

PAINFUL DIABETIC NEUROPATHY

GR Sridhar*

Neuropathic complications of diabetes are a major cause of distress. Even though neuropathy is not a single entity but a diverse group of disorders exhibiting a wide range of natural histories and clinical manifestations, the likelihood of clinical neuropathy increases with increasing duration of hyperglycemia (1). The prevalence varies from 10.7 - 62.0% (2). Patients generally complain of foot or leg pain that is burning, tingling, lancinating, aching or tearing. These may be present without abnormal neurological signs or decreased nerve conduction velocity.

In a group of 779 persons with diabetes mellitus from our data base (3), who were clinically and biochemically worked-up, burning and paresthesia was complained of by 124 (15.9%) and burning only without paresthesia by a further 49 (6.3%) (Table 1). In addition a comparison of neuropathic symptoms in relation to known duration of diabetes is also given (Table 2).

Table 1 : Prevalence of neuropathic symptoms in diabetes : EDC data (n=779)

Burning and paresthesia + :	124(15.9%)
Burning +, no paresthesia:	49(6.3%)
No burning or paresthesia:	606(77.8%)

Table 2 : Comparison of neuropathic symptoms vs duration of known diabetes mellitus: EDC data (n=779)

Duration of DM (yrs)	B+P+*	B+P-**	BP-***
0	19 (15%)	13 (26.5%)	165 (17%)
>0, <1	16 (13%)	10 (20%)	119 (20%)
1-5	48 (39%)	12 (24.5%)	193 (32%)
6-10	28 (23%)	11 (22.5%)	89 (15%)
>10	13 (10%)	3 (6%)	40 (6%)

* Burning and paresthesia are both present

** Burning only, no paresthesia

***No burning or paresthesia

It is apparent that neuropathic symptoms were present in more than 20% of patients, with a majority complaining of both paresthesia and burning sensation. Most had diabetes for less than ten years. Either the duration of diabetes was longer than the known duration, or sensations were

attenuated by progressive neuropathy. Burning sensation without paresthesia were complained of more frequently by those with diabetes for less than a year. A combination of burning and paresthesia was found mostly in those having diabetes for one to five years (Table 2).

Pathophysiology

The exact pathogenesis of diabetes neuropathy is not known. The current concept is that nerve damage begins early in the course of diabetes and worsens imperceptibly, eventually becoming clinically evident (1). A number of causes singly or together are believed to result in diabetic neuropathy.

- **Polyol pathway** : Neural tissue has a sorbitol pathway, in which glucose is converted to sorbitol by an enzyme aldose reductase. Sorbitol is later converted into fructose by polyol dehydrogenase. Animal models of diabetes showed that there was accumulation of sorbitol and fructose within the nerve. These were associated with decreased nerve myoinositol, a precursor of the polyphosphoinositides, which are important components of nerve cell membrane. Polyphosphoinositides are involved in regulating the opening and closing of ion channels. They could form a part of the membrane and be involved with the passive transport of sodium ions and thereby the depolarization of nerve fibre. Thus hyperglycemia, nerve cell membrane derangement and symptomatic sensory neuropathy could all be interlinked.

- **Vascular dysfunction** : Another hypothesis suggests that reduced endoneural blood flow and nerve ischemia could be primary contributors to diabetic neuropathy. Reduced nerve blood flow was shown in experimental animals. Vasodilators could prevent slowing of nerve conduction velocity. Human sural nerve biopsies from patients with diabetic neuropathy showed vascular basement membrane thickening, platelet aggregation, occluded vessels, suggesting endoneural ischemia. Impaired perfusion of peripheral nerves could contribute to diabetic neuropathy, including the rare form of acute painful insulin neuritis, resulting from rapid glycaemic control (4.5).

* From Endocrine and Diabetes Centre, 15-12-16 Krishnanagar, Visakhapatnam 530 002.

- **Oxidative stress** : A common factor between the polyol pathway and vascular dysfunction could be oxidative stress and resultant neuropathy. Sequential conversion of glucose to sorbitol and fructose depletes the cellular NADPH and NAD⁺ stores, rendering it vulnerable to reactive oxygen species. Ischemia also induces reactive oxygen species. Experimentally, antioxidant therapy improved nerve conduction studies in animal models. Objective methods of nerve function are preferable in animal studies, because clinical measures such as nocifensive reflex activity as a measure of hyperalgesia may not genuinely indicate peripheral neuropathy, but may be rather due to the extremely poor health of the animals (6).
- **Loss of neurotrophic support** : Recent evidence suggests that loss of neurotrophic support could result in diabetic polyneuropathy. Neurotrophic factors are proteins that promote the survival of specific neuronal populations. Many have other roles such as inducing neuronal morphological differentiation, enhancing nerve regeneration and otherwise altering the physiological characteristics of neurons (7). Nerve growth factor (NGF) supports the small fibre sensory neurons and sympathetic neurons whose degeneration is important in symptoms of sensory polyneuropathy. NGF levels were reduced in diabetes, and its retrograde axonal transport to the neuronal cell bodies is impaired. Reduced expression of NGF in the skin was also reported.
- **Other causes** : A variety of other causes were implicated in the pathogenesis of diabetic neuropathy such as non-enzymatic glycation (8,9), and perhaps also insulin resistance and hyperinsulinemia (10).

Pathology

Quantitative morphological data of nerve fibre pathology showed a significant relationship between clinical measures of neuropathic severity and myelinated fibre loss. However there are no morphological differences between patients with type 1 and type 2 diabetics, nor between those with and without painful neuropathy (11). Occlusion of vasa vasorum, neuronal structural changes, decreased axonal diameters, axonal enlargement are all seen. Heterogenous morphological changes are consistent with diverse and inconsistent subjective symptoms.

Clinical features and natural history

Positive sensory symptoms are numbness, tingling, sharp lancinating pains, dull aches, burning pain and a tightness of calf, hyperesthesia. Most symptoms are worse at night. With worsening neuropathy the symptoms may become more intense, but many patients find the symptoms resolve after normal sensation is lost.

Physical signs consist of sensory loss in the most distal portions of the feet. Different sensations may be affected differently, and each should therefore be tested individually.

Evaluation and Investigations

Diabetic neuropathy is approached by clinical measures, morphological features, electrodiagnosis and sensory testing.

- **Clinical measures** : Clinical assessment is necessary to establish whether neuropathy is present or not and to exclude non neuropathic causes (1). In addition it distinguishes distal sensory polyneuropathy from other forms such as asymmetrical proximal motor neuropathy. In addition they help in monitoring progress with treatment.
- **Morphological** : Nerve biopsy is an invasive technique limited to well-defined groups. Sural nerve tissue is used for morphological study, and must be correlated with clinical date. When performed, full thickness sural nerve biopsy is preferred.
- **Electrodiagnosis** : Electrodiagnosis is sensitive, specific, reproducible and easily standardized. To evaluate symmetric distal diabetic polyneuropathy, nerve conduction studies and conventional needle electromyography are employed. A combination of motor and sensory nerve conduction studies are done in upper and lower limbs.
- **Sensory testing** : Quantitative sensory testing (QST) is the determination of sensory threshold for specific somatosensory modalities using equipment capable of providing accurate stimuli, combined with established psychophysical testing methods. It has emerged as an extension of sensory portion of the clinical examination. It is simple, noninvasive and nonaversive.

Management

The goals of management are to reduce the risk of developing neuropathy in the first place, and if it has already developed, to prevent secondary complications arising out of it, and to attenuate neuropathic symptoms.

- **Prevention of neuropathy :** The DCCT and UKPDS showed good glycemic control can prevent or postpone the onset of microvascular complications including neuropathy. The difficulty is in achieving euglycemia or close to normoglycemia. Every effort must be made to attain as normal a control of glycemia as possible. Given the limitations, further improvements depend on new technologies such as gene therapy, pancreatic transplant or more efficient modes of delivering insulin and monitoring blood glucose. Routine foot care to prevent injuries to insensitive feet is imperative.

Pharmacological interventions to treat pain

- **Tightening of glycemic control and NSAIDS:** It is known that hyperglycemia can interfere with opioid receptors, and conversely neuropathic pain may improve with better glycemic control. If they fail, pain can be suppressed, often by nonsteroidal anti-inflammatory drugs (NSAIDS). Narcotics are not advisable because of addiction potential, risk of constipation and worsening of autonomic neuropathy, NSAIDs are particularly useful when coexisting musculoskeletal problems coexist, as they often do. Ibuprofen (600 mg QID) helps, but must be used with caution because of the risk of nephrotoxicity, especially in persons with diabetes.
- **Tricyclic antidepressants :** These drugs provide relief by blocking the reuptake of norepinephrine and serotonin at central synapses that are involved in inhibiting pain. They do not depend on mood elevation. Tricyclics led to more than 50% pain relief in 30% of patients with neuropathic pain. The commonly used agents are amitriptyline, nortriptyline and imipramine. There is little to choose one over the other, except for relative advantages: nortriptyline and imipramine have less anticholinergic side effects than amitriptyline. Low doses of amitriptyline or nortriptyline (10-25 mg at bedtime) are started and gradually increased until pain is relieved or intolerable side effects occur. Older patients must be asked about urinary retention and glaucoma before starting these agents.
- **Anticonvulsants :** Anticonvulsants are also useful in controlling neuropathic pain (12). They act by a variety of actions including: voltage-gated ion channels, ligand-gated ion channels, GABA, glutamate, glycine, combined voltage/ligand-gated channels and NMDA

receptors. The primary action on these receptors is to reduce ion flow by inhibiting high-frequency firing, which results in reduced excitatory synaptic transmission or enhanced inhibitory synaptic transmission. Ultimately there is an increased refractory period for the cell membrane and a slower rate of firing action potentials in the damaged neurons. Carbamazepine is the older agent, but gabapentin is the drug of choice, where available. Phenytoin and valproate may also be beneficial, although published evidence is less compared to the former. Carbamazepine is started at a low dose, 100 mg BID and increased to 200 mg TID or until side-effects occur. Leukopenia must be watched for. Complete blood counts are ideally done before starting the drug, within a few days of starting and then frequently over the first three months. Gabapentin is started at 300 mg a day and increased until 2400 mg a day or until pain control. Side effects include lightheadedness, somnolence and loss of balance.

- **Capsaicin :** This is a topical agent applied over painful areas. It depletes the neuropeptide substance P, which has an important role in pain terminals at the nerve terminals. Capsaicin (0.075% QID) is applied to the painful area. Common side effect is a transient worsening of the pain for the first few days.
- **Other agents:** Given the unsatisfactory response to most available agents, other drugs were also used including mexiletine, an antiarrhythmic agent and venlafaxine, an antidepressant (13). Similarly a vitamin D3 derivative (14) and traditional medicines such as Kampo medicines (15) were shown to prevent neurotrophic deficits in experimental animals.

Future therapies

- **Aldose reductase inhibitors :** At present aldose reductase inhibitors remain an unproven therapy. They improve measures of neuropathy, especially motor nerve conduction velocity. In future they may be useful in arresting the progress of diabetic neuropathy.
- **Preventing oxidative stress :** Alpha-lipoic acid (ALA) is a lipophilic free-radical scavenger that can prevent neuropathic abnormalities in animals. Limited clinical trials published so far were of short duration and do not allow firm conclusions to be drawn.