TABLE 121-8 HEREDITARY NEUROPATHIC DISORDERS

	INHERITANCE PATTERN	GENETIC DEFECT	CLINICAL FEATURES
Hereditary sensorimotor neuropathies	AR, AD, or X-linked	See E-Table 121-4	Pes cavus, distal atrophy and weakness, hammer toes
Familial amyloid polyneuropathy	AD	Transthyretin Gelsolin Apolipoprotein Al	Pain, autonomic dysfunction
Fabry disease	X-linked	α-Galactosidase	Cardiac ischemia, renal disease, stroke, cutaneous angiokeratomas
Tangier disease	AR	Apolipoprotein A	Low HDL levels, orange tonsils
Refsum disease	AR	Phytanic acid oxidase	Retinitis pigmentosa, cardiomyopathy, deafness, ichthyosis

AD, Autosomal dominant; AR, autosomal recessive; HDL, high-density lipoprotein.

mellitus and alcoholism are the most common causes of polyneuropathy in developed countries. As many as one third of acquired neuropathies are cryptogenic in which the etiology can never be identified. Causes of monneuritis multiplex include systemic vasculitis (rheumatoid arthritis, systemic lupus erythematosus, Wegener's granulomatosis, Churg-Strauss syndrome, polyarteritis nodosa) and primary peripheral system vasculitis (25% of cases).

Because of the many causes, it is important to approach the patient with neuropathy systematically, beginning with the patient's history and physical examination. It is essential to determine which nerves are involved (motor, sensory, or autonomic) and in what specific combination (Table 121-9). Small-fiber neuropathies often manifest with unpleasant or abnormal sensations such as a burning pain, electric shock-like sensations, cramping, tingling, pins and needles, or prickly feelings such as the limb "feeling asleep." Large-fiber neuropathies can manifest as numbness, tingling, or as gait ataxia. Symptoms suggesting motor nerve involvement include muscle weakness that typically involves the distal foot muscles. Autonomic nerve involvement is suggested by symptoms of orthostatic hypotension, impotence, cardiac arrhythmia, or bladder dysfunction.

The distribution of muscle weakness is important. In axonal neuropathies, the weakness predominantly involves the distal lower extremity muscles, and in demyelinating neuropathies the weakness can involve both proximal and distal muscles as well as facial muscles. Most neuropathies result in *symmetrical* weakness. If asymmetry is present, motor neuron disease, radiculopathy, plexopathy, compressive mononeuropathies, or mononeuritis multiplex should be considered. The intensity and distribution of painful dysesthesias can be informative. Although many axonal neuropathies are associated with a burning sensation in the feet, pain as the chief complaint suggests specific causes of neuropathy (Table 121-10). A neuropathy that manifests with acute, asymmetrical weakness, and severe pain suggests vasculitis.

In patients with severe, asymmetrical proprioceptive deficits, with sparing of motor function, the site of the lesion is usually the sensory neuron. This specific syndrome has a relatively limited differential diagnosis, including paraneoplastic process, Sjögren's syndrome, cisplatinum toxicity, vitamin B_6 toxicity, and HIV infection.

Most neuropathies are relatively insidious in onset, particularly those associated with metabolic or endocrine disorders. Acute neuropathies may be caused by a vasculitic process, toxin exposure, porphyria, or GBS. GBS is commonly preceded by a viral illness, immunization, or a surgical procedure. The neurologic history must thoroughly explore potential toxic exposures such as prior medications and alcohol use (E-Table 121-3).

TABLE 121-9 DIFFERENTIAL DIAGNOSIS OF NEUROPATHIC DISORDERS BASED ON SYMPTOMS

MOTOR SYMPTOMS ONLY	SENSORY SYMPTOMS ONLY	AUTONOMIC SYMPTOMS
Porphyria	Cryptogenic sensory polyneuropathy	Amyloid neuropathy
Charcot-Marie-Tooth	Metabolic, drug-related, or toxic neuropathy	Diabetic neuropathy
Chronic inflammatory demyelinating polyneuropathy	Paraneoplastic sensory neuropathy	Fabry disease
Guillain-Barré syndrome		Guillain-Barré syndrome
Lead neuropathy		Hereditary sensory or autonomic neuropathy
Motor neuron disease		Porphyria

TABLE 121-10 NEUROPATHIES ASSOCIATED WITH PAIN

Alcoholic neuropathy	Heavy metal toxicity (arsenic, thallium)
Amyloidosis	Hereditary sensory or autonomic neuropathy
Cryptogenic sensorimotor neuropathy	HIV sensorimotor neuropathy
Diabetic neuropathy	Radiculopathy or plexopathy
Fabry disease	Vasculitis
Guillain-Barré syndrome	

HIV, Human immunodeficiency virus.

Because many neuropathies are hereditary, it is essential to obtain a detailed family history, specifically inquiring about a history of gait instability, use of adaptive equipment, or skeletal deformities of the feet. Hereditary neuropathies may be autosomal recessive, autosomal dominant, or X-linked. In some situations it may be helpful to actually examine family members because the severity of disease may vary considerably from one generation to the next. The most common hereditary neuropathy is CMT disease (see later discussion).

A complete neurologic examination should always be performed in a patient complaining of numbness. If the patient shows evidence of upper motor neuron involvement in addition to the sensory loss, vitamin B_{12} or copper deficiency should be considered, even in the absence of apparent anemia. An elevated