ABSTRACT

Diabetic neuropathy is now the most common neuropathy in industrialized countries and may be the most common in the world. The prevalence of sensory neuropathic symptoms, particularly pain, is about 30% among patients with diabetes. Moreover, the prevalence of diabetic neuropathy increases with age, from about 5% in patients between the ages of 20 and 29 to approximately 44% in those between the ages of 70 and 79, and with duration of disease, particularly after 20 years. Prevalence is also higher in patients with poor glycemic control. The most prominent manifestations of diabetic neuropathy are pain and trophic ulcers, both of which are associated with considerable morbidity and disability.

The prevalence of sensory neuropathic symptoms, particularly pain, is high among patients with diabetes—about 30% in patients with type 1 diabetes mellitus (insulin dependent) and more than 30% higher in those with type 2 diabetes mellitus (noninsulin dependent).1 Diabetic neuropathy is a disorder of great heterogeneity, both in the wide variability of its clinical presentation and in its classification, as shown in the Table. In some patients, diabetic neuropathy is subclinical; in others, thepredominating distal sensation of numbness is unpleasant but not disabling. In still other patients, the disturbances in nerve function can be life threatening. Although uncommon, an early onset of severe sensory neuropathy is sometimes seen in young adults with poorly controlled type 1 diabetes. Genetic factors are most probably responsible for the increased susceptibility to metabolic injury among some patients but not others.

DISTAL SYMMETRICAL SENSORY POLYNEUROPATHY

The most common type of diabetic neuropathy is distal symmetrical sensory polyneuropathy (DSSP), which occurs about 10 times more frequently than the other types and is often associated with potentially severe autonomic disturbances. Each of the subtypes of DSSP follow a length-dependent pattern, i.e., affecting the feet first and then progressing upwards, suggesting involvement of the long fibers first, then shorter and shorter fibers. All types of nerve fibers are involved in DSSP, but the small myelinated and unmyelinated fibers are predominantly affected.

In small-fiber DSSP, there is a loss of body temperature and pain sensation (as tested by a pinprick), accompanied by a relative sparing of position sense, light touch, vibratory sensations, tendon reflexes, and muscle strength. Distal degeneration of axons that follow a dying-back pattern and are associated with regeneration in the proximal stump has been documented in small-fiber DSSP.
By contrast, large myelinated fibers are predominantly involved in the large-fiber subtype, with selective loss of light touch, proprioception, vibratory sensations, all of which manifests as sensory ataxia, tendon reflexes, and distal muscle weakness. Large-fiber DSSP was often seen in the past when there was no treatment for diabetes, but this diabetic neuropathy is less common today.

The most common subtype of DSSP is the mixed type, which involves small and large fibers.

Pain is the most common disabling symptom of DSSP, but there are no specific morphologic findings. Trophic changes leading to loss of pain sensations distally are the main cause of foot ulcers, idiopathic bullae (bullosis diabeticorum), osteoarthropathy, and dystrophic changes in areas with decreased pain sensation and muscle strength.

**Autonomic Neuropathy**

Autonomic neuropathy occurs mainly in patients with type 1 diabetes (insulin dependent) and can be severe. This may be manifested by cardiovascular disturbances such as loss of R-R variations by electrocardiogram, gastrointestinal problems such as gastroparesis, urinary dysfunction (eg, neurogenic bladder), and erectile dysfunction.

**Focal and Multifocal Neuropathies**

Focal and multifocal sensorimotor neuropathies are less common than DSSP but are very disabling because they lead to pain and motor deficits. Inflammatory nerve lesions and vasculitis have been documented in a high proportion of patients with focal and multifocal diabetic neuropathies.

Focal and multifocal neuropathies include cranial, thoracoabdominal, and proximal diabetic neuropathies. Cranial neuropathies include oculomotor nerve palsies, with third-nerve palsy being most common. These palsies are far more common in patients with type 2 diabetes. Typically, the onset is abrupt, and the pupil of the eye is spared.

Thoracoabdominal neuropathies occur in older patients and are usually unilateral. Onset is abrupt or rapid and is accompanied by pain.

Proximal diabetic neuropathy is characterized by rapid onset of burning pain along the anterior aspect of the thigh, which worsens at night and increases with contact. There are also signs of early atrophy of the quadriceps.

**Nondiabetic Neuropathies**

Patients with diabetes are also subject to a number of neuropathies that are not exclusive to diabetics and are seen in the nondiabetic population. These neuropathies include chronic inflammatory demyelinating polyneuropathy (CIDP), nerve entrapment neuropathies, and neuropathy due to renal failure. Although these neuropathies occur in persons with and without diabetes, they are nevertheless more common in patients with diabetes.

**Pathophysiology and Pathogenesis**

There are 2 major hypotheses to explain the pathophysiology of diabetic neuropathy: the metabolic hypothesis and microangiopathy. The metabolic hypothesis holds that neuropathy results from several factors, including activation of the polyol pathway and protein kinase C and from increased oxidative stress. Alternatively, microangiopathy has been implicated as a cause of diabetic neuropathy. Although thickening

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**Table. Classification of Diabetic Neuropathy**

- Distal symmetrical sensory polyneuropathy (DSSP)
  - Small-fiber type (myelinated and unmyelinated fibers)
  - Large-fiber type (myelinated fibers)
  - Mixed type
- Autonomic neuropathy
- Focal and multifocal neuropathy
  - Cranial diabetic neuropathy (eg, oculomotor palsy)
  - Thoracoabdominal diabetic neuropathy
  - Proximal diabetic neuropathy
- Nondiabetic neuropathy (in diabetics and nondiabetics)
  - Chronic inflammatory demyelinating polyneuropathy
  - Entrapment neuropathies
  - Neuropathy due to renal failure
of the capillary basement membrane is not specific for diabetes, its association with increasing age and duration of diabetes has been well documented.

The pathogenesis of diabetic neuropathy is well recognized as a multifactorial disorder. Neuropathies involving length-dependent nerve fibers predominantly are more likely to result from a selective vulnerability of these particular neurons. By contrast, neuropathies with focal or multifocal involvement are more likely the result of ischemic and/or inflammatory mechanisms.

REFERENCES