Ann Natl Acad Med Sci (India), **46(2):** 118-136, 2010

Screening, Early Detection and Diagnosis of Diabetic Neuropathy

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Abstract

Diabetic neuropathy (DN) refers to symptoms and signs of neuropathy in a patient with diabetes in whom other causes of neuropathy have been excluded. Distal symmetrical neuropathy is the commonest, accounting for 75% of DN. Asymmetrical neuropathies may involve cranial nerves, thoracic or limb nerves. Asymmetric neuropathies in diabetic patients should be investigated for entrapment neuropathy. Diabetic amyotrophy, initially considered to result from metabolic changes, and later to ischaemia, is now attributed to immunological changes.

For screening, early detection and diagnosis of DN, symptoms, signs, quantitative sensory testing, nerve conduction study, autonomic testing and other modalities are used; and two of these five are recommended for clinical diagnosis. Despite all the advances, proper history and thorough neurological examination of the lower limbs constitute the essential prerequisites for the clinical diagnosis of DN.

The neuropathies are among the most common of the long-term complications of diabetes, affecting up to 50% of patients (1). Members of an international consensus meeting on the outpatient diagnosis and management of DN agreed on a simple definition of DN as "the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes" (2). It was also agreed that neuropathy cannot be diagnosed without a careful clinical examination- absence of symptoms cannot be equated with absence of neuropathy, as asymptomatic neuropathy is common. The importance of excluding nondiabetic causes was emphasized in Rochester Diabetic Neuropathy Study, in which up to 10% of peripheral neuropathy in diabetic

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patients was deemed to be of nondiabetic causes (1).

There is a higher prevalence of DM in India (4.3%) (3) compared with the West (1%–2%) (4). Probably Asian Indians are more prone to insulin resistance and cardiovascular mortality (5). The epidemiology and natural history of diabetic neuropathy (DN) remain poorly defined, partly because of poor patient selection and the variable criteria for what constitutes a diagnosis of DN. The incidence of DN in India is not well known but in a study from South India, 19.1% type II diabetic patients had peripheral neuropathy (6). Diabetic autonomic neuropathy accounts for silent myocardial infarction and shortens the lifespan resulting in death in 25%-50% patients within 5-10 years of the onset of autonomic diabetic neuropathy (7). According to an estimate, two thirds of diabetic patients have clinical or subclinical neuropathy. The diagnosis of subclinical DN requires electro-diagnostic testing and quantitative sensory and autonomic testing. The prevalence of neuropathy increases with the duration of diabetes mellitus. In a study, the incidence of neuropathy increased from 7.5% on admission to 50% at 25 years follow up (8). There is increasing evidence that measures of neuropathy, such as electrophysiology and quantitative tests, are predictors of not only end points, including foot ulceration, but also of mortality (9).

Table 1 gives the classification of DN used in this paper.

Table 1: Classification of Diabetic Neuropathies

Symmetrical Polyneuropathies

- Distal sensory or sensorimotor polyneuropathy
- Large-fiber neuropathy
- Small-fiber neuropathy
- Autonomic neuropathy

Asymmetrical Neuropathies

- Cranial neuropathy (single or multiple)
- Truncal neuropathy (thoracic radiculopathy)
- Lumbosacral radiculopathy (asymmetrical proximal motor neuropathy)
- Limb mononeuropathy (single or multiple)
- Entrapment neuropathy

Combinations

- Polyradiculoneuropathy
- Diabetic neuropathic cachexia
- Symmetrical polyneuropathies

DISTAL SYMMETRICAL POLY-NEUROPATHY (DSPN)

DSPN is the commonest type of DN and probably accounts for 75% of DNs. It may be sensory or motor and may involve small or large fibers, or both. Sensory impairment occurs in glove and stocking distribution and motor signs are not prominent. Fiber dependent axonopathy results in increased predisposition in taller people (10). DSPN is further classified into large fiber and small fiber neuropathy. Large fiber neuropathy is characterised by painless paraesthesias with impairment of vibration, joint position, touch and pressure sensations, and loss of ankle reflex. In advanced stage, sensory ataxia may occur. Small fiber neuropathy on the other hand is associated with pain, burning, and impairment of pain and temperature sensations, which are often associated with autonomic neuropathy. Nerve conduction studies are usually normal but quantitative sensory and autonomic tests are abnormal. Autonomic neuropathy is usually associated with DSPN; but diabetic autonomic neuropathy does not occur without sensory motor neuropathy.

Painful DN

About 10% of diabetic patients experience persistent pain (11). Pain in DN can be spontaneous or stimulus induced, severe or intractable. DN pain is typically worse at night and can be described as burning, pins and needles sansations, shooting, aching, jabbing, sharp, cramping, tingling, cold, or allodynia. Some patients develop predominantly small fiber neuropathy manifesting with pain and paraesthesias early in the course of diabetes that may be associated with insulin therapy (insulin neuritis) (12).

Diabetic autonomic neuropathy

Diabetic autonomic neuropathy affects various organs of the body resulting in cardiovascular, gastrointestinal, urinary, sweating, pupils, and metabolic disturbances. Autonomic nerve involvement can occur as early as one year after the diagnosis of DM. Diabetic autonomic neuropathy usually correlates with severity of somatic neuropathy. It ranges from subclinical functional impairment of cardiovascular reflexes and sudomotor functions to severe cardiovascular, gastrointestinal, or genitourinary dysfunction. Orthostatic hypotension, resting tachycardia, and heart rate unresponsiveness to respiration are hallmark of diabetic autonomic neuropathy (7, 8).

ASYMMETRIC NEUROPATHIES

Cranial neuropathy

Cranial neuropathy in diabetic patients most commonly involves the oculomotor nerve, followed by trochlear and facial nerve in order of frequency. Third nerve palsy with pupillary sparing is the hallmark of diabetic oculomotor palsy and is attributed to nerve infarction. The pupillary fibers are peripherally located and therefore, escape in diabetic oculomotor palsy (5, 6, 7).

Diabetic Truncal neuropathy is associated with pain and paresthesia in T4–T12 distribution in chest or abdominal distribution. Bulging of abdominal wall may occur because of muscle weakness. It usually occurs in older patients with NIDDM. The onset may be abrupt or gradual and the patient may be confused with an intra-abdominal, intra-thoracic disease, or herpes zoster. Electromyography may show paraspinal denervation (5, 7).

Asymmetrical proximal diabetic neuropathy

It is also referred to as diabetic amyotrophy but should better be called as diabetic proximal neuropathy (13). The other examples of proximal DN include thoracic radiculopathy and proximal diffuse lower extremity weakness that should be grouped under a single term diabetic polyradiculopathy, as these are diverse manifestations of same phenomena: root or proximal nerve involvement. The patients complain of pain in low back, hip, anterior thigh, typically unilateral but may be bilateral. Within days or weeks, the weakness and wasting of thigh and leg muscles follows. Knee reflex is reduced or absent. Numbness or paraesthesias are minor phenomena. Weight loss occurs and weakness may persist indefinitely. In about 50% patients with diabetic proximal neuropathy, DSPN may coexist. Nerve biopsy shows multifocal nerve fiber loss suggesting ischaemic injury and perivascular infiltrate suggesting an immune mechanism (8). Diabetic amyotrophy, which was initially thought to be attributable to metabolic changes, was later regarded as ischaemic because of biopsy changes but now is considered to be attributable to immunological abnormality (14). This has prompted intravenous immuno-globulins (IVIg) and cyclophosphamide therapy, which have resulted in rapid recovery (15).

In patients with proximal DN, especially if it is bilateral and the distal muscles are also involved, electrodiagnostic testing may show demyelinating features resembling chronic inflammatory demyelinating

neuropathy (CIDP). In such patients apart from CIDP, monoclonal gammopathy and vasculitic neuropathy should also be considered (15,16). Biopsy of obturator nerve has shown demyelination, inflammatory cell infiltrate, and immunoglobulin deposits in vasanervosa (17). Cerebrospinal fluid protein may be raised without lymphocytic pleocytosis. It is important to differentiate CIDP from lumbosacral radiculo-plexoneuropathy attributable to ischaemic origin because of different therapeutic options. Diabetic patients are 11 times more vulnerable to develop CIDP (18) and they respond to immunomodulation by corticosteroid, plasma exchange, or IVIg.

Limb neuropathies

There are two major mechanisms of limb neuropathies in diabetics, viz., nerve infarction and entrapment. Nerve infarctions are associated with abrupt onset pain followed by variable weakness and atrophy. The recovery is slow over a period of months, as the primary pathology is axonal degeneration. Median, ulnar, and peroneal nerves are most commonly affected (16).

Entrapment Mononeuropathy

In diabetic patients, nerve entrapment is commoner than nerve infarction. The entrapment neuropathies have insidious onset, with characteristic electrodiagnostic features such as conduction block or segmental nerve conduction slowing in the entrapped segment of the nerve. Carpal tunnel syndrome is three times more common in diabetic patients than in the normal population. The other entrapment neuropathies in diabetic patients are ulnar, radial, lateral femoral cutaneous nerve of thigh, peroneal and medial and lateral planter nerves (18).

SCREENING, EARLY DETECTION AND DIAGNOSIS OF DIABETIC NEUROPATHY

For screening and early detection, a proper history and thorough physical examination is essential, in addition to other ancillary investigations discussed below.

A) SCREENING SYMPTOMS:

A number of simple symptom screening questionnaires are available to record symptom quality and severity. The Michigan Neuropathy Screening Instrument (MNSI) is a brief 15-item questionnaire that can be administered to patients as a screening tool for neuropathy (19). Other similar symptom scoring systems have also been described (20). It is well recognized that both symptoms and deficits may have an

adverse effect on quality of life (QOL) in DN (21). The NeuroQol, a recently developed and validated QOL instrument, also includes a symptom checklist and may be used as outcome measure in future clinical studies (22).

B) SCREENING SIGNS:

For diagnosis of DN, bedside examination should include assessment of muscle power, sensations of pinprick, joint position, touch, and temperature. Vibration test should be done by tuning fork of a 128 Hz. Sensory examination should be performed on hands and feet bilaterally. In old age (≥70 years) vibration and ankle reflex may be reduced normally and should be considered abnormal only if these are absent rather than reduced in a patient with DN.

The use of composite scores to assess clinical signs was pioneered by Dyck and colleagues (23,24), who first described the Neuropathy Disability Score (NDS) and later the Neuropathy Impairment Score (NIS), based on the Vibration perception threshold (VPT); temperature perception on dorsum of foot; Pin-prick and Achillis reflex. A modified NDS has been used in several large studies (25) and can also be used in the community by a trained

Table 2: Modified Neuropathy Disability Score (NDS)

		Right	Left
Vibration Perception Threshold (VPT) 128 Hz tuning fork; apex of big toe; Normal = can distinguish vibration/not vibrating	Normal = 0 Abnormal = 1		
Temperature perception on dorsum of the foot Use tuning fork with beaker of ice/warm water			
Pin prick Apply pin proximal to big toe nail just enough to deform the skin; trial pair = sharp, blunt; normal = can distinguish sharp / not sharp			
Achilles reflex	Present = 0 Present with reinforcement = 1 Absent = 2		
	NDS total out of 10		

nonspecialist (Table 2). It has been shown to be the best predictor of foot ulceration and the best neuropathic end point in a large prospective community study (25). The maximum NDS is 10, with a score of 6 or more being predictive of foot ulcer risk. Whatever methodology is used in the assessment and documentation of neuropathic signs, it should be noted that the neurological examination of the lower limbs is the important aspect in the clinical diagnosis of DN (26).

The autonomic function tests commonly used in DM are based on blood pressure and heart rate response to a series of maneuvers. Specific tests are used for evaluating gastrointestinal, genitourinary, sudomotor function, and peripheral skin blood flow.

Other simple devices for clinical screening:

Although the simple handheld screening devices are less sensitive than the more sophisticated QST devices, they have the advantage of being relatively inexpensive, easy to operate, and easily portable; therefore, their use in clinical practice is increasing.

a) Semmes-Weinstein monofilament is the most widely used device in clinical practice (27). The filament assesses pressure perception when gentle pressure is applied to the handle sufficient to buckle the nylon filament. Although filaments of many different sizes are available, it is the one that exerts 10 g of pressure that is the most commonly used to assess pressure sensation in the diabetic foot. A number of cross-sectional studies have assessed the sensitivity of the 10 g monofilament to identify feet at risk of ulceration, which varies from 86 to 100% (28). The most common algorithm recommends four sites per foot: generally the hallux and metatarsal heads 1, 3, and 5 (27).

b) The graduated Rydel-Seiffer tuning fork is used in some centers to assess neuropathy (29). This fork uses a visual optical illusion to allow the assessor to determine the intensity of residual vibration on a 0–8 scale at the point of threshold (disappearance of sensation).

c) The tactile circumferential discriminator assesses the perception of calibrated change in the circumference of a probe (a variation of two-point discrimination). Vileikyte et al. (30) reported 100% sensitivity in the identification of patients at risk of foot ulceration.

C) QUANTITATIVE SENSORY TESTING (QST):

QST are procedures requiring a power source where the intensity and characteristics of the stimuli are well

controlled and where the detection threshold is determined in parametric units that can be compared with established "normal" values (31). QST measures can be used to identify the sensory modalities affected and to estimate the magnitude of the deficit. QST may be used as ancillary test but is not recommended for routine clinical practice. In the diabetic population, vibration, thermal, and pain thresholds have proven valuable in the detection of subclinical neuropathy (32), in tracking the progression of neuropathy in large cohorts (33), and in predicting patients "at risk" for foot ulceration (34). The strengths of QST are accurate control of stimulus characteristics; the ability to assess multiple modalities; the use of well-established psychophysical procedures to enhance sensitivity; the ability to measure sensation at multiple anatomical sites, enabling the exploration of a potential distal-to-proximal gradient of sensory loss; and the availability of data from large, age-matched, "normal" comparison groups.

The limitations of QST are also clear. No matter what the instrument or procedure used, QST is only a semi-objective measure, affected by the subject's attention, motivation, and cooperation, as well as by anthropometric variables such as age, sex, body mass, and history of smoking and alcohol consumption (35). Further, QST is sensitive to changes in structure or function along the entire neuroaxis from nerve to cortex; it is not a specific measure of peripheral nerve function (31).

Recently, a consensus sub-committee of the American Academy of Neurology (36) stated, "QST testing for vibratory and cooling thresholds receives a Class II rating as a diagnostic test. Further, QST is designated as safe, effective and established, with a type B strength of recommendation. However, QST is unacceptable as the sole criteria to define diabetic neuropathy."

Vibration Perception thresholds (VPT). Multiple studies have documented the relation between loss of vibration sensation and the progression of a variety of indicators of DPN (37). Dyck et al. (38) used computer-assisted QST to evaluate three large cohorts and identified a "strong and consistent correlation" between sensory loss and other markers of DN. These studies confirmed that vibration thresholds are especially sensitive to mild or subclinical neuropathy. Davis et al. (39) also demonstrated that vibratory thresholds can detect subclinical neuropathy in children and adolescents with type 1 diabetes. Boulton et al. (40) documented

that vibration thresholds provided a strong indication of "risk" for future ulceration across a wide range of ages and durations of diabetes. In a 4-year prospective study (41), patients with baseline threshold elevated above a fixed value (i.e., 25 V with the biosthesiometer) were seven times more likely to develop foot ulcers (34). The strength of the relationship between elevated VPT and foot ulceration is illustrated by the finding, in 1,035 type 1 and type 2 diabetic patients, that each 1-unit increase in vibration threshold (voltage scale) at baseline increased the hazard of foot ulceration by 5.6% over a 1-year study period (42).

Thermal thresholds. Thermal energy is conducted in thinly myelinated A or unmyelinated C fibers and is principally transmitted in the crossed anterolateral tracts of the spinal cord. As is the case with vibration, altered thermal thresholds have been well documented in patients with DN defined by other criteria (37,38), and their elevation has been associated with progression of neuropathy and ultimately with foot ulceration (43). Abnormal thermal thresholds have been reported in 75% of subjects with moderate-to-severe DPN, and elevated heat-pain thresholds were detected in 39% of these subjects (44). Generally, there is a high correlation between elevated thermal and vibration thresholds, but these measures can be dissociated, suggesting a predominant small- or large-fiber neuropathy in individual patients. It is technically more challenging to measure thermal thresholds compared with vibration thresholds; the evaluation generally takes longer and the smallest detectable difference has been reported as approximately double that of vibration (45).

D) ELECTROPHYSIOLOGY:

Whole nerve electrophysiologic procedures (e.g., NCV, F-waves, sensory, and/or motor amplitudes) have emerged as an important method of tracing the onset and progression of DPN (46). An appropriate battery of electrophysiologic tests support the measurement of the speed of both sensory and motor conduction, the amplitude of the propagating neural signal, the density and synchrony of muscle fibers activated by maximal nerve stimulation, and the integrity of neuromuscular transmission. These are objective, parametric, noninvasive, and highly reliable measures. However, "standard" procedures, such as maximal NCV, reflect only a limited aspect of neural activity and that only in a small subset

of large-diameter and heavily myelinated axons. A key role for electrophysiological assessment is to rule out other causes of neuropathy or to identify neuropathies superimposed on DPN. Unilateral conditions, such as entrapments, are far more common in diabetic patients (47,48). Sharma et al. (18) reported that the odds of occurrence of CIDP were 11 times higher among diabetic than nondiabetic patients. The symmetry of electrophysiological measures, and the nature and magnitude of the deficits, can help identify additional causes for neurological deficits.

Specific electrophysiologic measures in DPN

Nerve Conduction Velocities

- NCV is only gradually diminished by DPN, with estimates of a loss of 0.5m/s/year. In a 10-year natural history study of 133 patients with newly diagnosed type 2 diabetes, NCV deteriorated in all six nerve segments evaluated, but the largest deficit was 3.9 m/s for the sural nerve (i.e., 48.3 to 44.4 m/s); peroneal motor NCV was decreased by 3.0 m/s over the same period (49).
- NCV provides a sensitive but nonspecific index on the onset of DPN and can be valuable in detecting subclinical deficits (50).
- NCV can trace the progression of DPN and can provide a valuable measure of the severity of DPN and "quality of life related to peripheral nerve involvement" (51).
- Changes in NCV are related to glycemic control (52). In the DCCT, subjects who were "free of confirmed neuropathy at baseline" had a 40.2% incidence of abnormal NCV in the conventionally treated group and only 16.5% in the group receiving intensive therapy after a period of 5 years (53). This was associated with a between-group difference of 4.0 m/s for the peroneal nerve and 3.9 m/s for the sural nerve.
- Changes in NCV can reflect underlying structural pathology in large-diameter axons, including atrophy, demyelination, and loss of fiber density (54).
- NCV can improve with effective therapy (55) or with transplantation (56).

Amplitudes, area, and duration

Peak amplitude of either the SNAP or the CMAP driven by maximal stimulation reflects the number of responding fibers and the synchrony of

their activity. There is a strong correlation between myelinated fiber density and whole-nerve sural amplitude (57) in DPN. Russell et al. (58) calculated that a change of 1.0 V in sural nerve SNAP amplitude is associated with a decrease of 150 fibers/mm^2, while a loss of 200 fibers/ mm^2 is associated with an approximate 1.0-mV reduction in the mean amplitude of the CMAP from the ulnar, peroneal, and tibial nerves. Longitudinal studies suggest an average loss of SNAP amplitude at a rate of 5% per year in DPN over a 10-year period (49). Measuring the total area of the SNAP and CMAP has been suggested as a means of assessing the contribution of slower conducting fibers, but these measures are severely limited by variability. Area alone, or in association with peak amplitude, can also be used to estimate the degree of temporal dispersion and conduction block.

F-waves

F-waves reflect the antidromic conduction of the compound neural volley to the ventral spinal cord, the activation of a subpopulation of spinal motor neurons, the orthodromic conduction of the newly established volley, and the postsynaptic activation of a portion of the muscle fibers in the innervated muscle. Because of its "long-loop" nature, this measure is sensitive to factors that alter the speed of conduction, especially those widely distributed along the nerve. A subtle change affecting each node may not be detected in measures focused on an isolated distal segment, but may accumulate and become evident in the long latency F-wave response. F-wave procedures have been reported as a sensitive and reliable tool in patients with axonal polyneuropathy (59). However, changes limited to the distal segment of the axon, including possible therapeutic benefits, may be poorly represented in F-wave measures. Minimal latency is the most frequent measure of F-wave activity. However, the addition of chronodispersion, duration, persistence, and amplitude can add sensitivity to slower conducting axons (59).

E) OTHER METHODS OF ASSESSMENT

Nerve biopsy: The nerve biopsy, typically of the sural nerve, posterior to the lateral malleolus, has been used for many years in the study of peripheral neuropathy (60). When undertaken at a center with sufficient expertise, it is a useful diagnostic procedure in patients with neuropathy of a known origin or in diabetic patients with atypical neuropathies (60). However, this is an

invasive procedure with recognized sequelae that might include persistent pain at the biopsy site, cold intolerance, unpleasant though mild mechanically elicited sensory symptoms, and sensory deficits in the sural distribution (61). These prolonged sensory symptoms and sensory loss appear to occur more commonly in diabetic than in nondiabetic subjects (61,62). Thus, with the widespread availability of accurate QST and electrophysiological techniques, biopsies are rarely required for the routine diagnosis of DPN. For clinical diagnostic purposes, a fascicular or subtotal biopsy should suffice; if the nerve is left in continuity, a greater possibility of regeneration across the gap exists (60). In addition to assessing responses to therapy, nerve biopsies have also been used to help determine the etiopathogenesis of neuropathy.

Nerve exposure: A number of published studies investigating the pathogenesis of neuropathy have studied the sural nerve in vivo without actually biopsying it. These have included using microelectrodes to measure endoneurial oxygen tension (63) and the use of epineurial vessel photography and fluorescein angiography to study the neural microvasculature (12). More recently, the same group used a new minimally invasive technique of microlight-guide spectrophotometry to measure blood flow and oxygen saturation in the sural nerve (64). However, these techniques are only used in specialist research units investigating the etiopathogenesis of DPN.

Skin biopsy: The significance and usefulness of immunohistochemically quantitated cutaneous nerves in the morphological assessment of DPN is increasingly being recognized (65). It was the discovery of the panaxonal marker, protein gene product 9.5, that allowed the direct visualization of epidermal nerve fibers. This technique, though still invasive, only requires a 3-mm skin biopsy and enables a direct study of small nerve fibers, which are difficult to assess electrophysiologically (65). Recently, this method was used to assess early neuropathic changes in diabetes and IGT (66).

Noninvasive assessment

MRI has been used to assess involvement of the spinal cord in neuropathy. In an exploratory study, Eaton et al. (67) used MRI of the cord and demonstrated that patients with DPN had a lower cross-sectional cord area than healthy control subjects in the cervical and thoracic regions, leading

them to suggest that DPN is not simply a disease of the peripheral nerves.

Recently, **confocal corneal microscopy** in the assessment of diabetic polyneuropathy has been reported. In confocal microscopy, the cornea is scanned and the images of Bowman's layer, which contains a rich nerve plexus, are examined for nerve fibre density, length, and branch density. These parameters are significantly reduced in DN and correlated with the severity of neuropathy. Because of its noninvasive nature, confocal microscopy may have great potential in assessing nerve structure in vivo without need for nerve biopsy (68, 69).

Conclusion:

DN is diagnosed in presence of somatic or autonomic neuropathy when other causes of neuropathy have been excluded. About 10% of diabetic patients may have other causes of neuropathy. DN cannot be diagnosed without careful examination, because DN may be asymptomatic in a number of patients. At least one of each of the five criteria is needed in research protocols: symptoms, signs, quantitative sensory, autonomic testing and electrodiagnostic tests. However, in clinical practice two of five criteria have been recommended and is important to prevent under-diagnosis or misdiagnosis of DN.

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