24 *Recent Advances in Management of Painful Diabetic Neuropathy*

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Abstract: Painful diabetic neuropathy are common and present a major challenge to the practicing physician. Pain is universal symptom in patients with rare acute sensory neuropathy and is present in only upto 50% of those patients with the common chronic sensory motor neuropathy. The first step in symptom management is to stabilize glycemic control. There is increasing evidence that blood glucose flux may exacerbate neuropathic pain, so avoiding swings of glycemia from hypoglycemia may help. It is possible that hyperglycemia and its consequent biochemical features may directly cause neuropathic pain. Other theories of the genesis of pain in diabetes include the presence of spontaneous electrical activity in diseased distal axone and also the possibility of ephaptic transmission between efferent autonomic fibers and afferent nociceptive fibers. The approach should be to exclude all non-diabetic causes, remembering that diabetic neuropathy is a diagnosis of exclusion of other potential pathologies. Glycemic control should be assessed particularly looking at A1c and blood glucose profiles.

All treatments for painful neuropathy target the symptoms rather than the underline pathophysiologic abnormalities. All potential treatments have side effects, and these should be discussed with the patients. First line agents in many centers remain the tricyclic antidepressants, which should be taken at night. Side effect are common; however, the tricyclic agents, specially those with the anticholinergic effect cause symptoms, such as dry mouth and urinary retention. The use of antiarrhythmics, such as maxiletine, has generally been disappointing. Thus anticonvulsant drugs such as gabapentin have been the main stay of management. Among the other listed drugs, tramadol has also been shown to be efficacious in the management of neuropathic pain.

INTRODUCTION

Diabetic neuropathy (DN) is a common and troublesome complication of diabetes mellitus, leading to great morbidity and mortality and resulting in huge economic burden for care of the patients with diabetes mellitus.[1,2] It is the most common cause of leg pain in patients with diabetes and is responsible for 50- to 75% of non-traumatic amputations.[3] Reduced sensation to sensory stimuli including pain, temperature, touch, and vibration in the feet and lower parts of the legs in diabetes patients is invariably a result of sensory neuropathy and may go unnoticed by patients for years unless specifically tested for and demonstrated. Paradoxically, some patients may experience spontaneous painful or paresthetic symptoms while concurrently having marked loss of sensation on neurological examination, a condition described as the "painful/painless leg." The explanation for this is not an uncommon finding is that the sensory nerves to the feet are severely diseased and fail to conduct stimuli. Proximally, however, spontaneous electrical activity in diseased peripheral axons is interpreted by the patients as pain and is perceived in the area (i.e., the foot) that the nerve used to innervate.

Diabetic neuropathy is a heterogeneous disorder that encompasses a wide range of abnormalities affecting proximal and distal peripheral sensory and motor nerves as well as the autonomic nervous system. For these reasons, it has been difficult to obtain precise estimates of the true prevalence, and the odds vary from 10 to 90% in diabetic patients depending on the criteria and the methods used to defined neuropathy.[1,4] Twenty-five percent of patients attending a diabetes mellitus clinic volunteered symptoms; 50% were found to have neuropathy after a single clinical test such as the ankle jerk or vibration perception threshold (VPT) test; almost 90% tested positive to sophisticated tests of autonomic function or peripheral sensation.[5] Neurological complication occurs equally in type 1 and type 2 diabetes mellitus and additionally in various forms of acquired diabetes.[6] The major morbidity associated with somatic neuropathy is foot ulceration, the precursor of gangrene and limb loss. DSPN increases the risk of amputation by 1.7-fold; 12-fold if there is deformity (itself a consequence of neuropathy) and 36-fold if there is a history of previous ulceration.[7] Once autonomic neuropathy sets in, life can become quite dismal, and mortality rate approximates 25- to 50% within 5 to 10 years.[8]

DEFINITION

Members of an International Consensus Meeting on the outpatient diagnosis and management of diabetic peripheral neuropathy (DPN) agreed on a simple definition of diabetic neuropathy as "*the presence of symptoms and/or signs of peripheral nerve dysfunction in people with diabetes after the exclusion of other causes*".[9] This group also agreed that neuropathy cannot be diagnosed without a careful clinical examination and that absence of symptoms must never be equated with absence of neuropathy. The importance of excluding non diabetic causes was emphasized in the Rochester Diabetic Neuropathy Study[6,11], in which up to 10% of peripheral neuropathy in diabetes was deemed to be of non diabetic causation.[10] For day-to-day clinical practice, DPN is a clinical diagnosis. It is generally agreed that DPN should not be diagnosed on the basis of one symptom, sign, or test alone; a minimum of two abnormalities (i.e., abnormal symptoms and signs) is recommended.[10-12]

EPIDEMIOLOGY

DPN is by far the most common of all the diabetic neuropathy and may be divided into the following two main types; acute sensory neuropathy and chronic sensory-motor neuropathy. Acute sensory neuropathy is a distinct variety of the symmetrical polyneuropathies with an acute or subacute onset characterized by severe sensory symptoms, usually with few if any clinical signs. It is usually precipitated by an episode of glycemic instability (such as ketoacidosis or even after the institution of insulin), and its natural history is one of gradual improvement of symptoms with establishment of stable glycemic control and appropriate symptomatic treatments.

Chronic sensory-motor neuropathy is by far the most common form of DPN. It is usually of insidious onset and may be present at the diagnosis of type 2 diabetes in up to 10% of patients. Whereas up to 50% of patients with chronic DPN may be asymptomatic, 10 to 20% may experience troublesome symptoms sufficient to warrant specific therapy. Sensory-motor neuropathy is often accompanied by autonomic dysfunction. Its late sequelae, which include foot ulceration, Charcot neuroarthropathy and, occasionally, amputation, should in many cases be preventable. The prevalence of chronic DPN increases both age and duration of diabetes, and this diagnosis is more common in those whose glycemic control has been suboptimal in previous years.

CLASSIFICATION OF DIABETIC NEUROPATHIES

Numerous classification of the variety of the syndromes affecting the peripheral nervous system in diabetes has been proposed in recent years. The classification shown in Table 24.1 is based on, that was originally proposed by Thomas.[12]

PATHOGENESIS

There are currently four major hypothesis about how hyperglycemia causes diabetic complications, namely:

- Increased flux of glucose and other sugars through the polyol pathway.
- Increased intracellular formation of advanced glycation end-products (AGEs).
- Activation of protein kinase C (PkC) isoforms.
- Overactivity of the hexokinase pathway.

Recent work suggests that all four mechanisms can be attributed to mitochondrial overproduction of superoxide (a reactive oxygen species) as a result of excess glucose metabolism. This provides a unifying hypothesis that can also explain the cumulative nature of glucose-induced tissue damage and hyperglycemic memory.[13]

The polyol pathway is based on a family of aldoketoreductase enzymes, which can utilize as substrates a wide variety of sugar-derived carbonyl compounds, and reduce these by nicotinic acid adenine dinucleotide phosphate (NADP) to their respective sugar alcohols (polyols): for example, glucose is converted to sorbitol, and galactose to galacitol. Sorbitol is then oxidized to fructose by the enzyme sorbitol dehydrogenase (SDH), with NAD^+ being reducted to NADH.

AGEs have been shown to cross-link proteins (e.g. collagen, extracellular matrix proteins), accelerate atherosclerosis, reduce nitric oxide synthesis, induce endothelial dysfunction, and alter extracellular matrix composition and structure.

A third hypothesis proposes that hyperglycemia increases the formation of diacylglycerol leading to activation of protein kinase C (PkC). PkC alters the transcription of genes for fibronectin, type IV collagen, contractile proteins, and extracellular matrix proteins in endothelial cells and neurons.

It has also been suggested that hyperglycemia could cause diabetic complications by shunting glucose into the hexosamine pathway. Activation of the hexosamine pathway by hyperglycemia may result in many changes in both gene expression and in protein function that together contribute to the pathogenesis of diabetic complications. It has recently been discovered that all four of the different pathogenic mechanisms can stem from a single hyperglycemia induced process, namely overproduction of superoxide by the mitochondrial electron-transport chain[14] (Fig. 24.1).

HYPERGLYCEMIC NEUROPATHY

It is encountered in newly diagnosed diabetes or those with poor glycemic control and characterized by pain and parasthesias in the feet. Nerve conduction velocity (NCV) is slowed and is rapidly reversed by improving the glucose scontrol.

DIABETIC SYMMETRIC DISTAL POLYNEUROPATHY (DSDP)

Common in both type 1 and type 2 diabetes. The muscle weakness is mild but sensory symptoms predominate. They have pain and parasthesias in stocking and glove distribution and decreased sensations of coldness, numbness, tingling or burning. Pain may be dull, lacinating, burning, pricking, stabbing or cramp like, often worse at night. Autonomic features may or may not be present and ankle reflexes are absent.

INSULIN NEURITIS

It is usually seen in patients on starting insulin or while tightening the glucose control with insulin. They have severe painful sensory neuropathy which is worse at night with minimal clinical signs. NCV may be normal and recovers over one year.[15]

ACUTE PAINFUL NEUROPATHY WITH SEVERE WEIGHT LOSS

More common in males (type 1 DM). There is dramatic weight loss by upto 50%, severe burning pain in feet and legs, no objective signs, often with anorexia and depression. Symptoms improve over 6 to 24 months.

CRANIAL NEUROPATHIES

Acute onset isolated 6th and 3rd nerve palsies, 50% with 3rd nerve palsy have retro and supra orbital pain. Pain may persist for several days, pupil is spared and recovery is within 3 to 6 months.

DIABETIC TRUNCAL RADICULONEUROPATHY

Occurs in 5th to 6th decade (Types 1 and 2 DM), have unilateral burning pain over a focal area on the chest or abdomen, weight loss and recovery over 2 to 6 months.

Diabetic Lumbosacral Radiculoplexus Neuropathy (Bruns-Garland Syndrome)

Proximal symmetric/asymmetric motor neuropathy, usually elderly males (type 2 DM), with severe burning pain back, hips and thighs but no objective sensory loss. Proximal weakness is present and weight loss about 10 to 20 kg. Recovery occurs over 1 to 3 years.

DIAGNOSIS

1. A careful *history*, pain, discomfort, or numbness in the legs should be inquired. Patients with no spontaneously volunteered symptoms might, if asked, describe numbness or say that their "feet feel dead". Neuropathic pain and dysesthesias usually experienced in the stocking and glove distribution, site of pain varies with the type of diabetic neuropathy, quality of pain can be variable and affects quality of life.
2. Atypical features that might suggest a non-diabetic cause of neuropathy include rapid progression, foot drop, back or neck pain, marked asymmetry, weight loss, and family history.
3. *Neurologic examination:* In long-standing sensorymotor neuropathy, small muscle wasting may be seen. Dry skin suggests coexisting sympathetic dysfunction. Look for ulcers, deformities, or charcot changes.
4. *Electrodiagnostic Testing:* Quantitative assessment of sensory modalities and electro-physiological studies may help to define the severity of neuropathy but will not distinguish between neuropathy due to diabetes or other causes. EMG and NCV detect involvement of large diameter sensory fibers conveying JPS and vibration, but may fail to detect involvement of small diameter sensory fibers conveying pain and temperature. Normal NCV and EMG do not rule out the diagnosis of a small fiber painful sensory polyneuropathy.

THERAPY OF DIABETIC NEUROPATHY

- Preventive
- Specific
- Symptomatic.

Preventive Therapy

The DCCT (Diabetes Control and Complications Trial) has shown definitively that in type 1 diabetic patients, the risk of DPN and autonomic neuropathy can be reduced with improved blood glucose control.

Specific Therapy

A large number of therapeutic agents have been proposed for the management of painful symptoms. The efficacy of several of tricyclic antidepressants,[16] anticonvulsants, SSRIs, opioids, N-methyl-D-asparate (NMDA) receptor antagonists, and antiarrhythmics has been demonstrated in multiple randomized controlled trials. There are several new and emerging therapeutic options for painful DPN, including the α_2-δ ligand pregabalin, the protein kinase C beta inhibitor ruboxistaurin, which is currently in Phase III clinical trials; the dual action serotonin/norepinephrine inhibitor duloxetine, for which preliminary data has been presented at recent society meetings; and the novel NMDA receptor antagonist perzinfotel (EAA-090), which is currently in Phase II clinical trials. Aldose reductase inhibitors (Alrestatin/ Sorbinil / Tolrestat / Zepolrestat), Gangliosides (cronassil-GM-1), Gamma-Linolenic Acid, Nerve growth factor (recombinant human NGF/ Insulin like GF-1/ ALCAR), IVIG, Pancreatic transplant are also being tested.

GUIDELINES FOR PHARMACOTHERAPY

- Initiate monotherapy, start with the lowest possible dose and titrate the dosage gradually. Add a second drug if required
- There is no correlation with regards to dose serum level and pain relief
- Individual variability exists for all drugs
- Lack of response may be due to improper dose titration or early polytherapy
- Goal of therapy is to increase functional activity
- Duration of treatment is variable
- Attempt may be made to taper the medication 6 months after pain relief

TRICYCLIC ANTIDEPRESSANTS

The use of tricyclic drugs in the management of neuropathic pain is supported by several randomized control study.[5,16] Although these drugs remain the first line treatment for symptomatic neuropathy in many centers, their use is restricted because of the frequency and severity of side effects. The mechanism of action of the tricyclic agents is not clear but may occur through inhibition of reuptake of norepinephrine and serotonin but also through effects on sodium channels and the N-methyl-D-aspartate (NMDA) receptors.[17]

Selective Serotonin Reuptake Inhibitors—(SSRIs)

Trials of SSRIs as treatment for diabetic neuropathy have been generally disappointing. Such agents work by the inhibition of presynaptic reuptake of serotonin but not norepinephrine. There is some evidence to support the use of paroxetine and citalopram in dosages of up to 40 mg/day from small controlled studies.

Duloxetine

Nonselective dual reuptake inhibitor of serotonin and norepinephrine. Two double blind placebo-controlled trials have demonstrated its efficacy in the management of depression (40%) and neuropathy pain.[18] Effective dose is 60-120 mg /day orally, improvement may be noticed by 1-2 weeks and side effects include GI distress, dry mouth and headache.

Anticonvulsants

Gabapentin is now widely used for neuropathic symptoms. The side effect profile may again be troublesome, but appears to be less so than that of the tricyclics. Reported effects include sedation, dizziness, headache, pedal edema, and weight gain. It should be noted that the average dose required for pain relief in clinical trials was ~ 1.8 g/day. A newer drug***, pregabalin***, which is a central nervous system-active compound and an analog of the neurotransmitter-aminobutyric acid, has recently been introduced. Preliminary evidence suggests that this agent may be a useful addition to the anticonvulsants that are helpful in the management of neuropathic pain.[18]

Local Anesthetic and Antiarrhythmics

Lidocaine results in sodium channel blockage, dampening both peripheral nociceptor sensitization and ultimately central nervous system hyperexcitability. Although early studies suggested that intravenous lidocaine administration might be beneficial in relieving neuropathic pain, the potential side effects and the need for intravenous administration was problematic. The oral analog of lidocaine, mexiletine, has been reported to be of benefit in some studies,[19] but it is not widely used because of side effects and the need for regular electrocardiogram monitoring with its use.

Sympatholytic Agents

Clonidine (oral/transdermal/intrathecal)

- Peripheral alpha-2 receptor agonist with CNS activity
- Used to manage CRPS
- Helps to abolish SMP encountered in 37% cases of diabetic painful polyneuropathy.

NMDA Antagonists

This is a relatively new class of drugs and includes dextromethorphan and memantine. Examples includes Ketamine, Amantadine, Memantine (20-55 mg per day), Dextromethorphan (380 mg per day).

Opioids

Opioids have not traditionally been used in the management of diabetic neuropathic pain, but recent trials of two agents do suggest efficacy. First, tramadol, which is an opioid- like, centrally acting synthetic narcotic analgesic, has been confirmed to be efficacious in a randomized, controlled trial, and a follow-up study suggests that it can be used safely up to 6 months for sustained pain relief.[20,21] More recently, two studies have confirmed the efficacy of controlled-release oxycodone.[22] The side effects of both drugs are predictable and include somnolence, nausea, and constipation; addiction is also problematic. It may be that opioids such as tramadol and oxycodone may be considered as add-on therapies for patients failing to respond to nonopioid medications in the first instance. Examples include Tramadol (100-400 mg per day), Methadone (1-15 mg per day), Oxycodone (30 to 60 mg per day), Levorphanol, Pethidine, Morphine.[21]

Topical Agents

Capsaicin, which is found in red pepper, depletes tissue of substance P and reduces chemically induced pain. Although several controlled studies combined in meta-analysis seem to provide some evidence of efficacy in diabetic neuropathic pain, it may be best reserved for those with localized discomfort rather than those with widespread generalized neuropathic pain.[23]

Topical nitrate: Some recent data suggest that impaired nitric oxide (NO) synthesis plays a role in the pathogenesis of diabetic neuropathy, and in experimental models it has been shown that impaired neuronal NO generation induces hyperalgesia.[24] If this is confirmed in larger randomized studies, this could provide a very useful alternative and local treatment for the relief of neuropathic symptoms. It includes Capsaicin (0.075% applied QID for 6 to 8 weeks), Lidocaine (Lidoderm 5% skin patch).

Acupuncture

A number of masked studies support the use of acupuncture. In the most recently published report, benefits of acupuncture lasted for up to 6 months and reduced the use of other analgesics.[27] There is, however, a need for controlled studies to confirm these observations.

Other Physical Therapies

Many other physical therapies have been proposed. Controlled evidence has been provided for the use of percutaneous nerve stimulation,[27] static magnetic field therapy,[28] low-intensive laser therapy,[29] and monochromatic infrared light.[26] Electrical spinal cord stimulation has been used to treat several chronic painful conditions, including phantom limb pain, vascular disease, and severe neuropathy.

New Potential Therapies Now in Clinical Trials

Two treatments that might be useful in opposing some of the pathogenetic factors that are thought to lead to neuropathy are now in clinical trials.

α-lipoic-acid: This free radical scavenger antioxidant has been shown to be efficacious in the management of painful neuropathies when administered parenterally.[27] A large 4-year, multicenter study to confirm the efficacy of this agent in diabetic neuropathy is in progress and should be completed in 2005.

Protein kinase C inhibition: Elevated protein kinase C activity is thought to play a substantial role in the etiology of diabetic microvascular complications. Studies have been conducted using a protein kinase C- β inhibitor (LY333531).[30] A preliminary study suggested the possibility of this agent improving positive symptoms of allodynia and prickling pain. Large, phase III, multicenter clinical trials are in progress.[28]

Foot Care in Neuropathic Patients

It must be remembered that the neuropathic diabetic foot does not ulcerate spontaneously. Rather, it is the combination of neuropathy with other extrinsic factors (e.g., ill-fitting footwear or a foreign body in shoe) or intrinsic factors (e.g., high foot pressures or a plantar callus that results in ulceration). Thus, all patients with neuropathic deficit must be considered as being at risk of foot ulceration and require more frequent review, education in routine foot care, and regular podiatric assessments.

Miscellaneous Agents

- Baclofen
- Levodopa
- GLA
- Nerve growth factor
- Methylcobalamin

- Bupropion (150 to 300 mg per day)
- α-Lipoic acid (600-1200 mg per day IV).
  *Free radical scavenger and antioxidant
  *Alternative therapies—TENS/Acupuncture.

Drug Selection for Painful Neuropathy

First Line Medications

- Gabapentin
- Pregabalin
- Tricyclic antidepressants/duloxetine
- Tramadol/opioids
- Lidocaine patch (5%).

Second Line Medications

- Carbamazepine
- Lamotrigine
- Other antidepressants
  (Citalopram/Bupropion/Paroxetine/ Venlaflaxine).

[*Recommendations of the faculty of the fourth international conference in the mechanics and treatment of neuropathic pain Dworkin, et al 2003].

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