Classification, Differential Diagnosis, and Staging of Diabetic Peripheral Neuropathy

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The peripheral nerve disorders associated with diabetes are complex and probably involve a variety of causative mechanisms. This may give rise to difficulty in the classification of individual cases. A broad separation into rapidly reversible or more persistent phenomena is helpful. The former, which can be categorized as "hyperglycemic neuropathy," include minor sensory symptoms, reduced nerve conduction velocity, and resistance to ischemic conduction failure. From analogy with experimental studies in animals, nerve hypoxia is likely to play a significant role in their origin. Of the more persistent phenomena, a distal symmetric polyneuropathy that predominantly affects sensory and autonomic function is the most common manifestation. A distal axonopathy of dying-back type may represent the underlying pathogenetic basis. Other more persistent phenomena consist of focal and multifocal lesions giving rise to cranial, thoraco-abdominal, and limb neuropathies, including proximal lower limb motor neuropathy (diabetic amyotrophy). Some of these may have an ischemic basis. Multifocal proximal lesions can summate to produce an approximately symmetric diffuse distal neuropathy. Focal lesions at sites of entrapment or external compression may reflect an abnormal susceptibility of diabetic nerve to compressive damage. There is also evidence that focal inflammatory, including vasculitic, lesions may be involved in proximal lower limb neuropathies. Finally, superimposed chronic inflammatory demyelinating polyneuropathy may occur. For the evaluation of possible treatment regimens, it is essential that cases should be correctly classified as to type. Thus, the features falling into the category of hyperglycemic neuropathy should not contaminate the assessment of distal symmetric polyneuropathy. For this type, a widely accepted scheme for staging devised by P.J. Dyck is available. Other schemes are also available for the assessment of such cases, with differing degrees of complexity. Evaluation by serial nerve biopsies has also been proposed.
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CIDP, chronic inflammatory demyelinating polyneuropathy; RICF, resistance to ischemic conduction failure.

Although there have been past claims based on clinical and pathological considerations that diabetic neuropathy is a unitary condition (1), it has become increasingly evident that a wide variety of disturbances may affect the peripheral nervous system in subjects with diabetes and that the underlying causative mechanisms are likely to be correspondingly complex (2). The classification that I favor is given in Table 1.

HYPERGLYCEMIC NEUROPATHY

Patients with newly diagnosed or poorly controlled diabetes frequently show reduced nerve conduction velocity that improves rapidly with the establishment of euglycemia (3). The rapidity of the recovery indicates that it is unlikely to depend on nerve fiber regeneration or remyelination. Such patients often also exhibit increased resistance to ischemic conduction failure (RICF) (4), which also resolves rapidly with control of the diabetes. RICF is associated with a reduction of ischemic and post-ischemic paresthesias (5). These abnormalities are also present in experimental diabetes in the rat, and it seems likely that the rodent provides a model for these rapidly reversible phenomena in humans. The reduced nerve conduction velocity in the streptozotocin-diabetic rat seems to be at least partly explicable by nerve hypoxia (6,7). The probable explanation for RICF is enhanced anaerobic glycolysis secondary to hyperglycemia (8).

Patients with poorly controlled diabetes may experience uncomfortable sensory symptoms distally in the lower limbs that clear rapidly with the establishment of euglycemia. Such symptoms may also reflect nerve hypoxia. It has recently been shown experimentally that hyperglycemic but not normoglycemic hypoxia alters the after potential and fast K^+ conductance in rat axons by cytoplasmic acidification (9). This could result in the generation of ectopic discharges that might provide an explanation for the positive sensory symptoms that occur.

SYMMETRIC POLYNEUROPATHY

Peripheral nerve manifestations other than hyperglycemic neuropathy are more persistent. Broadly speaking, these can be subdivided into symmetric polyneuropathies, on the one hand, and focal and multifocal neuropathies on the other, although multiple proximal lesions can summate to produce a distally accentuated symmetric involvement (10).

The most common of these more persistent manifestations is a symmetric distal polyneuropathy. It is predominately sensory and autonomic, with relatively minor motor involvement. A recent study (A.J.M. Boulton, S. Tesfaye, P.K.T., S. Tsigos, J.D. Ward, R.J. Young, unpublished obser-

vations) investigated a total of 669 patients from three hospital diabetic clinics. Of these, 49.2% were men and 50.8% women. Their mean age was 65.4 ± 11.1 (SD) years. Of the patients, 9.6% were receiving insulin treatment, and information was not available for 1.5%; the remainder were being treated by diet or hypoglycemic drugs. For patients with a symmetric polyneuropathy, sensory involvement was present in 61.6% and motor in 11.8%. Autonomic involvement (excluding impotence) was evident in 32.6% and impotence in 39.2%.

This distal sensory/autonomic polyneuropathy is usually of insidious onset and, once established, is largely irreversible (11). As the neuropathy advances, the sensory loss extends proximally up the limbs. Later it affects the anterior abdominal wall and then spreads laterally around the trunk. Ultimately the vertex of the head and the central face may be affected. Variants have been described, including painful small-fiber (12) or pseudosyringomyelic (13) syndromes and an ataxic syndrome (diabetic pseudotabes). It is as yet uncertain whether there is a regular sequence of fiber involvement, with small fibers affected initially and larger fibers later, or whether the small- and large-fiber types represent either side of a continuous spectrum of fiber damage (14). There are some indications that small-fiber damage is the salient manifestation, to which large-fiber damage may be added. Guy et al. (15) found that thermal sensibility, indicating small-fiber damage, could be impaired in isolation or in combination with loss of vibration sense, indicating additional large-fiber involvement; the reverse pattern, i.e., selective loss of vibration sense, was not encountered. Serial studies on individual patients are required.

Autonomic neuropathy is regularly associated with a sensory neuropathy. Almost any aspect of autonomic function may be affected. In most instances, the symptoms are not severe, but cases with devastating autonomic dysfunction are encountered, usually in patients with IDDM. Such patients may experience incapacitating gastroparesis, nocturnal diarrhea, orthostatic hypotension, or cystopathy. Once established, autonomic neuropathy is substantially irreversible (11).

ACUTE PAINFUL DIABETIC NEUROPATHY

This condition merits separation as a distinct syndrome. Archer et al. (16) described a series of patients who, following profound and precipitate weight loss, developed severe unremitting burning pain distally in the lower limbs. This was most troublesome at night and was associated with unpleasant contact cutaneous hyperesthesia in the legs. Motor function and tendon reflexes, apart from loss of the ankle jerks in some patients, were preserved. Sensory loss was often slight. Autonomic dysfunction, apart from impotence, was not prominent. This syndrome has been described in women with anorexia nervosa (17) and may follow the establishment of tight diabetic control (18).

FOCAL AND MULTIFOCAL NEUROPATHIES

Isolated peripheral nerve lesions may be a feature in older diabetic patients. These may affect the cranial, thoraco-abdominal, or limb nerves. Of the cranial nerves, the third is the most commonly affected (19), with the sixth and seventh nerves being next in frequency. The onset of a third-nerve palsy is often abrupt and associated with pain. Truncal neuropathy may present as girdle-like pain, with or without accompanying cutaneous sensory impairment or hyperesthesia (20). Sometimes there is focal weakness of the anterior abdominal wall (21,22).

TABLE 1
Classification of diabetic neuropathy

"Hyperglycemic neuropathy"
Symmetric polyneuropathy
Sensory/autonomic polyneuropathy
Acute painful diabetic neuropathy
Focal and multifocal neuropathy
Cranial neuropathy
Thoraco-abdominal neuropathy
Focal limb neuropathies
Diabetic amyotrophy
Mixed forms

Focal lesions of limb nerves are accepted as being more common in diabetic subjects than in the general population. These are often at common sites of entrapment or external compression, suggesting an abnormal vulnerability of diabetic nerve to mechanical injury (23).

Diabetic amyotrophy consists of unilateral or asymmetric bilateral proximal lower limb weakness, often of acute or subacute onset and frequently accompanied by pain. Sensory loss is usually not prominent. Bilaterally symmetric proximal lower limb weakness of insidious onset has been separated as a distinct syndrome (24), but the justification for this requires validation. At times, both proximal and distal lower limb muscles are affected in diabetic amyotrophy (diabetic paraplegia). Upper limb involvement is rare.

DIFFERENTIAL DIAGNOSIS OF DIABETIC NEUROPATHY

The main diagnostic problems usually arise in patients with NIDDM in whom there is an accompanying symmetric polyneuropathy or a focal or multifocal neuropathy. NIDDM is a relatively common disorder in the older age-groups, and a chance association with a neuropathy from another cause is possible.

In a patient with a small-fiber sensory polyneuropathy with autonomic features, amyloidosis may need exclusion, as may lepromatous leprosy in a patient from an endemic area and without autonomic symptoms. Nerve thickening may provide a diagnostic clue in both of these disorders. If diagnostic doubt exists, nerve biopsy is merited.

For pure sensory neuropathies with large-fiber involvement, conditions such as vitamin B_{12} deficiency, paraneoplastic neuropathy, or neuropathy related to Sjögren's syndrome will require consideration and appropriate investigation (25). For a Sjögren's-syndrome neuropathy, the occurrence of xerophthalmia and xerostomia and the presence of tonic pupils and facial sensory loss may be valuable pointers. Paraproteinemic neuropathy may be purely sensory.

If motor involvement is prominent, the possibility of chronic inflammatory demyelinating polyneuropathy (CIDP) or, particularly in older subjects, paraproteinemic neuropathy will arise. Severely reduced motor nerve conduction velocity, which is often patchy, and the demonstration of conduction block will suggest CIDP or neuropathy related to an IgG or IgA paraprotein. Nerve biopsy to look for inflammatory infiltration is usually desirable. Rarely is purely sen-

sory CIDP encountered, but in such cases, motor nerve conduction velocity is usually also markedly reduced. It is possible that CIDP may be superimposed on diabetic neuropathy as a secondary event (26). Nerve conduction velocity tends to be diffusely reduced in neuropathy related to IgM paraproteins. On nerve biopsy, the finding of IgM deposition on surviving myelin and the demonstration of widely spaced myelin ultrastructurally will establish that the neuropathy is related to the paraprotein.

The syndrome of acute painful diabetic neuropathy is usually sufficiently characteristic for it to be readily recognized, but because of the relative lack of abnormal findings on examination, the symptoms run the risk of being attributed to psychoneurosis.

Occasionally, slowly evolving symmetric distal motor neuropathy of the axonopathy type is encountered in diabetic individuals with no indication of any causation on investigation other than diabetes (27). The nature of these cases is at present uncertain.

In an acute, painful diabetic third-cranial-nerve palsy, compression of the nerve from an intracranial aneurysm is the most important condition to enter into the differential diagnosis. Diabetic third-nerve lesions characteristically spare pupillary function, whereas this is not true of compressive neuropathy. This is not an absolute distinction, however, and magnetic resonance angiography may be required. Truncal mononeuropathies or radiculopathies may need the exclusion of spinal compressive lesions.

Diabetic amyotrophy has to be distinguished from cauda equina and other lumbosacral plexus lesions such as malignant invasion. The evolution of diabetic amyotrophy often provides the solution, with a rapid onset and subsequent improvement. The finding of a markedly increased latency of the response in the quadriceps muscles on electrical stimulation of the femoral nerve in the groin can be helpful diagnostically (28). Recent observations by Said et al. (29) made on biopsy of the intermediate cutaneous nerve of the thigh have indicated that in a proportion of patients with proximal lower limb diabetic neuropathy, inflammatory changes, including evidence of vasculitis, are demonstrable. This again may reflect a secondary autoimmune process.

ASSESSMENT AND STAGING OF DIABETIC NEUROPATHY

The ability to assess treatment regimens for diabetic neuropathy necessitated the establishment of reliable criteria for its evaluation and staging. This has been done for symmetric polyneuropathy because it is the most important manifestation. Its pathological basis is a degenerative neuropathy, probably involving a distal axonopathy of dying-back type (13). It is thus important that assessment should not be contaminated by the use of symptoms and electrophysiological changes of the kind that are rapidly reversed by the control of hyperglycemia. A landmark in the development of reliable evaluation procedures was the study by Dyck et al. (30). The gold standard for identification of the presence and severity of neuropathy was the Index of Pathology, which combined reduction in myelinated fiber density with abnormalities detected in surviving teased myelinated nerve fibers. It was shown that assessment both clinically by a Neuropathy Symptom Scale and a Neurologic Disability Score and electrophysiologically through nerve conduction studies gave a valid discrimination between neuropathy and absence of neuropathy. A limitation of the Index of Pathology is that it does not include an evaluation of unmyelinated axons, and teased fiber studies fail to sample small myelinated fibers adequately.

In a further study, Dyck (31) produced a scheme for the staging of neuropathy. Four stages were proposed: stage 0, no neuropathy; stage 1, asymptomatic neuropathy; stage 2, symptomatic neuropathy; stage 3, disabling neuropathy. Categorization of the neuropathy is given as an overall stage (0–3) subdivided into motor (M), sensory (S), and autonomic (A) components, with each staged separately from 0 to 3, and finally a designation indicating which components of the assessment were abnormal. The minimal criterion for a diagnosis of polyneuropathy was the presence of two or more abnormalities from the NSS or neuropathic defects as assessed by the NDS, nerve conduction testing, quantitative sensory testing (vibration or cooling sensory thresholds), or a quantitative autonomic examination (heart rate variability on deep breathing or the Valsalva maneuver), with at least one being an abnormality of nerve conduction or quantitative autonomic testing. Inability to walk on the heels was used to discriminate between milder (2a) and more severe (2b) patients with stage 2 diabetic polyneuropathy (32).

The Mayo Clinic assessment is elaborate and time consuming. A simpler scheme was devised by Feldman et al. (33), the results of which correlate well with those of the Dyck evaluation. It may prove more practical for general use. A brief questionnaire and screening examination is first administered. This can be performed by nonneurologist physicians or nurse practitioners. If patients score above a threshold level, they are then assessed by the Michigan Diabetic Neuropathy Score (MDNS), which combines a quantified neurological evaluation, concentrating on the abnormalities that occur in diabetic polyneuropathy, and a battery of nerve conduction studies. On the basis of this combined clinical and electrophysiological evaluation, patients are again categorized into four stages: 0, no neuropathy; 1, mild neuropathy; 2, moderate neuropathy; 3, severe neuropathy. A comparison of a group of 56 patients assessed in this way and according to the Mayo Clinic classification showed a good correlation. This scheme and the Mayo Clinic assessment were devised for the evaluation of symmetric diabetic polyneuropathy. Dyck et al. (34) have also proposed minimal criteria for the diagnosis of diabetic autonomic neuropathy and for focal neuropathies, including cranial neuropathy, carpal tunnel syndrome, truncal radiculopathy, and proximal asymmetric lower limb neuropathy.

An alternative approach for the evaluation of sensory polyneuropathy has been to use changes in serial nerve biopsies for the assessment of neuropathy. This has been incorporated into a number of recent treatment trials. Assessments are made of myelinated fiber density and the amount of regenerative activity (35). This approach suffers from the disadvantage that nerve biopsy is invasive and has a low but significant complication rate (36). In addition, the finding of increased regenerative axonal sprouting does not provide information as to whether the sprouts are functional. There is some evidence that diabetic polyneuropathy may represent a central-peripheral distal axonopathy (37), and if the regenerating axons at the periphery are not connected centrally to the second-order afferent neurons, no functional benefit will result. Ultimately, it is necessary to show stabilization or improvement of neurological function. Because of the slow

time course of diabetic polyneuropathy, studies with the length of the Diabetes Control and Complications Trial (38) will be required.

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