methylmalonic acid or homocystine level can also help confirm this diagnosis in patients with borderline B_{12} levels. The presence of weakness and upper motor neuron signs without associated sensory loss suggests ALS.

If the neuropathy is associated with mental status abnormalities, then pyridoxine intoxication or deficiencies of thiamine, niacin ("dementia, diarrhea, dermatitis"), and vitamin B_{12} should be considered in the differential diagnosis. Lyme disease (see Chapter 90) may result in both peripheral nervous system symptoms (facial nerve palsies, paresthesias, weakness) and central nervous system symptoms (dementia, headache). Acquired immunodeficiency syndrome (AIDS) can also affect both the central and the peripheral nervous systems. GBS and CIDP usually occur at the time of HIV seroconversion, whereas sensory neuropathy, mononeuritis multiplex, and CMV polyradiculopathy generally occur in the context of low CD4 counts in the terminal stages of the disease.

Once a preliminary differential diagnosis is developed based on the history and neurologic examination findings, laboratory studies can confirm the diagnosis. Laboratory tests to identify potentially treatable causes of neuropathy are included in Table 121-11. Additional studies can be ordered based on the suspected diagnosis. An impaired glucose tolerance test is found in more than half of patients with cryptogenic sensory peripheral neuropathy and is more sensitive than tests of fasting glucose or hemoglobin A_{1c} (HbA_{1c}). In a patient with acute, asymmetrical weakness and sensory loss, screening for an inflammatory process (ESR, ANA, RA, SS-A, SS-B) is appropriate. In addition, genetic testing is now available for most patients with CMT disease. If a monoclonal protein is identified on serum protein electrophoresis, a skeletal survey, urine immunofixation electrophoresis, and bone marrow biopsy should be ordered to rule out an underlying lymphoproliferative disorder. If the patient has a monoclonal protein associated with autonomic dysfunction, congestive heart failure, or renal insufficiency, a biopsy (rectal, abdominal fat, or sural nerve) should be considered for diagnosis of amyloidosis. CIDP can be associated with a monoclonal gammopathy, and in this situation patients should be treated with immunosuppressive therapy. Monoclonal gammopathies observed in patients with an axonal peripheral neuropathy are frequently benign (monoclonal gammopathy of unknown significance) and do not necessarily warrant therapy.

TABLE 121-11 PERIPHERAL NEUROPATHY LABORATORY STUDIES

STANDARD TESTS	TESTS INDICATED IN SELECTED CASES
B_{12}	Anti-Hu antibody
Complete blood count	ESR, ANA, RF, SS-A, SS-B
Glucose tolerance test	Genetic studies for Charcot-Marie-Tooth
Rapid plasmin reagin	Human immunodeficiency virus
SMA20	Lyme antibody
Serum protein electrophoresis and immunofixation electrophoresis	Phytanic acid
Thyroid function tests	24-hr urine for heavy metals
Nerve conduction studies or electromyogram	Quantitative sensory testing
	Lumbar puncture
	Nerve biopsy
	Skin biopsy
	Tilt table testing

A lumbar puncture is indicated only if an acquired demyelinating neuropathy such as GBS or CIDP is being considered. In these cases one expects to find "albuminocytologic dissociation" with an elevation in cerebrospinal fluid (CSF) protein and a relatively normal white blood cell (WBC) count. If the CSF WBC count is greater than 50/mm^3, Lyme disease, HIV-associated disease, or a paraneoplastic process must be considered.

Electrodiagnostic studies consisting of nerve conduction testing and EMG can be a helpful extension of the physical examination. These studies are useful in defining whether the neuropathic process is caused by a primarily axonal or demyelinating process. In general, axonal degeneration decreases the amplitude of the compound muscle action potential out of proportion to the degree of reduction in peripheral nerve conduction velocity, whereas demyelination produces prominent reduction in conduction velocities. Nerve conduction testing can help determine, in the case of a demyelinating neuropathy, whether the process has an acquired or hereditary cause. A uniform slowing of nerve conduction usually suggests a hereditary cause. Electrodiagnostic studies can identify subclinical neuropathy (in patients receiving potentially neurotoxic medications) and can quantitate the extent of axon loss. Finally, these studies can localize the lesion in the case of radiculopathies, plexopathies, and multiple mononeuropathies.

Sensory nerve biopsies should be obtained for diagnosis of a vasculitic neuropathy because treatment involves potentially toxic medications. Performing a muscle biopsy in addition to the nerve biopsy may improve the diagnostic yield and should be considered because the inflammation is random and focal and easily missed. Nerve biopsies are not indicated in "cryptogenic" neuropathies, diabetic neuropathy, or motor neuron disease. If nerve conduction studies are normal, skin biopsies allow quantification of the number of epidermal nerve fibers. A length-dependent decrease in the number of these fibers can help confirm a small fiber neuropathy.

Treatment

Despite a very thorough history, examination, and laboratory studies, the cause of as many as one third of neourpathics remain unknown. In this situation, the focus of management is pain control. Patients with neuropathy frequently report a burning, searing, and aching sensation in their feet and hands that interferes with sleep. Neuropathic pain is difficult to treat but may respond to various medications having different mechanisms of action (Table 121-12). It is important to "start low and taper slow" and to treat for a minimum of 4 weeks before concluding that an agent is ineffective. In patients with a vasculitic neuropathy, therapy with corticosteroids in addition to a cytotoxic agent can stabilize and in some cases improve the neuropathy.

Prognosis

Peripheral neuropathies caused by axonal degeneration are generally progressive unless the underlying cause can be identified and treated. Recovery from axonal degeneration requires nerve regeneration, a process that often requires 2 to 3 years. Prognosis