REVIEW

Diabetic neuropathy

V Bansal, J Kalita, U K Misra

Postgrad Med J 2006;**82**:95–100. doi: 10.1136/pgmj.2005.036137

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% DN. Asymmetrical neuropathies may involve cranial nerves, thoracic or limb nerves; are of acute onset resulting from ischaemic infarction of vasa nervosa. Asymmetric neuropathies in diabetic patients should be investigated for entrapment neuropathy. Diabetic amyotrophy, initially considered to result from metabolic changes, and later ischaemia, is now attributed to immunological changes. For diagnosis of DN, symptoms, signs, quantitative sensory testing, nerve conduction study, and autonomic testing are used; and two of these five are recommended for clinical diagnosis. Management of DN includes control of hyperglycaemia, other cardiovascular risk factors; α lipoic acid and L carnitine. For neuropathic pain, analgesics, non-steroidal anti-inflammatory drugs, antidepressants, and anticonvulsants are recommended. The treatment of autonomic neuropathy is symptomatic.

See end of article for authors' affiliations

Correspondence to: Professor U K Misra, Department of Neurology, Sanjay Gandhi Post Graduate Institute of Medical Sciences, Raebareilly Road, Lucknow 226014, India; ukmisra@sgpgi.ac.in

Submitted 15 April 2005
Accepted 16 June 2005

Diabetic neuropathy (DN) is a common disorder and is defined as signs and symptoms of peripheral nerve dysfunction in a patient with diabetes mellitus (DM) in whom other causes of peripheral nerve dysfunction have been excluded. There is a higher prevalence of DM in India (4.3%)[1] compared with the West (1%–2%).[2] Probably Asian Indians are more prone for insulin resistance and cardiovascular mortality.[3] 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.[4] DN is one of the commonest causes of peripheral neuropathy. It accounts for hospitalisation more frequently than other complications of diabetes and also is the most frequent cause of non-traumatic amputation. Diabetic autonomic neuropathy accounts for silent myocardial infarction and shortens the lifespan resulting in death in 25%–50% patients within 5–10 years of autonomic diabetic neuropathy.[5 6] According to an estimate, two thirds of diabetic patients have clinical or subclinical neuropathy. The diagnosis of subclinical DN requires electrodiagnostic testing and quantitative sensory and autonomic testing. All types of diabetic patients—insulin dependent diabetes mellitus (IDDM), non-insulin dependent diabetes mellitus (NIDDM), and secondary diabetic patients—can develop neuropathy. 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.[7] The box gives the classification of DN.

DISTAL SYMMETRICAL POLYNEUROPATHY (DSPN)

DSPN is the commonest type of DN and probably accounts for 75% of DNs (fig 1). Many physicians incorrectly presume that DSPN is synonymous with DN. It may be sensory or motor and may involve small or large fibres, or both. Sensory impairment occurs in glove and stocking distribution and motor signs are not prominent. The sensory symptoms reach up to knee level before the fingers are involved because of length dependent dying back process. Fibre dependent axonopathy results in increased predisposition in taller people.[9] DSPN is further classified into large fibre and small fibre neuropathy. Large fibre neuropathy is characterised by painless paresthesia with impairment of vibration, joint position, touch and pressure sensations, and loss of ankle reflex. In advanced stage, sensory ataxia may occur. Large fibre neuropathy results in slowing of nerve conduction, impairment of quality of life, and activities of daily living. Small fibre 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. Small fibre neuropathy results in morbidity and mortality. Autonomic neuropathy is usually associated with DSPN; but diabetic autonomic neuropathy does not occur without sensory motor neuropathy.

PAINFUL DIABETIC NEUROPATHY

About 10% of diabetic patients experience persistent pain.[10] 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, shooting, aching, jabbing, sharp, cramping, tingling, cold, or allodynia. Some patients develop predominantly small fibre neuropathy manifesting with pain and paresthesia early in the course of diabetes that may be associated with insulin therapy (insulin neuritis).[11] It is of less than six

Abbreviations: DN, diabetic neuropathy; DM, diabetes mellitus; DSPN, distal symmetrical polyneuropathy; NCV, nerve conduction velocity; ARI, aldolase reductase inhibitor; ALC, acetyl L carnitine; NGF, nerve growth factor; CIDP, chronic inflammatory demyelinating neuropathy

Clinical classifications of diabetic neuropathies[8]

Symmetric
- Diabetic polyneuropathy
- Painful autonomic neuropathy
- Painful distal neuropathy with weight loss ''diabetic cachexia''
- Insulin neuritis
- Polyneuropathy after ketoacidosis
- Polyneuropathy with glucose impairment
- Chronic inflammatory demyelinating polyneuropathy with diabetes mellitus

Asymmetric
- Radiculoplexoneuropathies
  - Lumbosacral
  - Thoracic
  - Cervical
- Mononeuropathies
- Median neuropathy at wrist
- Ulnar neuropathy at the elbow
- Peroneal neuropathy at the fibular head
- Cranial neuropathy

months duration, symptoms are aggravated at night, and manifest more in feet than hands. Sometimes acute DN pain is associated with weight loss and depression and has been termed as diabetic neuropathic cachexia.[12] This syndrome commonly occurs in men, and can occur at any time in the course of both type I and type II diabetes. It is self limiting and responds to symptomatic treatment. In these patients amyloidosis, heavy metal toxicity, Fabry's disease, and HIV should be excluded.

Chronic painful DN

Chronic painful DN refers to painful neuropathy occurring over more than six months. These patients may develop tolerance to drugs and even get addicted. Neuropathy can develop even before the onset of clinically diagnosable diabetes mellitus, which is known as ''impaired glucose tolerance neuropathy''. Symptoms, electrodiagnostic studies, and reduced nerve fibre density are consistent with small fibre neuropathy although the changes are less prominent compared with their florid diabetic counterparts.[13] The patients with undiagnosed painful neuropathies therefore should undergo a glucose tolerance test.[14] In patients with newly diagnosed diabetes, intermittent pain and paresthesia in distal lower limbs may suggest hyperglycaemic neuropathy, which improve as the hyperglycaemia is controlled. In DN, sensory loss renders the patient vulnerable to foot injuries, ulcers, and foot destruction. Foot care therefore is integral part of DN management.

Diabetic autonomic neuropathy

Diabetic autonomic neuropathy affects various organs of the body resulting in cardiovascular, gastrointestinal, urinary, sweating, pupils, and metabolic disturbances. Because of diversity of symptoms, autonomic DN often goes unnoticed by both the patient and the physician. 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. Table 1 summarises clinical manifestations of autonomic diabetic neuropathy.

Asymmetrical proximal diabetic neuropathy

It is also referred to as diabetic amyotrophy but should better be called as diabetic proximal neuropathy.[15] 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 weakness of pelvifemoral muscles occurs abruptly in a stepwise manner in the people above 50 years of age. Most of these patients have NIDDM but it is unrelated to the severity or duration of diabetes. 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 (fig 2). Knee reflex is reduced or absent. Numbness or paresthesia are minor phenomena. Weight loss occurs in more than half the patients. Stepwise progression occurs over months. Pain subsides long before the motor symptoms improve, which may take months although mild to moderate

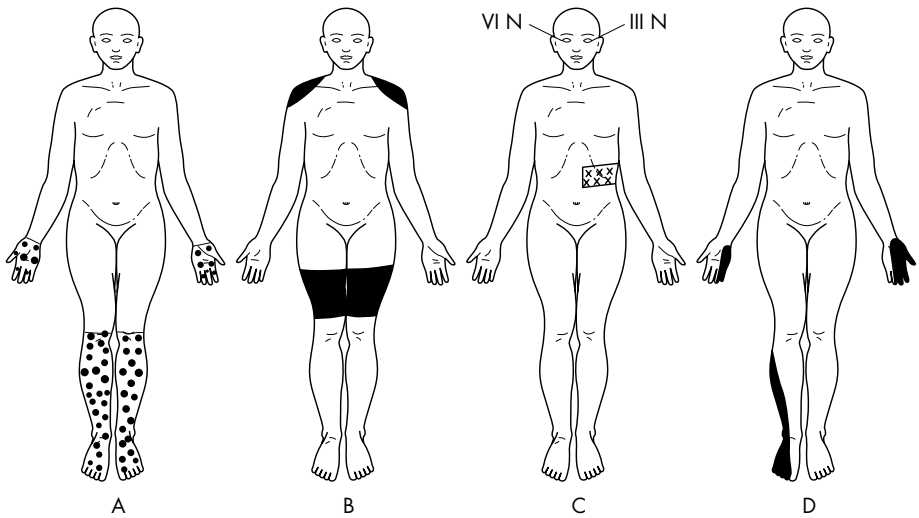

Figure 1 Schematic diagram showing types of diabetic neuropathy. (A) Distal symmetrical peripheral neuropathy, (B) proximal neuropathy, (C) cranial and truncal neuropathy, and (D) mononeuropathy multiplex.

Table 1 Clinical manifestations of autonomic diabetic neuropathy

Cardiovascular	Gastrointestinal	Genitourinary	Miscellaneous
Tachycardia	Oesophageal dysfunction	Erectile dysfunction	Hypoglycaemia unawareness
Exercise intolerance	Gastroparesis	Retrograde ejaculation	Miosis
Painless myocardial infarction	Diarrhoea	Cystopathy	Argyll Roberson pupil
Orthostatic hypotension	Constipation	Neurogenic bladder	Heat intolerance
	Incontinence		Sweating disturbance, Gustatory sweating

weakness may persist indefinitely. In about 50% patients with diabetic proximal neuropathy, DSPN may coexist. Nerve biopsy shows multifocal nerve fibre 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.[16] This has prompted intravenous immunoglobulins (IVIg) and cyclophosphamide therapy, which have resulted in rapid recovery.[17 18]

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.[17 19] Biopsy of obturator nerve has shown demyelination, inflammatory cell infiltrate, and immunoglobulin deposits in vasanervosa.[20] Cerebrospinal fluid protein may be raised without lymphocytic pleocytosis.

It is important to differentiate CIDP from lumbosacral radiculoplexoneuropathy attributable to ischaemic origin because of different therapeutic options. Diabetic patients are 11 times more vulnerable to develop CIDP[21] and they respond to immunomodulation by corticosteroid, plasma exchange, or IVIg.

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, thoracic disease, or herpes zoster. The symptoms may generally persist for months before gradually subsiding. Electromyography may show paraspinal denervation.

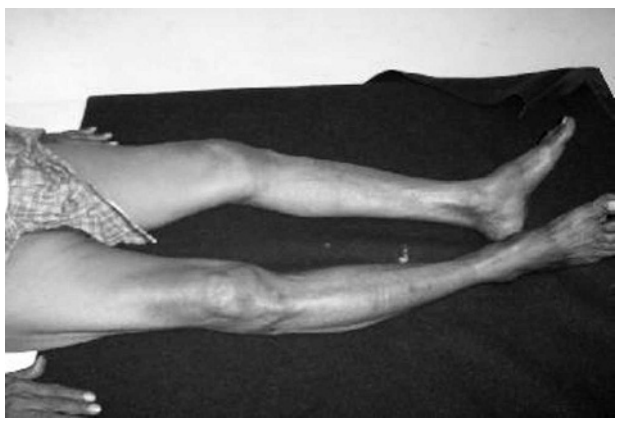

Figure 2 Proximal muscle wasting in a 55 year old diabetic male patient with diabetic lumbosacral radiculoplexoneuropathy. He had severe pain and weight loss for three months.

Limb neuropathies

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

Mononeuropathy

In diabetic patients, nerve entrapment is commoner than nerve infarction. The entrapment neuropathies have insidious onset, have 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 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.

Cranial neuropathy

Cranial neuropathy in diabetic patients, most commonly involve 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 fibres are peripherally located; therefore escape in diabetic oculomotor palsy.

Multiple neuropathies

Multiple neuropathies refer to the involvement of two or more nerves. As in mononeuropathy the onset is abrupt in one nerve and occurs earlier than the other nerves, which are involved sequentially or irregularly. Nerve infarctions occur because of occlusion of vasa nervosum and should be differentiated from systemic vasculitis.

DIAGNOSIS OF DN

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. For touch sensation mono filament of 1 g is recommended. Sensory examination should be performed on hands and feet bilaterally. In old age (>70 years) vibration and ankle reflex may be reduced normally and considered abnormal if these are absent rather than reduced in a patient with DN. Quantitative sensory testing may be used as ancillary test but is not recommended for routine clinical practice.[22] The autonomic function tests commonly used in DM are based on blood pressure and heart rate response to a series of manoeuvres. Specific tests are used for evaluating gastrointestinal, genitourinary, sudomotor function, and peripheral skin blood flow. Nerve biopsy may be useful for excluding other

causes of neuropathy. Skin biopsy has been used when all other measures are negative in the diagnosis of small fibre neuropathy for quantification of protein gene product 9.5, which is a panaxonal marker.[23] Diabetes as a cause of neuropathy is diagnosed by exclusion of other causes in patients who present with painful feet and have impaired glucose tolerance test.[13] 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 non-invasive nature, confocal microscopy may have great potential in assessing nerve structure in vivo without need for nerve biopsy.[24]

The American Academy of Neurology recommends that DN is diagnosed in presence of somatic or autonomic neuropathy when other causes of neuropathy have been excluded.[25] 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: symptoms, signs, electrodiagnostic tests, quantitative sensory, and autonomic testing.[25] This may be necessary in research protocols. However. in clinical practice two of five criteria have been recommended.[26] Underdiagnosis or misdiagnosis of DN in clinical practice has been emphasised in the GOAL A1C study in which 7000 patients were evaluated and only 38% with mild and 61% with severe neuropathy were detected. This study highlighted the importance of education of physician in diagnosing DN.[27]

Nerve conduction studies

Motor nerve conduction, F response, and sensory nerve conduction studies are important methods of documentation and follow up of nerve functions in DN. Motor nerve conduction studies are affected in a small subset of DN (large fibre neuropathies). Even in large diameter fibre neuropathy nerve conduction velocity (NCV) is insensitive for many pathological changes known to be associated with DN. The nerve conduction changes are non-specific and key to the diagnosis lies in excluding other causes or those superimposed on DN. Entrapment neuropathies are common in diabetic patients and result in unilateral NCV changes, especially across the entrapped segment of the nerve. The commonest abnormality in diabetes is reduction in the amplitude of motor or sensory action potentials because of axonopathy. Pronounced slowing of NCV suggests demyelinating neuropathy, which is rarely associated with diabetes; therefore pronounced slowing of NCV in a diabetic patients should prompt investigations for an alternative diagnosis. However, the likelihood of CIDP occurring in diabetic patients is 11 times higher than the normal population.[21] The NCV is gradually diminished in DN, with estimates of a loss of about 0.5 m/s/y.[28]

In a study on 133 patients with newly diagnosed IDDM followed up for 10 years it was shown that NCV diminished in six nerves evaluated. The maximum deficit was 3.9 m/s in sural nerve (48.3–44.4 m/s) whereas peroneal motor NCV was reduced by 3 m/s over same period.[29] A similar slow rate of decline was shown in DCC trial. A simple rule is that a1% fall in Hb1Ac improves the conduction velocity by about 1.3 m/s.[28] There is however strong correlation between myelinated fibre density and whole sural nerve amplitude.[30]

PATHOGENESIS

The cause of DN though remains unknown but ischaemic and metabolic components are implicated. Hyperglycaemia induces rheological changes, which increases endothelial vascular resistance and reduces nerve blood flow. Hyperglycaemia also causes depletion of nerve myoinositol through a competitive uptake mechanism. Moreover, activation of polyol pathway in the nerve through enzyme aldose reductase leads to accumulation of sorbitol and fructose in the nerve and induces non-enzymatic glycosylation of structural nerve proteins. Hyperglycaemia also induces oxidative stress. Activation of protein kinase C has been linked to vascular damage in DN. These changes result in abnormal neuronal, axonal, and Schwann cell metabolism, which result in impaired axonal transport. Direct measurement of glucose, sorbitol, and fructose in nerves of diabetic patients showed correlation with the severity of neuropathy. Endoneural hypoxia is produced by increased vascular resistance and reduced blood flow in the nerve. Hypoxia leads to further capillary damage, which in turn aggravates disturbance in axonal transport and reduced Na-K ATPase activity leading to axonal atrophy and impairment of nerve conduction.

Unfortunately the basic research in DN has focused on carbohydrate metabolism; whereas amino acids, electrolytes, and lipid biochemical changes, which are associated with DM, have not been investigated with same vigour.

MANAGEMENT OF DIABETIC NEUROPATHY

Disease modification

The treatment of DN is aimed at preventing the progression of neuropathy and providing symptomatic relief.

Glycaemic control

The relation between hyperglycaemia and development of severity of neuropathy has been shown in retrospective and prospective studies. A classic study on 440 diabetic patients who were followed up over 25 years, showed an increase in clinically detectable DN from 12% at the time of diagnosis of diabetes to about 50% after 25 years and those with poorest diabetic control had the highest prevalence.[7] Significant effect of intensive insulin therapy on prevention of DN were shown in DCC trial.[31] The prevalence rate for clinical or electrophysiological evidence of neuropathy was reduced by 50% in those treated by intensive therapy during five years. Only 3% of the primary prevention cohort treated by intensive insulin therapy showed minimal signs of DN compared with 10% of those treated with conventional regimen. In the secondary prevention cohort, intensive insulin therapy reduced the prevalence of DN by 50% (7% compared with 16%) in intensive and conventional groups respectively. The results of DCC trial support the need for strict glycaemic control.[31] In the UK prospective diabetes study, control of blood glucose was associated with improvement in vibration perception.[32] Reduction of odds ratio for the development of autonomic neuropathy to 0.32 was reported in the Steno trial.[33]

Association of vascular risk factors with DN

The risk factors for development of DSPN in 1172 patients with type I DM was studied over 7.3 (SD 0.6) years. Clinical evaluation, quantitative sensory testing, autonomic function tests, serum lipids and lipoprotein, glycosylated Hb, urinary albumin excretion rate, and serum creatinine were measured in 276 patients. In this study 23.5% developed neuropathy, which apart from the glycaemic control was related to potentially modifiable cardiovascular risk factors including raised serum triglyceride, body mass index, smoking, and hypertension.[34] A stepwise progressive study of treatment of type II diabetic patients with hypotensive drugs, angiotensin converting enzyme inhibitors, calcium channel blockers, hypoglycaemic agents, aspirin, hypolipidaemic agents, and antioxidants. This study argues for the multifactorial nature

of neuropathy and need for managing multiple metabolic abnormalities.[33]

Aldolase reductase inhibitors (ARIs)

ARIs reduce the flux of glucose through polyol pathways, inhibiting accumulation of sorbitol and fructose, and preventing reduction of redox potential. In a randomised placebo controlled trial, 219 patients with symptomatic polyneuropathy were treated for one year by tolrestat, which resulted in significant improvement in autonomic tests and vibration perception compared with placebo.[35] A dose dependent increase in nerve fibre density, particularly small unmyelinated nerve fibres, was shown in a 12 month study of zenarestat, which was accompanied by increase in NCV.[36] ARIs have been used for over 20 years but so far their clinical efficacy in humans has not been proved. It seems that the starting point of therapy should be early DM. Large trials with sufficient power (>600 patients) and long duration (>5 years) are needed and the penetration of experimental drug across the blood-nerve barrier needs to be shown. A number of new ARIs are being tested in clinical trials. It seems, however, that ARIs themselves may not be able to achieve metabolic change in patients with multiple metabolic derangements and the role of adjuvants may need to be tested.

α Lipoic acid

This is a natural cofactor of dehydrogenase complex and is a redox modulating agent. It has been shown to be effective in ameliorating both somatic and autonomic DNs. It was found that 600 mg α lipoic acid intravenously five days/week for 14 treatments ameliorated symptoms of DN.[37] γ Linoleic acid is an essential fatty acid and is metabolised to α linolenic acid, which is a constituent of neuronal membrane phospholipids. It is a substrate of prostaglandin E formation and is important for preservation of nerve blood flow. A multicentre, double blind, placebo controlled trial for one year showed significant improvement of clinical and electrodiagnostic measures.[38] Its lipid lowering effect may be an additional benefit in diabetic patients.

Carnitine

Acetyl L carnitine (ALC) in two multicentre placebo controlled trials on 1335 patients showed that 500 and 1000 mg thrice daily resulted in significant improvement in sural nerve fibre numbers and vibration perception, however NCV and amplitude did not improve. Pain was reported by 26.7% patients, which was significantly improved in a group taking 1000 mg thrice daily at 6 and 12 months but not in the 500 mg thrice daily group. The adverse events included pain, paresthesia, hyperesthesia, cardiovascular, and gastrointestinal symptoms. These results suggested that ALC has significant effect on small nociceptive fibres.[39]

Neurotrophic therapy

In view of experimental evidence of decreased expression of nerve growth factor (NGF) and its receptor Trk A, several trials on trophic factors in DM have been carried out. Trk A reduces retrograde axonal transport of NGF and reduces support of small myelinated neurons and their neuropeptides, for example, substance P and calcitonin gene related peptide. Both are potent vasodilators. Recombinant human NGF restores these neuropeptide levels to normal and prevents manifestation of sensory neuropathy in animals.[40] NGF in 250 subjects with symptomatic small fibre neuropathy improved neurological impairment score and small nerve fibre function cooling threshold (Aδ fibres) and ability to perceive heat pain (C fibres). These results were consistent with postulated action of NGF on Trk A receptors present in small fibre neurons. This led to two large trials but recombinant human NGF was not found to be beneficial.[41]

Vascular endothelial growth factor (VEGF) gene transfer to small mammals has been shown to improve nerve conduction and blood vessel density and increase nerve blood flow.[42] A number of approaches using neuropeptides or other molecules have failed to halt progression of DN in clinical trials despite promise in experimental or in vitro studies.

SYMPTOMATIC TREATMENT

Painful paresthesia especially when the pain is of lancinating type can be helped by tricyclic antidepressants and anticonvulsants such as phenytoin, carbamazepine, and gabapentin. Based on randomised controlled trials there was no superiority of any of these anticonvulsants over the others. It is however recommended that these anticonvulsants should be used in DN when the other interventions have failed.[43]

Tramadol is effective in the treatment of neuropathic pain in placebo controlled trials. Depending on the quality of pain, different drugs have been recommended. For paresthesia and lancinating pain tricyclic antidepressants and fluphenazine are recommended. For superficial burning pain and allodynia capsaicin and isosorbide dinitrate spray and for focal or neuropathic pain carbamazepine or other anticonvulsants are recommended.

Neuropathic pain

Pain relief is one of the most challenging issues in DN. Among the drugs used in DN, the numbers needed to treat (NNT) refers to the number of patients to be treated to obtain 50% pain relief in one patient. It is a useful parameter to compare the efficacy of different drugs. For tricyclic antidepressant, NNT was 1.4, for dextromethorphan 1.9, for carbamazepine 3.3, for tramadol 3.4, for gabapentin 3.7, for capsaicin 5.9, for selective serotonin reuptake inhibitors 6.7, and for mexiletine10.[44] However if pain is categorised according to Aδ, C fibre, spinal cord or cortical, the choice of drug may be guided by the following scheme.

Type C

The patient with DN present with lancinating, burning, dysesthetic pain because of peripheral sympathetic fibres, which are unmyelinated C type. These fibres used substance P as neurotransmitter and their depletion by capsaicin often relieves the pain. Clonidine also relieves this type of pain by sympathetic blocking action; if clonidine fails then local mexiletine may be tried. With the progression of neuropathy pain may ameliorate spontaneously but this should be regarded as progression of neuropathy.

Aδ pain

This is a deep seated, dull, gnawing pain that does not respond to the above mentioned drugs. Some patients respond to intravenous insulin infusion within 48 hours even without control of hypoglycaemia.[45] The drugs useful in this type of pain are tramadol, dextromethorphan, and antidepressants (tricyclic and selective serotonin reuptake inhibitors). Recently duloxetine, a potent dual reuptake inhibitor of serotonin or adrenaline (epinephrine), or both, has been introduced for treatment of neuropathic pain. In a randomised controlled trial on 457 patients with DN, 60–120 mg duloxetine daily resulted in significant pain relief. In 20% patients, however, duloxetine had to be withdrawn because of side effects.[46] Antiepileptic drugs such as phenytoin, carbamazepine, lamotrigine, topiramate have been used. However, no relative superiority of these drugs has been reported. It is however recommended that anticonvulsants should be used when other measures have failed. Concern about phenytoin has been raised as in randomised trials its benefit has not been established, moreover it may precipitate hyperosmolar diabetic coma by inhibiting insulin secretion.[47] Topiramate has been reported to have additional

benefit such as it lowers blood pressure, improves lipid profile, decreases insulin resistance, and increased cutaneous nerve fibre regeneration.[48] It should be started at low dose 15 mg daily and increased gradually.

Analgesics are not of much benefit and narcotics should be avoided because of possible addiction. However, non-steroidal anti-inflammatory drugs (ibuprofen 400 mg four times daily) has been reported to relieve neuropathic pain.[49] Tramadol also is useful in relieving pain but is avoided because of addiction potential. In a small study, calcitonin 100 IU daily relieved pain in 39% patients by two weeks.[50]

Transcutaneous nerve stimulation, magnetic field therapy, infrared light therapy, and spinal cord stimulation has been tried in small number of patients with painful DN.

The autonomic symptoms also require special attention in DN patients. Postural hypotension is helped by raising the head end of the bed, increasing salt intake to 10–20 g/day, small frequent meals, two cups of strong coffee, increased fluid intake, elastic stockings, fludrocortisone 200 μg or ibuprofen 400 mg thrice daily (better tolerated than indomethacin). Gastropathy is helped by small, frequent low fat meals and metoclopramide or cisapride 10 mg thrice daily. Diabetic diarrhoea is helped by tetracycline, metronidazole, and bile chelators. Erectile dysfunction is helped by sildenafil and cystopathy by doxazosin, Crede's manoeuvre, and clean intermittent self catheterisation.

Large fibre neuropathy

The management of large fibre neuropathy is by gait and strength training, pain management as discussed above, orthopaedic devices, tendon lengthening for Achilles contracture, and immunomodulation as detailed above.

ACKNOWLEDGEMENTS

We thank Mr Rakesh Kumar Nigam for secretarial help.

Authors' affiliations

V Bansal, J Kalita, U K Misra, Department of Neurology, Sanjay Gandhi PGIMS, Lucknow, India

Funding: none.

Conflicts of interest: none declared.

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