence of central nervous system symptoms or signs, the occasional presence of muscle cramps, occasional relapsing course, and the tendency for a favorable outcome. He also noted that two of the cases occurred after an acute illness, two were associated with menstrual irregularities, one was post partum, and one possibly associated with syphilis. Westfall, in 1876, referred to this condition as “Landry’s ascending paralysis.”

Then, in 1916, Guillain and colleagues reported on two soldiers who developed an acute paralysis associated with loss of muscle stretch reflexes. They emphasized the presence of elevated CSF protein concentration with a normal cell count (albumino-cytologic dissociation). Their report did not recognize Landry’s prior observations. Guillain and colleagues state in their original paper, that the illness 

is characterized by motor difficulties, loss of the deep tendon reflexes with preservation of cutaneous reflexes, paresthesias with slight impairment of objective sensation, muscle tenderness, slight alteration in nerve conduction and electromyographic patterns, and a remarkable increase in cerebrospinal fluid albumin in the absence of a cellular reaction (albumino-cytologic dissociation).

Although the general clinical observations are attributed to Guillain and Barré, Andre Strohl probably was responsible for the electrophysiologic aspects. Guillain and Barré further developed their concept of the disease in subsequent publications, including Travaux Neurologiques de Guerre in 1920. Strohl’s name largely was eliminated in the subsequent publications by Guillain and Barré. Death from respiratory failure remained a common outcome until the late 1940s when the development of ICUs and mechanical ventilation allowed for an overall reduction in mortality from GBS. Additional landmarks in clinical thinking on GBS include the observation by C. Miller Fisher of a variant associated with ophthalmoplegia, ataxia, and areflexia, published in 1956.

Pathophysiology

In 1949 the classic clinical pathologic correlations were first reported by Haymaker and Kernohan. In 50 cases of what was called Landry-Guillain-Barré syndrome, they noted predominant inflammatory abnormalities in the anterior spinal roots. Because inflammatory cells were not present in more distal segments of peripheral nerves until late in the illness, they described the disorder as a “polyradiculoneuropathy.” The subsequent seminal neuropathologic study by Asbury and coworkers in 1969 described findings in 19 patients, noting abundant lymphocytic infiltration in spinal roots and nerves, leading them to conclude, “the pathologic hallmark of idiopathic polyneuritis is a perivascular mononuclear inflammatory infiltrate.”

Inflammatory demyelinating neuropathy

The pathology is classically that of a mononuclear inflammatory infiltrate in the endoneurium and myelin sheath. Patchy segmental multifocal demyelination is present along peripheral nerves, including nerve roots, whereas the axons themselves are relatively spared except in more severe cases. Inflammatory infiltrates are comprised of lymphocytes, monocytes, and occasional plasma cells and tend to be perivascular. Less commonly, polymorphonuclear leukocytes are seen. The abnormalities are prominent around ventral roots and in the plexus and proximal nerve trunks but in some cases are present to an equal or greater extent distally along peripheral nerves. Similar inflammatory abnormalities also can be seen in dorsal roots and autonomic
ganglia. In occasional patients there is axonal degeneration; in such cases, degeneration of anterior horn cells and dorsal root ganglia cells can be present, suggesting chromatolysis. Although most of the pathology is found in the peripheral nervous system, there are occasional case reports that demonstrate perivascular inflammation in the central nervous system. A few weeks after the onset of demyelination, Schwann’s cells are noted to proliferate. Several weeks later, as inflammation resolves, remyelination becomes evident.

Animal models resembling GBS were developed as early as 1955 by Waksman and Adams. Experimental allergic neuritis depends on the sensitivity of the P2 protein of peripheral nerve myelin and closely resembles human GBS in terms of clinical, electrophysiologic, and pathologic features. In humans, however, there is no clear evidence that the primary inflammatory attack is directed at the P2 protein. A second animal model, galactocerebroside neuritis, involving antibodies against galactocerebroside, has been developed in rabbits. This animal model is not as similar pathologically as experimental allergic neuritis, because the cellular component of the nerve attack is not demonstrable. In addition, antigalactocerebroside antibodies are not present in human GBS. Although most of the pathologic observations have emphasized lymphocyte-mediated delayed hypersensitivity as a possible mechanism, there is evidence to suggest the role of circulating autoantibodies directed against the myelin sheath. Perhaps GBS is a syndrome with a variety of immunologic mechanisms to account for an acute or subacute peripheral neuropathy.

**Campylobacter, Guillain-Barré syndrome, and axonal Guillain-Barré syndrome**

In 1984 Kaldor and Speed reported serologic evidence of *Campylobacter jejuni* infection in 38% of a group of patients from Australia who had GBS. Subsequent reports supported this association, including that of Vriesendorp and colleagues, in which 15% of 58 patients who had GBS had evidence of recent Campylobacter infection. Many additional studies confirm the association between Campylobacter infection and subsequent GBS. Rees and Hughes found *Campylobacter jejuni* in stool samples of 11% of patients who had GBS, along with serologic abnormalities in an additional 5 of 36 patients. Of the 25% of patients overall who had stool culture or serologic evidence for Campylobacter infection, most had experienced diarrhea as an antecedent illness. In these series, there was a tendency for patients to have predominantly an axonal neuropathy as opposed to a demyelinating neuropathy and the presence of IgG anti-GM1 ganglioside antibodies.

Although GBS typically is a demyelinating neuropathy, there is a subgroup of patients who have clinical, electrophysiologic, and pathologic features indicating primarily an axonal injury as opposed to loss of the myelin sheath. Feasby and colleagues in 1986 noted a subgroup of patients who had GBS and who had electrophysiologic findings of axonal degeneration, usually with severe paralysis and slow recovery, and pathologic changes in two cases indicating axonal degeneration without demyelination, and called this variant “axonal GBS.” There has been disagreement about whether or not this represents an axonal variant of GBS or whether or not it represents a truly distinct type of peripheral neuropathy.

Griffin and colleagues reported four patients who died 7 to 60 days after the onset of clinically diagnosed GBS. Two of these patients had serologic evidence of recent *Campylobacter jejuni* infection. Autopsy findings in three patients studied 7 to 18 days after onset of symptoms showed ongoing wallerian degeneration of ventral and dorsal root fibers and peripheral nerves with mild demyelination or lymphocytic
infiltration. Macrophages were present in the periaxonal space of myelinated inter-nodes, and occasional intra-axonal macrophages also were present. The patients studied 60 days after the onset of symptoms showed extensive loss of large fibers in roots and peripheral nerves and only mild demyelination and remyelination. These carefully studied cases confirm that GBS, as defined clinically, can be associated with a severe sensory-motor neuropathy in which the predominant lesion involves axons of motor and sensory fibers, and that an axonal form of GBS can follow *Campylobacter jejuni* infection.18–20 A pure motor acute axonal neuropathy, a frequent cause of paralysis in China, also has been associated with antiganglioside antibodies.20,21

The prevailing theory for the association between *Campylobacter* infection and GBS is based on the lipopolysaccharide coat, which is rich in glycoconjugates. This lipopolysaccharide coat has similarities to human glycoconjugates, and it may be that antibodies generated against the lipopolysaccharide coat cross-react with glycoconjugates on peripheral nerves. Therefore, it may be that there is a shared epitope between the *Campylobacter* organism and human peripheral nerves18 or so-called molecular mimicry.22

Illa and colleagues23 reported axonal GBS in seven patients that began 5 to 15 days after parenteral injection of gangliosides. These patients had high titers of IgG GM1 antibodies with specificity for motor nerve terminals. Studies by Yuki and colleagues24–27 indicate that the neuroepitope could be GM1 ganglioside or GD1a ganglioside. The Fisher variant of GBS has been associated with antibodies against GQ1b gangliosides.27–29 Therefore, it may be that glycolipids or glycoproteins having epitopes similar to GM1 or GD1a are the immunologic attack site in the axonal forms of GBS.18

**Guillain-Barré syndrome clinical features**

GBS is the most common cause of acute nontraumatic generalized paralysis in young adults, with an annual incidence of 1.2 cases per 100,000 in developed countries. GBS can affect any age group from children to the elderly, although epidemiologic studies suggest that there is a peak in young adults and a second smaller peak in the fifth to seventh decades. It occurs in men slightly more often than in women.

**Antecedent events**

A variety of antecedent events precede the development of acute ascending paralysis. Roper and colleagues10,30 prospectively studied patients who had GBS at Massachusetts General Hospital, noting that 49% had a prior upper respiratory tract infection, 10% had a diarrhea illness, and 3% had some form of pneumonia. In 3% of cases, Epstein-Barr virus infection was implicated and cytomegalovirus (CMV) infection occurred in 3%. Generalized malaise was noted in 3%, and another 3% had miscellaneous associated antecedent events, including Hodgkin’s disease, surgery, systemic lupus, or vaccination. In 27% of patients, there was no prior identifiable illness or antecedent event.30 Other reported associations with GBS have included viral hepatitis, mycoplasma, Lyme disease, and sarcoidosis. Reports of GBS in the setting of HIV infection suggest a stronger association than expected by chance occurrence.91 *Campylobacter jejuni* infection as a cause of an acute diarrhea illness can be associated with subsequent GBS (described previously). Vaccinations occasionally are implicated. Widespread public attention and notoriety occurred with the swine flu vaccination program in 1975 as a result of the suggestion of an increased incidence of GBS associated with the vaccine.
**Symptoms and signs**

Usually patients experience an acute respiratory or gastrointestinal illness that lasts for several days and then resolves. This is followed in 1 to 2 weeks by the development of ascending paralysis. Typically, the legs are involved initially, and within a few days, the arms. Although described as an ascending paralysis, the weakness usually is approximately as marked in proximal limb muscles as in distal muscles. Patients often present with a complaint of difficulty walking, trouble arising from a chair or going up or down stairs, or simply instability of gait. Weakness tends to progress, usually over a course of 1 to 3 weeks. On occasion, patients have a fulminant rapidly progressive course in which paralysis becomes maximal within 1 or 3 days. Overall, approximately 50% of patients who have GBS reach maximal weakness by 1 week, 70% by 2 weeks, and 80% by 3 weeks into the course of the illness. Although symptoms are predominantly motor, patients commonly have mild paresthesias or mild objective sensory deficits on examination, in particular those involving position and vibration sense. Limb weakness is symmetric, and there is symmetric loss of the muscle stretch reflexes. Approximately one third of patients develop respiratory involvement requiring mechanical ventilation, and 50% develop cranial nerve involvement, most often facial weakness. One half of patients develop oropharyngeal weakness and 10% to 20% a degree of ocular involvement. Approximately 50% of patients develop autonomic dysfunction (including fluctuations of blood pressure, heart rate, ileus, or urinary retention). After the progression of weakness stops, patients tend to plateau for 2 to 4 weeks and then recover slowly. The recovery is such that by 6 months into the course of illness, 85% of patients are ambulatory. In 3% of cases there is recurrence of the paralytic illness, although some of these patients instead may have a chronic inflammatory neuropathy as opposed to recurrent GBS.

Overall, the mortality from the acute illness is reported as from 2% to 5%. Approximately 50% of patients have some degree of long-term residual symptomatic abnormality. Fifteen percent to 20% of patients have residual motor weakness at 1 year, and 5% remain severely disabled. This generally favorable natural history is the standard basis against which any therapeutic modality must be compared.

**Laboratory testing**

Within the first few days, most patients typically develop an abnormal spinal fluid profile, with high CSF protein concentration in the absence of a pleocytosis (albumino-cytologic dissociation). Glucose concentration is normal as are cultures. The elevation of CSF protein concentration is presumed to result from an increased permeability of the blood-CSF barrier. In the first day or 2, the CSF protein concentration commonly is normal. In Ropper’s series, 34% of patients had normal CSF protein concentrations when measured in the first week, whereas in the second week only 18% were normal. Serial CSF studies may be necessary to demonstrate an abnormality. Up to 5% to 10% of patients who have GBS may have a lymphocytic pleocytosis with as many as 100 white blood cells per mm$^3$. In patients who have a CSF pleocytosis, the possibility of GBS associated with HIV infection, CMV, Lyme disease, or sarcoidosis should be considered.

Approximately 5% of patients who have GBS have abnormal liver function tests. Occasionally, patients demonstrate increased muscle enzymes, as seen in many forms of acute denervation. In severe or sudden cases of paralysis, stool cultures for *Campylobacter jejuni* may be positive, and many of these patients have associated anti-GM1 antibodies in serum.

Electromyography and nerve conduction studies can document the presence of a peripheral neuropathy that is of a demyelinating type. A demyelinating
neuropathy tends to produce very slow nerve conduction velocities, dispersed compound muscle action potentials (CMAP), and multifocal conduction block. Early on, the abnormalities on nerve conduction studies may be limited to very prolonged F waves. Because the neuropathy typically is a demyelinating type with sparing of the axons, there usually is little fibrillation on electromyography needle examination. In the first few days, the nerve conduction studies may be normal or only mildly abnormal. The electrophysiologic abnormalities tend to lag behind the clinical examination. Severe reduction in the CMAP amplitude may predict the long-term outcome. Miller and colleagues\textsuperscript{37} showed that CMAP amplitudes less than 10% of normal were associated with a less favorable long-term prognosis. Similarly, the North American Guillain-Barré Study Group noted worse prognosis associated with CMAP amplitude less than 20% of normal. Such observations are not universally accepted, as Triggs and colleagues found that 50% of patients who had severely reduced CMAP amplitudes were clinically normal at 1 year.\textsuperscript{38}

In patients who have an axonal form, the electrophysiologic picture differs in that the nerve conduction studies show low amplitude responses, the conduction velocity is reduced more mildly, and the needle examination shows profuse fibrillation.

\textbf{Fisher syndrome}

In 1956 Fisher\textsuperscript{4} reported “an easily recognizable syndrome...characterized among other features by total external ophthalmoplegia, severe ataxia and loss of the tendon reflexes.” This well recognized variant of GBS has been given the eponym, Fisher syndrome, and accounts for approximately 5\% of the cases of acute GBS in most series. Patients typically present with diplopia followed within several days by ataxia or clumsiness of the limbs. Some patients describe dizziness. Over the first week of neurologic symptoms, patients usually develop hypoactive or absent muscle stretch reflexes. One half of patients describe paresthesias. Occasionally, other cranial nerves are involved, resulting in oropharyngeal or facial weakness. Approximately one third of patients develop associated severe limb weakness with respiratory failure. The ophthalmoplegia evolves over 1 to 3 days and usually is severe or complete and symmetric. Most patients have ptosis. Pupillary function tends to be normal. The presence of ataxia has raised the question of cerebellar involvement. There may be intention tremor, suggesting a cerebellar deficit. Some patients have unsteadiness, lightheadedness, or dizziness. Vertigo, nystagmus, cerebellar dysarthria, and scanning speech, however, usually are absent. Patients who have Fisher syndrome most often have an elevated spinal fluid protein concentration, but they are more likely than those who have typical GBS to have normal CSF. A study comparing elevation of CSF protein with anti-GQ1b antibodies in 123 patients who had Fisher syndrome observed albumino-cytologic dissociation (high CSF protein) 59\% during the first 3 weeks of illness compared with serum anti-GQ1b IgG antibody positivity in 85\%.\textsuperscript{39} The electrophysiologic studies show mild slowing of nerve conduction velocities compared with typical GBS and are more likely to be normal in the limbs than in GBS.

\textbf{Differential diagnosis of patients who have Guillain-Barré syndrome}

The differential diagnosis includes the spectrum of illnesses causing acute or subacute paralysis. Spinal cord compression, transverse myelitis, and spinal cord infarction should be considered. Peripheral neuropathies from a variety of causes can mimic GBS, including critical illness polyneuropathy; various toxins, including nitrofurantoin, chemotherapeutic drugs, and heavy metal poisons, such as arsenic and thallium; autoimmune inflammatory diseases, such as systemic lupus and
polyarteritis nodosa; meningoradiculitis, as can be seen with Lyme disease, HIV infection, carcinomatous meningitis, and sarcoidosis; a paraneoplastic acute peripheral neuropathy; acute intermittent porphyria; and diphtheria. Hypokalemic periodic paralysis, myasthenia gravis, botulism, and poliomyelitis also should be considered. Then, presence of an acute or subacute flaccid paralysis in the setting of CNS signs and symptoms (such as encephalitis) should raise the question of West Nile virus infection.

For patients who present with an acute and early-on predominantly sensory neuropathy with distal burning numbness followed in days to weeks by motor involvement, a toxic neuropathy should be considered, as from chemotherapy; nitrofurantoin; heavy metals, such as arsenic and thallium; and the presence of a B vitamin deficiency, in particular thiamine.

**Suggested laboratory evaluation for patients who have Guillain-Barré syndrome**

Patients who present with an acute or subacute paralytic syndrome resembling GBS should have the following laboratory studies considered in every case:

1. If there is evidence pointing to a focal spinal cord lesion, patients should have emergent MRI scan of the appropriate level of the spine. The presence of focal spinal pain, a discreet sensory level, prominent bladder and bowel dysfunction, paraparesis without arm involvement, or selective areflexia in the legs with normal reflexes in the arms all should mandate careful exclusion of a myelopathy by performing an emergency MRI scan.
2. CSF should be analyzed for evidence of a myelitis and for the albumino-cytologic dissociation typical of GBS. If the spinal fluid is sampled within the first few days and is normal, a repeat study a week or 2 into the illness may be helpful if the diagnosis remains unclear. If there is a significant pleocytosis, consider HIV infection, CMV, Lyme disease, and sarcoidosis.
3. Appropriate blood work includes complete blood cell (CBC) count, electrolytes, and liver and renal function tests. With regard to underlying conditions, which can mimic or be associated with GBS, serum tests for an autoimmune inflammatory disease, such as systemic lupus and polyarteritis nodosa, should be done. All patients should be screened for HIV infection, and selected patients screened for Lyme disease, sarcoidosis, and West Nile virus infection.
4. Urine collection for acute intermittent porphyria is indicated.
5. Tests for hypokalemic periodic paralysis, myasthenia gravis, botulism, poliomyelitis, and diphtheria depend on the clinical evidence and suspicion and are not necessary in every patient.
6. Heavy metal poisoning can produce an acute or subacute peripheral neuropathy. In patients who have a predominantly axonal form of GBS, heavy metal screens should be obtained, particularly for arsenic and thallium. Similarly, patients who have pancytopenia, elevated liver function tests, and a history suggestive of a systemic illness also should be screened carefully for heavy metal poisoning. Patients who have recurrent episodes of acute neuropathy also should be screened carefully for toxins.
7. When the antecedent illness is gastrointestinal syndrome with diarrhea, stool cultures and serologic studies may reveal evidence for *Campylobacter jejuni*.
8. Screening for infection from Epstein-Barr virus, CMV, hepatitis virus, and *Mycoplasma pneumoniae* should be considered.
9. A careful review of patients’ prior medication lists for any potentially neurotoxic drug, such as nitrofurantoin, may lead to a diagnosis of drug-induced toxic
neuropathy, as might a history of recent cancer chemotherapy. Megadose vitamin exposure, in particular pyridoxine, also should be considered.

**Treatment of Guillain-Barré syndrome**

All patients who have suspected GBS should be hospitalized for vigilant monitoring resulting from the high risk for respiratory failure and need for intubation and mechanical ventilation. Baseline spirometry, including FVC, and oximetry should be obtained. Indications for intubation include an FVC dropping below 12 mL/kg or, in a normal-sized adult, FVC falling below 1 L. Patients who are subjectively dyspeic or look to be struggling to breathe should be intubated, even if their FVC is above these levels. In general err on the side of early intubation rather than later. A simple bedside estimate of FVC can be made by having patients count out loud. If a patient can take a maximal inspiration and then can count up to 25, the FVC probably is approximately 2 L. A patient who can count up to 10 probably has approximately 1 L FVC.

The cornerstone of treatment is that of meticulous general medical support. There should be a low threshold for putting patients in an ICU. All patients who are having progression of their weakness should be in an ICU. The common complications of GBS include respiratory failure, dysautonomia (especially cardiac arrhythmias, which may occur in 5% of cases), pneumonia, bladder dysfunction, pain, depression, phlebitis, pulmonary embolus, and syndrome of inappropriate antidiuretic hormone. Further complications from immobility and bed rest include decubiti; secondary compression neuropathy, such as ulnar neuropathy and peroneal neuropathy; and the psychiatric sequelae associated with a prolonged immobilizing stay in an ICU. Intense back and limb pain improve with corticosteroids and other drugs used for neuropathic pain.

**Immunotherapy**

**Corticosteroids** To date there have been no studies that demonstrate the effectiveness of corticosteroids in the treatment of GBS. There have been retrospective non-randomized studies along with several small prospective randomized studies, which have shown no clear benefit. The use of high-dose intravenous methylprednisolone, as reported by Hughes, also has shown no benefit. The Dutch GBS Study Group recently reported results of a prospective randomized control trial of IV methylprednisolone (500 mg/day for 5 days) versus placebo. All patients also received intravenous immunoglobulin (IVIG). In this large study of 225 patients, there was no significant difference between treatment with methylprednisolone and those receiving placebo. In summary, to date there is no compelling evidence to support the use of corticosteroids in patients who have GBS. The Quality Standards Subcommittee of the American Academy of Neurology published its practice parameter on immunotherapy for GBS syndrome concluding that corticosteroid therapy is not beneficial.

**Plasma exchange** In 1978, Brettle and colleagues first reported the benefits of plasma exchange (PE) in the treatment of GBS. Several large randomized trials have subsequently demonstrated benefit of PE in treating GBS. The North American GBS Study Group, the French, and the Swedish studies all have shown comparable benefit. In the North American GBS Study Group, the total volume of exchange was 200 mL/kg over 1 to 2 weeks or approximately 4 to 5 exchanges of 3.5 to 4 L on average. There was no clear difference in the occurrence of complications in the PE versus the control group. The time to improve one clinical grade, which was defined as coming off the ventilator or being able to walk, decreased by 50% in the
PE group (19 days versus 40 days in the untreated group). The percent of patients was improved at 1 month, and the average clinical grade, was approximately 15% to 20% better in the PE group than in the control group. In addition, the time to regain independent walking was decreased by approximately 40% in the PE group (53 days versus 85 days in the untreated patients). No benefit was shown in this study when PE was started later than 2 weeks from onset of symptoms, leading to the suggestion that it be used as early as possible when the diagnosis is made. Approximately 10% of patients are found to “rebound” and they often improve with repeat PE. The American Academy of Neurology practice parameter on immunotherapy for GBS syndrome performed a meta-analysis of all six PE studies, revealing that the proportion of patients on the ventilator 4 weeks after randomization was reduced to 48 of 321 in the PE group compared with 106 of 325 in the control group (relative risk [RR], 0.56; 95% CI, 0.41 to 0.76; \( P = 0.0003 \)). In a meta-analysis of four studies for which the outcome was available, 135 of 199 PE and 112 of 205 control patients had recovered full muscle strength after 1 year (RR, 1.24 in favor of PE; 95% CI, 1.07 to 1.45; \( P = 0.005 \)). One class II trial demonstrated a convincing beneficial effect of PE in more mildly affected ambulatory patients. In the meta-analysis, the RR of serious adverse events was similar in the PE and control groups. 

The practice parameter recommendation is:

\[ \text{PE is recommended for nonambulant patients within 4 weeks of onset (level A, class II evidence) and for ambulant patients within 2 weeks of onset (level B, limited class II evidence). The effects of PE and IV immunoglobulin (IVIg) are equivalent.} \]

**Intravenous immunoglobulin** High-dose IVIG initially was reported to be beneficial in GBS by Kleyweg and colleagues in 1988. In 1992, the Dutch GBS Study Group reported a prospective randomized trial comparing IVIG with PE. In their study, IVIG was given at a dose of 0.4 g/kg per day for 5 days and was shown to be as beneficial as PE. The IVIG-treated patients showed a significantly shorter time to improve one disability grade, and somewhat fewer complications occurred in the IVIG group. Smaller series have suggested the greater possibility of clinical worsening during and after IVIG treatment along with an increase in the relapse rate of patients after treatment with IVIG. The PE group in the Dutch study had outcome results similar to the control group (untreated group) of the North American Plasma Exchange Trial. Brill and colleagues prospectively compared IVIG with PE in the treatment of 50 patients who had GBS. Standard outcome measures did not differ between the two groups. Overall, 61% of the PE-treated patients and 69% of the IVIG patients improved by one disability grade at 1 month. The complication rate was found somewhat higher in the PE group. They concluded that the efficacy of IVIG in the treatment of GBS is similar to that of PE, and that it can be used with safety. There was no difference in the relapse rate between the two therapies. This compares with the Dutch GBS Study Group, which reported 34% improvement of one disability grade within 1 month of receiving PE compared with 53% in those receiving IVIG and the reported 59% improvement rate of the PE-treated patients in the North American trial. Brill and colleagues also noted an increased frequency of complications in the PE group, including pneumonia, venous thrombosis, and line sepsis, compared with the IVIG group (19 versus 5). In the Dutch GBS study, 68 complications were noted in the PE group compared with 39 in the IVIG group. A prospective multicenter trial revealed that PE followed by IVIG showed no significant benefit compared with PE alone in any measured outcome, indicating that combination therapy (PE followed by IVIG)
Studies of IVIG in children who have GBS also indicate a beneficial effect. In general, IVIG is considered safe. Mild side effects, including headache, nausea, myalgia, fever, or chills, are reported in 1% to 15% of patients. There are sporadic anecdotal reports, however, of more severe complications, including transmission of hepatitis C, acute renal failure, nephrotic syndrome, stroke, myocardial infarction, aseptic meningitis, and reversible encephalopathy with cerebral vasospasm. Toxicity may be a result of sucrose toxicity, allergic phenomena, and effects of the high protein concentration on blood viscosity.

In the American Academy of Neurology practice parameter on immunotherapy for GBS, a meta-analysis of three trials comparing IVIG with PE revealed nonsignificant trends in favor of IVIG. There were no significant differences in the meta-analysis of time until discontinuation of mechanical ventilation and the proportions of patients dead or disabled after 1 year between the IVIG- and PE-treated groups. In each trial, there were more adverse events in the PE group than in the IVIG group. The practice parameter recommendation is:

IVIg is recommended for patients with GBS who require aid to walk within 2 (level A recommendation) or 4 weeks from the onset of neuropathic symptoms (level B recommendation derived from class II evidence concerning PE started within the first 4 weeks and class I evidence concerning the comparisons between PE and IVIg started within the first 2 weeks). The effects of IVIg and PE are equivalent.

Currently, there is evidence to support the use of PE or IVIG early on in the course of GBS. Current data do not provide an indication of one therapy being clearly superior to the other.

PATIENT TWO: CHRONIC SENSORY PERIPHERAL NEUROPATHY

Question: What to do with a Patient who Comes to the Office with Chronic Burning Numbness in the Feet?

Case presentation 2

A 52-year-old man presents with 2 to 3 years of gradual progressive burning, stinging, and tingling in the feet with a lesser extent of tingling in the fingertips bilaterally. He feels as though the feet are on fire and at times as though a blowtorch has been aimed at the soles. Shoes, socks, and even the light touch of bed sheets are very irritating and limit his ability to rest. When he is up on his feet walking around the pain becomes more severe. Intermittently there are sharp stabs or jabs of shooting and electrical shock pain in the feet. The examination shows decreased sensation in a stocking-glove pattern, which is symmetric. Muscle strength is normal. The muscle stretch reflexes are normal in the arms and at the knees but absent at the ankles. The legs are as shown in Fig. 1.

Discussion

This patient had a common clinical presentation of a chronic progressive sensory neuropathy with a great deal of burning discomfort. This type of predominantly small fiber sensory neuropathy has three common causes in my practice. The first cause is diabetes, and in the patient in Case Presentation 2, the presence of brown discoloration over the shins is a strong clue toward that as the underlying systemic disease—necrobiosis lipoidica diabeticorum. If a patient has type 1 diabetes, do not pursue any further tests to find the underlying cause. If there is no known history of diabetes and the screening studies are normal, then a glucose tolerance test is indicated. If all tests are normal and documentation of small fiber neuropathy is believed
essential then a skin biopsy should demonstrate loss of the small hypomyelinated fibers, although it will not provide the cause. The second clinical scenario associated with this neuropathy that is common is that of patients who have chronic alcohol over-use (and presumed toxicity to peripheral sensory nerves) or nutritional deficiency and, more specifically, vitamin B deficiency (usually thiamine). Therefore, a malnourished patient or one who has chronic alcohol use and who presents with this scenario is common. The third large group is one that has everything else, a veritable plethora of underlying conditions that can cause progressive burning–small fiber neuropathy. Some of the more serious conditions that can be diagnosed include chronic toxic neuropathies and amyloidosis and even those associated with a systemic vasculitis, such as Sjögren’s syndrome, and copper deficiency. Most of the patients in this third group, however, have no identifiable underlying cause that can be found, regardless of the degree of the workup.

In general, if a patient has diabetes or has a strong alcohol or nutritional problem, I do not pursue much additional workup. Otherwise, I do obtain nerve conduction studies and an electromyogram and screen patients not only for diabetes but also for liver and kidney function, thyroid function, vitamin B₁₂ level, CBC count, and serum protein electrophoresis to look for for a monoclonal gammopathy. I am more selective in sending studies for HIV, sarcoidosis, heavy metal poisoning, vasculitis, and other uncommon causes.

Approximately one third of the patients in my practice have chronic distal sensory neuropathy with or without pain and no clear cause. The literature provides a name for this condition, cryptogenic sensory neuropathy, and has observations that such patients should be expected to remain stable of slightly progressive over time. In these patients, management is symptomatic. Reflecting old school habits, I prefer starting with tricyclic antidepressant drugs (amitriptyline and nortriptyline); in an otherwise healthy adult, I start with 25 mg before bedtime; if a patient is small, frail, or sensitive to medications, however, I begin with 10 mg every night and increase the dose every week by 10 to 25 mg (Box 1). Most patients seem to improve at a dose of 25 to 75 mg at night. Most of my colleagues begin with gabapentin (300 mg at night) and increase weekly (to 300 mg three times a day). Should that fail, the next agents generally used in my universe are pregabalin (beginning at 50 mg at night with gradual increase) and duloxetine (beginning at 20–30 mg at night with gradual increase). Adjunctive pain control can be achieved with use of a mild narcotic (propoxyphene or codeine). For patients who have nutritional problems, vitamin B supplements, more specifically thiamine, may be of value although many patients seem to have residual long-term burning dysesthesias in spite of aggressive replacement therapy.
PATIENT THREE: SUBACUTE OR CHRONIC PROGRESSIVE MOSTLY MOTOR AND SOME SENSORY NEUROPATHY (THE CHRONIC INFLAMMATORY DEMYELINATING POLYNEUROPATHY SCENARIO)

Question: What to do with a Patient who Comes to the Office with Several Months of Progressive Weakness due to Neuropathy?

Case presentation 3
A 50-year-old man presents with 8 months of slowly progressive trouble with walking and balance and mild numbness and tingling in the feet.

The examination shows mild weakness in the arms at 4+/5 very symmetric and moderate weakness in the legs 3/5 in the forelegs and 4/5 in the hips and thighs. Sensation is clearly reduced in a stocking and glove distribution to light touch and sharp sensation and moderately reduced to vibration and positions sense in the toes. Cranial function is normal. He denies pain. Muscle stretch reflexes are absent throughout and the patient has no other deficits on examination. The scenario is one of predominant and significant motor neuropathy. Of course the patient has sensory involvement but the likely diagnosis is suspected based on the preponderance of motor deficits. Symmetry and absent stretch reflexes are similar to the collage of examination findings seen in GBS but the protracted time course lead to a suspicion of chronic inflammatory demyelinating...

Box 1
Suggested treatment of neuropathic pain

<table>
<thead>
<tr>
<th>Trigeminal neuralgia (sharp, stabbing face pain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine (100 mg three times a day), increased to 200 mg three times a day in 3–4 days, or oxcarbazepine beginning at 150 mg twice a day and increased</td>
</tr>
<tr>
<td>Baclofen (10 mg twice a day), increased gradually to maximum 20 mg four times a day</td>
</tr>
<tr>
<td>Gabapentin (300 mg at night), increased as needed</td>
</tr>
<tr>
<td>Pregabalin (50 mg twice a day) and increased gradually</td>
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<table>
<thead>
<tr>
<th>Limb neuralgia (sharp, stabbing, zinging lightning, bee-sting pain)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Phenytoin 100 mg orally two to three times a day</td>
</tr>
<tr>
<td>2. Carbamazepine</td>
</tr>
<tr>
<td>3. Baclofen</td>
</tr>
<tr>
<td>4. Gabapentin</td>
</tr>
<tr>
<td>5. Pregabalin</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Continuous burning dysesthesias and supersensitivity (as in a diabetic neuropathy patient)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Amitriptyline or nortriptyline (10–25 mg orally at night) or duloxetine (30 mg at night) and increased gradually</td>
</tr>
<tr>
<td>2. Gabapentin</td>
</tr>
<tr>
<td>3. Pregabalin</td>
</tr>
<tr>
<td>4. Duloxetine</td>
</tr>
<tr>
<td>5. Propoxyphene or acetaminophen with codeine</td>
</tr>
<tr>
<td>6. Carbamazepine (or oxcarbazepine) 100 mg (150) twice a day and increased gradually</td>
</tr>
<tr>
<td>7. Topical capsicain</td>
</tr>
<tr>
<td>8. Mexiletine</td>
</tr>
</tbody>
</table>
polyneuropathy (CIDP). It is written that if a patient presents with a GBS disorder and continues to progress beyond 8 weeks that it is by definition CIDP. Keys to establishing the diagnosis include the predominant motor involvement, absent stretch reflexes, elevation of spinal fluid protein, and nerve conduction studies showing marked slowing of velocity. If a patient has preserved muscle stretch reflexes, if the spinal fluid protein is normal, and if the nerve conduction studies do not show evidence for an acquired demyelinating neuropathy, then one should be cautious about making this diagnosis. Like it or not, with the large number of patients who have chronic neuropathy of unclear cause, it has become fashionable to assume they have variants of CIDP. Not only does this tend to derail the pursuit of the correct diagnosis but also all it leads too often to prolonged courses of a variety of immunotherapy. As corticosteroids are indicated for treatment of CIDP it is not unusual for a patient to receive 6 to 12 months of high-dose prednisone with no significant improvement before redirection of the diagnostic workup. Similarly, it is increasingly common for patients who have semiquasi CIDP to be treated with IVIG or subcutaneous immunoglobulin for months or years without a confirmed diagnosis and without significant clinical improvement. A therapeutic trail of prednisone and IVIG is not unreasonable when the diagnosis is murky and there are no other good options (a good option always includes a second opinion at referral subspecialty center). But those therapeutic trials should be with clear understanding of the risk (medical in the case of corticosteroids and financial in the case of IVIG), a fixed time-frame for monitoring, and understanding that there needs to be clear-cut impressive improvement in the patient’s clinical status as reported by the patient and as confirmed by the clinician. Patients who have real CIDP do improve and the improvement is impressive. Treatment often is necessary for many years and, in some patients, decades although one should attempt to reduce and if possible withdraw treatment every 2 years or so.

Chronic Inflammatory Demyelinating Polyneuropathy Wannabes

A condition similar to CIDP can be associated with monoclonal gammopathy. A serum protein electrophoresis test (SPEP) should be obtained in every patient in whom CIDP is considered. In some patients who have an associated gammopathy the relationship is coincidental. In others, patients seem to have a chronic neuropathy associated with the gammopathy that otherwise is benign. Alternatively, the detection of a gammopathy may lead to the establishment of amyloidosis, lymphoma, Waldenström’s macroglobulinemia, and other serious underlying systemic/hematologic disorders. I propose that every patient who has a CIDP-type presentation and who has a monoclonal gammopathy be evaluated by a hematologist. One of the most striking CIDP-type presentations is the patient who has motor-sensory neuropathy, absent reflexes, elevated CSF protein, and a gammopathy and who has a modest improvement temporarily with immunotherapy. Limited benefit of treatment and the presence of gammopathy should trigger a search for osteosclerotic myeloma and POEMS syndrome. Be suspicious of hair or skin changes. Darkened skin, increased hairgrowth, and tight skin similar to scleroderma can be seen. Such patients need a metastatic bone survey and if any sclerotic or lytic lesions are detected then aggressive hematology-oncology consultation ensues. A sclerotic lesion may be solitary or may be one of many and when biopsied the presence of osteosclerotic myeloma can allow for an appropriate treatment program. In patients who have a solitary bone lesion, local radiation not only does cure the malignancy but also results in dramatic improvement in patients’ peripheral neuropathy.
PATIENT FOUR: MULTIFOCAL MOTOR AND SENSORY NEUROPATHIES
(MULTIPLE MONONEUROPATHIES)

Question: What to do with a Patient who Comes to the Office with Several Months of Patchy Asymmetric Weakness and Sensory Loss?

Case presentation 4

A 45-year-old woman presents with a 4-month history of symptoms. She initially had the onset of intense right though pain and sudden onset of foot drop and numbness over the top of the foot. Approximately 3 weeks later she noted numbness and tingling in the ulnar aspect of the left hand along with mild weakness. Two weeks prior to presentation, she developed intense left flank pain and weakness in the thigh. The examination shows the presence of a right foot drop and sensory findings of a peroneal neuropathy, weakness and sensory loss of a left femoral neuropathy, sensory and motor findings of a left ulnar neuropathy, weakness on lifting the right knee (hip flexor) and extending the knee (quadriceps), and weakness of the interosseous muscles of the left hand (finger spreading, ulnar nerve). Muscle stretch reflexes are reduced to normal except for an absent left knee jerk and absent right ankle jerk.

Discussion

This patient had a peripheral neuropathy characterized by patchy multifocal nerve dysfunction. The clinical picture often is referred to as mononeuritis multiplex. If the syndrome develops gradually over many years then the cause can be any one of several chronic predisposing conditions. When it develops over weeks to months, however, and in particular when associated with acute and painful onset of mononeuropathy, the condition becomes a medical emergency. In the patient in Case Presentation 4, it is essential to screen for vasculitis. Vasculitides known to cause mononeuritis multiplex include polyarteritis nodosa, Sjögren syndrome, and necrotizing vasculitis associated with mixed connective tissue disease. This patient needs an immediate serologic and systemic evaluation for vasculitis, including rheumatology consultation. Although the evaluation is in progress, I recommend that such a patient be empirically treated with high-dose corticosteroids (methylprednisolone [1000 mg daily for 3 days] and then reduced) and suggest hospitalization for treatment and expeditious evaluation. The reason for an emergent approach to these patients is that an active vasculitis is likely to produce nerve trunk infarctions resulting from involvement of the vasa nervorum. I have seen patients go on to infarct proximal nerve trunks in 3 to 4 limbs such that they cannot walk or use their arms adequately. Because nerve infarction damages the axon, the recovery phase is slow and incomplete. Axonal regeneration occurs at a snail’s pace of an inch per month (a millimeter per day) such that it may take 6 months to 2 years for strength to return—thus, the importance of treating empirically when mononeuritis multiplex is first suspected.

Other causes of mononeuritis multiplex include multiple myeloma, Waldenström’s macroglobulinemia, cryoglobulinemia, lymphoma, and sarcoidosis; in some parts of the world, leprosy should be considered. Diabetes mellitus is a known predisposing factor to the development of multiple mononeuropathies.

QUESTION: WHAT ABOUT A PATIENT WHO HAS LIFELONG SYMPTOMS OF TRANSIENT MONONEUROPATHIES?

If patients have a history going back to childhood or teenage years of multiple painless mononeuropathies that gradually recover, then a diagnosis of hereditary neuropathy with liability to pressure palsy should be pursued. This is an under-recognized cause of compressive neuropathies in otherwise healthy individuals.
Approximately 80% of patients have a positive family history and a genetic test is available to confirm the diagnosis. Patients tend to wake up with a foot drop from peroneal neuropathy that resolved over several months, and they wake with an ulnar neuropathy, median neuropathy, or a wrist drop from compressive radial neuropathy. They have defective myelin sheath that predisposes them to compressive nerve dysfunction. They do not have pain. The treatment is prevention with avoiding nerve compression and use of soft sleeping surfaces, such as a waterbed, padding, and so forth. The condition is autosomal dominant. A diagnosis spares a patient unnecessary surgery for carpal tunnel syndrome, ulnar nerve entrapment, a variety of other tests, and treatment that is of no value. The hereditary nature of the condition should be useful for other family members who are being evaluated for various mononeuropathies (Fig. 2).

QUESTION: WHAT ABOUT A PATIENT WHO HAS HAD MONTHS TO YEARS OF PURE MOTOR MONONEUROPATHIES?

An important consideration in patients who present with asymmetric painless weakness in the hands and forelegs is multifocal motor neuropathy. The patients come in after a gradual development of hand symptoms going back 6 to 12 months. Usually the symptoms are asymmetric and patients often have atrophy and fasciculation. Because there is no sensory loss and the indolent insidious progression, there often is a suspicion that patients may have amyotrophic lateral sclerosis or motor neuron disease. Patients who have amyotrophic lateral sclerosis, however, usually have upper motor neuron signs (hyper-reflexia) and often they have bulbar symptoms and signs that never occur in multifocal neuropathy. The nerve conduction studies should be central to confirming the presence of multiple motor mononeuropathies with areas of conduction block along the course if the nerve. Additionally, approximately 50% of these patients have anti-GM1 ganglioside antibodies in their serum. When confirmed with either of these studies, patients are treated with high-dose intravenous or subcutaneous gamma globulin and the majority actually improve in the setting of treatment.

Fig. 2. A 24-year-old man who had long thoracic nerve palsy. At age 12 he had a peroneal neuropathy, and he frequently awakens with tingling and weakness in the limbs. The 44-year-old mother of the patient has had bilateral ulnar nerve surgery, bilateral carpal tunnel release, and surgery for thoracic outlet syndrome. These two patients have hereditary neuropathy with liability to pressure palsy.
CASE PRESENTATION 5
A 45-year-old man presents with several years of gradual decline in running and he has quit playing sports due to twisting his ankles. He feels his balance is poor on uneven ground and when walking in dim light. He has no pain. He notes that his father and aunt had similar symptoms starting in adulthood but neither ever required a wheelchair. The examination shows normal muscle strength and bulk in the hips and thighs. There is mild weakness with foot dorsiflexion bilaterally. He also has mild weakness with extension of the fingers and spreading of the fingers; otherwise the upper extremity strength is normal. Sensory examination shows normal sharp sensation throughout but the patient’s vibrations sense is definitely reduced at the toes and to a lesser degree at the ankles. His proprioception also is slightly reduced at the toes. Gait shows the patient to have a mild steppage quality. Muscle stretch reflexes are uniformly absent. The appearance of the legs and feet are similar to those shown in the photos (Fig. 3).

DISCUSSION
This patient has a chronic, predominantly motor, peripheral neuropathy without the typical burning stinging tingling symptoms of patients who have an acquired (diabetic) neuropathy. The predominance of motor involvement, the fact that all the reflexes are absent even though the weakness is restricted to the most distal muscles, and the presence of dimorphic appearance (see Fig. 3) all point to a hereditary neuropathy lumped together as Charcot-Marie-Tooth disease [CMT]. The family history in this case adds further certainty to the diagnosis. There are several reasons to make this diagnosis. When made, it spares patients a costly and endless set of future diagnostic procedures.

Fig. 3. Pes cavus and hammertoe deformity in CMT. Hand atrophy CMT.
studies. Further, it gives patients an answer. Third, it allows for a clear understanding of prognosis. Extremely slowly progressive, nothing will change overnight—no surprises. Most patients do not require a wheelchair although those affected more severely might. There is no effect on cognition, bladder, bowel, and so forth. Patients feel better with an answer and a prognosis. The fourth reason to make the diagnosis is for family counseling purposes given the hereditary basis for the disease. Although most patients have an autosomal dominant form of CMT, there are a variety of subtypes with differing patterns of inheritance.

Question: What Should be Done in the Way of Laboratory Evaluation for Patient Five?

With some patients I do nothing. As there is no treatment at this juncture that is proved to slow the course of CMT, expensive gene testing for decision making regarding treatment cannot be justified. For general physicians, I suggest that the most cost-effective and useful diagnostic step is consultation with a neuromuscular specialist. Nerve conduction studies typically reveal absent responses in the legs and very slow conduction velocity in the arms. If the study is performed by a physician who has limited understanding of CMT, the report concludes something like, “very severe generalized peripheral neuropathy,” when a patient is in this case is really quite strong. The mismatch of abnormalities on the nerve conduction studies and the clinical examination should raise the question of hereditary neuropathy if it has not already been considered. Regarding speed of nerve conduction, we are born with motor nerves having sufficient myelin to provide approximately 25 m per second velocity. During the initial 3 years of life, myelin improves and matures such that by age 3, patients should have an adult range for nerve conduction, approximately 50 m per second speed of conduction. Patients who have CMT have lifelong detectable slow conduction velocity, often in the 20- to 30- m per second range. From age 3 up, the presence of velocities in the 20- to 30-m per second range indicates a problem with the myelin sheath. The other major group of patients who have demyelinating neuropathy (other than CMT) is those who have CIDP. Because CIDP is more rapidly progressive and typically improves with immunotherapy it is important to make the distinction. On nerve conduction studies the CMAP typically is dispersed and choppy in appearance whereas in CMT it typically is smooth. Patients who have CIDP have an elevation spinal fluid protein whereas patients who have CMT do not. Patients who have CMT have a very protracted course (often the history extends back for decades) and patients who have CMT have strikingly distal weakness, whereas CIDP are more likely to also have significant proximal weakness. The dysmorphic features (see Fig. 3) are never acquired from CIDP. Approximately 50% of patients who have CMT have a high arch (pes cavus) and approximately 30% have a very flat foot (pes planus). The cocked-up toes (hammertoe deformity) also are seen in most patients. Approximately 20% to 30% of patients have hypertrophic nerves that can be palpated on examination. If there is access to a genetic counselor it is ideal for patients to discuss the various genetic issues. Gene testing is widely available for many but not all subtypes of CMT. Although it seems obvious to run those tests in every patient who has suspected CMT, I suggest waiting until the neuromuscular consultation is completed. The full battery, or panel, of gene tests is extensive and cost is a major problem for patients who have limited resources; many insurance programs do not cover genetic testing. Even the Muscular Dystrophy Association neuromuscular clinic system in general does not cover genetic testing. Benefits must be weighed against the cost of extensive testing. In many patients a good neuromuscular specialist can pinpoint the subtype of CMT with sufficient accuracy so that if gene testing is desired then
a single test may suffice instead of a costly panel. The most common abnormalities are CMT1A duplication, Cx32, and dMFN2 mutations. I have cared for patients in whom a battery of gene tests were performed, with patients getting a large bill for out-of-pocket expenses, and because there is no specific proved treatment for any of the CMT conditions, the patients feel like the decision to test was in retrospect faulty. Because forms of CMT cannot be tested for, the patients may invest a small fortune in gene tests and still not have a specific answer.

The treatment is symptomatic. For significant foot drop we use ankle foot orthotics, although one third of our patients try them and conclude they are more comfortable and function better without. For those in whom hand function is affected, occupational therapy for selection of tools for activities of daily living is central to management. If patients have musculoskeletal ankle pain, we use analgesics, and if patients have muscle cramps, we use quinine or gabapentin. I tend to see these patients in long-term follow-up once per year. One important aspect of their follow-up (as they do not change much over 12 months) is to keep them informed and in the loop about new developments and potential clinical trials for treatment.

PATIENT SIX: ACUTE OR SUBACUTE SENSORY NEUROPATHY OR SENSORY ATAXIA

Question: What does it mean if a Patient Presents with Acute or Subacute Pure Sensory Neuropathy?

Case presentation 6

A 30-year-old woman presents with 3 weeks of progressive numbness and tingling in the feet and hands and wobbly ataxic gait. Examination shows markedly decreased position and vibration sense in the toes and fingertips, decreased sensation to pin prick distally in the limbs in symmetric fashion, and reduced muscle stretch reflexes. Muscle strength is normal. The patient has a very wide-based wobbly gait and with eyes closed tends to fall over.

Discussion

This patient has a sensory neuronopathy with the lesion located most likely in the dorsal root ganglia and affecting large sensory fibers, resulting in a profound degree of position and vibratory loss and ataxic gait (sensory ataxia). There are several causes to consider in such a patient. Given the presence of a 3-week history the patient may have an immune-mediated inflammatory sensory neuronopathy, in other words, a sensory form of Guillain-Barré syndrome. Such patients may have an elevated spinal fluid protein and may improve spontaneously or more rapidly with immunotherapy, such as IVIG or plasmapheresis. Alternatively, patients could have vitamin B₁₂ deficiency, which causes a sensory neuronopathy with involvement of the large fibers causing difficulty with position and vibration sense. Such patients often have subacute combined systems degeneration, which leads to a combination of dorsal column dysfunction, and descending corticospinal tract deficits, giving the patient some degree of spasticity, stiffness in the legs, and Babinski’s signs. Such patients should have a serum vitamin B₁₂ level and CBC count to screen for vitamin B₁₂ deficiency. Sjögren’s syndrome also can be associated with a sensory neuronopathy, and appropriate serologic studies are indicated.

Of great importance for a subacute presentation in otherwise healthy young persons is an occult malignancy leading to a sensory neuronopathy as a remote effect of carcinoma. Patients who have this condition typically have detectable levels of anti-Hu antibodies in serum. This paraneoplastic antibody should be screened in such patients; if positive, an aggressive search for an occult malignancy is indicated. The anti-Hu or antineuronal antibody type 1 can cause not only a sensory neuropathy but also
a paraneoplastic encephalomyelitis. The anti-Yo or anti-Purkinje cell antibody is associated with cerebellar degeneration, particularly in women who have ovarian cancer. Other paraneoplastic antibodies include the anti-Ri or antineuronal antibody type 2 which is associated with the opsoclonus/myoclonus syndrome in adults. There is an antibody against amphiphysin, which is seen in patients who have paraneoplastic stiff person syndrome. Those who have anti-voltage-gated calcium channels have Lambert-Eaton syndrome and small cell cancer of the lung.

In patients who have a pure sensory neuropathy as a paraneoplastic disorder, there is selective damage to the dorsal root ganglia associated with some degree of perivasculitic lymphocytic infiltration. There is diffuse distal symmetric symptomatology with early involvement of discriminative modalities, profound impairment of coordination, the presence of pseudoathetosis, uselessness of the limbs, and areflexia in the setting of relative preservation of strength. The underlying malignancies in such patients often are small cell carcinoma, but occasionally breast and prostatic cancer are associated with a pure sensory neuropathy. Patients who have received toxic chemotherapy, such as platinum or vincristine, may have that as the cause of their sensory symptoms. Some of the blood dyscrasias and those receiving megadoses of pyridoxine/vitamin B$_6$ can have a sensory neuronopathy from dorsal root ganglia involvement. Immuno-therapy and successful treatment of an associated malignancy (if the patient has that condition) are the main therapeutic options.

**PATIENT SEVEN: POEMS**

**Question: How to Approach a Patient who has Chronic Neuropathy and Changes in Skin and Hair?**

**Case presentation 7**

A 55-year-old teacher presented with 6 months of progressive weakness, sensory loss, and change in gait. He has had changes in speech and phonation. He also noted new hair growth (Fig. 4) and skin tightness and thickness. The examination shows that he is weak at 4/5 in the limbs and has reduced sensation in distal fashion and absent muscle stretch reflexes throughout. The presence of progressive proximal and distal symmetric weakness, distal sensory loss, and absent reflexes fits best with the CIDP presentation (described previously). His nerve conduction velocities are approximately 25 m per second and spinal fluid protein is elevated at 110 with normal cells. He had screens for diabetes, thyroid, vitamin B$_{12}$, heavy metals, and vasculitis that were normal. His neurologist believed this fit

![Fig. 4](image)

A 55-year-old teacher with 6 months’ progressive weakness and new hair growth.
best with CIDP and treated him with high-dose corticosteroids. He had mild improvement in strength for 2 months but then seemed to progress. Also, he developed a steroid psychosis on prednisone and became dysinhibited, delusional, and at times violent. Because his neuropathy symptoms were not responding well to the treatment and he could not tolerate corticosteroids he was referred for further assessment.

Discussion
The presence of new hair growth and tight thick skin in the setting a peripheral neuropathy should raise the question of Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, and Skin changes (POEMS) syndrome. Hair growth, scleroderma-like skin, hyperpigmentation, and whitening the nails all can be seen as the (skin changes seen in POEMS). The neuropathy of POEMS is similar to that seen in CIDP and it is common for patients to initially receive that diagnosis and associated management. They tend not to respond favorably to treatment of the long term, however, and eventually present for progressive neuropathy. The endocrine problems with POEMS may have been another factor in this patient. The key toward a favorable outcome for him is to suspect POEMS and obtain a SPEP, which in every case reveals

<table>
<thead>
<tr>
<th>Box 2</th>
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<tr>
<td>Sensory mononeuropathies 2009</td>
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</tbody>
</table>

| Meralgia paresthetica: lateral femoral cutaneous neuropathy (meros = thigh, algos = pain, paresthetica = tingling) |
| Causes: sporadic, diabetes, obesity, pregnancy, pelvic disease, holster, toolbelt, surgical table, familial |

| Cheiralgia ("hand pain") paresthetica: superficial radial sensory neuropathy |
| Handcuffs, IV, blood draws (legal stuff) |

| Gonyalgia paresthetica: infrapatellar branch of the saphenous nerve |
| Idiopathic, knee trauma, surgery, "influenza knee" |

| Saphenous neuropathy: same differential |
| Digitalgia paresthetica: digital neuropathy |
| Fingers > toes |

| Notalgia paresthetica: posterior rami of T2-T6 (notos = back) |
| Cause unknown but benign tingling, itching, burning |

| ? Due to sharp right angle course of the nerve through the multifidus muscle |

| Intercostal neuropathy |
| Mostly thoracic |

| Mental nerve neuropathy: numb chin syndrome |
| Diabetes, herpes zoster, pregnancy |

| Radicular pain |

| Ominous: 25% malignancy; look for mets at the base of the skull or CSF |

| Facial sensory neuropathy: trigeminal neuropathy |

| Sarcoïdosis, Sjögren's syndrome, scleroderma |
a monoclonal gammopathy. Then the patient needs a bone survey looking for evidence of osteosclerotic myeloma. If a sclerotic bone lesion is found, then a biopsy secures the diagnosis and provides the justification for treatment. Treatment options include radiation if solitary and chemotherapy if multiple lesions are detected.

**Question: Is there any Low-Hanging Fruit in the Management of Patients who have Peripheral Neuropathy?**

Regardless of the cause and type of neuropathy, patients are prone to the following common symptoms, although at times the focus is so much on diagnosis and primary treatment that there is failure to methodically address the common symptomatic issues that may benefit patients more than anything else.

1. Mechanical problems from weakness: splints for foot drop and wrist drop can have a major impact on function and in the case of ankle-foot orthotics can reduce the risk for falls and further ankle trauma.
2. Neuropathic “pain” (see **Box 1**).
3. Muscle cramps. Cramps can occur with any peripheral nerve or nerve root disorder in which the motor component is affected. Most true muscle cramps are neurogenic and not the result of muscle disease. It helps to ask patients about their cramps and if they want treatment. If treatment is desired then I suggest the following: for patients who have severe muscle cramps, there are several medications that work nicely to control the symptoms. Quinine (260 mg), one tablet each evening, is safe and the most consistently effective. Unfortunately, in 2007, the Food and Drug Administration (FDA) required all but one manufacturer of quinine to remove their respective products from the market, and the FDA also strongly advises that the one remaining available product (Qualaquin [324 mg]) be used only for the treatment of malaria and not for the treatment of muscle cramps (because of concerns over the safety of the quinine). In my opinion, low-dose quinine (260 mg daily) is remarkably safe but these regulatory actions may make quinine more difficult to provide to patients. Quinine is in tonic water but a full glass daily provides only 40 to 50 mg of quinine. If quinine is ineffective or unavailable, then the tendency is to use gabapentin at low doses; baclofen, oxcarbazepine, tizanidine, zinc, or vitamin E may be useful in selected patients.
4. Restless lags syndrome (RLS): there are several conditions that are well established to predisposing to the development of RLS. Anemia, in particular iron deficiency, is associated with RLS. And patients who have peripheral neuropathy for any cause also are predisposed. So it behooves clinicians to explore RLS in all patients who are followed for peripheral neuropathy, as patients are relatively easy to treat with dopaminergic drugs or low-dose opioids.
5. Know the sensory mononeuropathies (**Box 2**).

**REFERENCES**


