CHAPTER 38

Treatment Of Painful Diabetic Neuropathy

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Painful diabetic neuropathy is an increasingly common clinical condition which may present to the podiatric physician. Treatment of painful diabetic neuropathy is challenging and may require several attempts with different treatment therapies.

The podiatrist is often faced with the difficult task of treating a chief complaint of "painful, burning feet." Most often, the diagnosis is peripheral neuropathy with a long list of etiologic differentials, the most common being diabetes. A brief outline of the etiology, diagnosis, and therapeutic guidelines for treatment of painful diabetic peripheral neuropathy will be discussed.

ETIOLOGY

Diabetic neuropathy may be divided into three categories: focal motor neuropathy, autonomic neuropathy, and diffuse symmetric neuropathy. Focal motor neuropathies are relatively rare, have an acute onset, and many times are transient in nature. Areas affected by diabetic motor neuropathies are the lumbosacral plexus, sciatic, femoral, and ulnar, median, and cranial nerves. Characteristic signs and symptoms in the lower extremity include asymmetrical pain, atrophy, and weakness localized to the quadriceps and proximal leg muscles. A proposed etiology of focal motor neuropathy associated with diabetes is a thrombolytic occlusion of the vasonervorum with secondary infarction of nerve fascicles. The differential diagnosis includes compression or entrapment neuropathies, and space-occupying lesions affecting the above-mentioned nerve roots. Treatment is usually directed symptomatically, and spontaneous resolution over weeks to months is common.

Autonomic neuropathy associated with diabetes mellitus can affect several organ systems, which include the cardiovascular, gastrointestinal, genitourinary, and sudomotor (sweat gland) systems. Presenting signs and symptoms may include orthostatic hypotension, impotence, diarrhea, constipation, and cardiac abnormalities. Autonomic neuropathy tends to have an insidious onset and is progressive in nature. Therapy is generally directed towards the affected organ systems, as well as blood glucose control.

Symmetrical distal polyneuropathy may present as paresthesias, dysesthesias (or "burning feet"), and possibly distal weakness of the legs. Cutaneous and vibratory sensation and proprioception may be diminished. The subjective feelings of burning or stabbing (hyperesthesia), may be secondary to damaged nerve endings attempting to regenerate. Etiologic factors include a disruption of biochemical pathways, with a rise in tissue sorbitol and fall in tissue myoinositol, and decreased sodium-potassium ATP-ase activity. These changes result in damage to large and small myelinated fibers, and eventual neuropathy. Microvascular compromise, also associated with retinopathy and nephropathy, may or may not be a contributing factor. Regardless of the etiology, the common denominator is always hyperglycemia.

DIAGNOSIS

Painful diabetic neuropathy of symmetrical distal polyneuropathy can easily be diagnosed in a diabetic patient when other causes of the "burning foot" syndrome have been eliminated. The differential diagnosis may be divided into local and systemic categories. Local causes include: sciatica, tarsal tunnel syndrome and other nerve entrapments, causalgia, erythromyalgia, ischemia, vasculitis, contact dermatitis, and hyperkeratotic lesions.

Systemic causes include: drug and heavy metal toxicity, chemical toxicity, pernicious anemia, Guillian-Barre Syndrome, hypothyroidism, uremia, porphyria, amyloidosis, Fabry's disease, leprosy, peripheral vascular disease, carcinoma, AIDS/HIV, and psychosis. Although the differential diagnosis is lengthy, the most common cause of symmetrical painful neuropathy in

the United States is that which is associated with diabetes mellitus.

TREATMENT

Once a physician has made the diagnosis of painful diabetic neuropathy, the difficulty in treatment begins. The resistance to effective symptomatic relief is apparent by the number of proposed therapies. When treatment begins, the physician must always consider the therapy's physiologic risks and benefits to the patient, with the goal of improved comfort and function. When using pharmacologic agents, one must fully understand the drug's pharmacokinetics, pharmacodynamics, interactions with other drugs, and side effects. The team approach, through consultation with the patient's primary care physician, is recommended for total patient care.

Therapy may be directed in a pyramidal approach (Table 1), with the most conservative therapies at the base of the pyramid. The primary baseline of therapy should be directed at improved glucose control for the diabetic patient. Both subjective improvement of painful symptoms, and objectively measured improvement of motor nerve conduction velocities, have been documented with improved glycemic control in the diabetic patient.

Table 1

TREATMENT OF PAINFUL DIABETIC NEUROPATHY

Surgical Intervention
↑
Other Treatments
↑
(Antiepileptics, Aldose Reductase Inhibitors,
↑
Opioids, Clonidine)
↑
Mexiletene, TCAs *(Amitriptyline)*
↑
NSAIDs, Capsaicin Cream *(0.075%)*
↑
Physical Therapy, Analgesic Balms, Nutrition
↑
Improved Glycemic Control

The next baseline modality is physical therapy. Although efficacy of treatment may be undetermined, the associated low physiologic risk to the patient warrants an attempt. Treatment modalities may include transcutaneous electric nerve stimulation (TENS), interferential current, and other biofeedback modalities. Counter-irritants, such as analgesic balms, can be used in conjunction with physical therapy, or as another low-risk treatment option.

The analgesia efficacy of nonsteroidal anti-inflammatory drugs (NSAIDs) has been well-established in the treatment of pain associated with inflammation, but controlled trials of NSAIDs in neuropathic pain are almost non-existent. Although efficacy is questionable, given the relative safety of NSAIDs, therapeutic trials with these agents can be warranted for patients with painful diabetic neuropathy. The literature suggests Sulindac (Clinoril) because of its aldose reductase inhibitory activity.

Capsaicin, a topical analgesic cream, is a naturally-occurring substance derived from plants of the Solanaceae family, which includes the capsicum pepper. Although the precise mechanism of action is not fully understood, the possible mechanism is associated with the depletion of substance P in peripheral sensory neurons, causing skin and joints to become insensate to pain. Transient burning may be associated with the initial application, but this should disappear in several days. Minimal trial time is approximately one month of application, four times a day. The higher concentration (.075%) is recommended with diabetes-associated painful neuropathy.

A local oral anesthetic, mexiletene, has proven to be effective in the treatment of chronic painful diabetic neuropathy. It was originally developed as an anticonvulsant and anorexiant, and is structurally similar to lidocaine. In a double-blind study, pain was reduced with the use of mexiletene (versus placebo) in patients with chronic painful diabetic neuropathy. The attractive feature of mexiletene is that it is safe and has relatively few side effects when used in low dosages. Studies have shown it to have no effect on tendon reflexes, vibration threshold level, beat-to-beat variation in heart rate during deep breathing, and postural blood pressure response.

Tricyclic anti-depressants (TCAs) are a proven treatment modality for relief of neuropathic pain. Clinical experience is greatest with amitriptyline (Elavil), although desipramine is used as well. The analgesic effect of TCAs was first believed to be due to the relief of depression. However, amitriptyline's psychogenic effects usually take weeks to

achieve, while analgesic effects can occur within four to seven days. In fact, analgesic effects have been found to be independent of antidepressant effects. The most credible explanation for TCA's mode of action is the potentiation of noradrenergic activity in the central nervous system. Side effects include orthostatic hypotension, urinary retention, dry mouth, exacerbation of narrow-angled glaucoma, and sedative activities, which may limit their use in older patients. There are no adverse cardiac effects in patients with cardiac disease when used in moderate doses. Escalating doses begin with 10 to 25 mg at night, although up to 125 to 150 mg may be tried. Current literature reveals that TCAs are frequently used pharmacologic agents in patients with painful diabetic neuropathy.

Anticonvulsants, such as phenytoin (Dilantin) and carbamazepine, are reported to be efficacious in managing neuropathic pain. The reported success rate is low, and these drugs must be used with caution due to the large number of side effects, especially associated with carbamazepine. Clinical experience is greatest with carbamazepine, and it is often administered first. The response of individual patients to drugs in this category can vary remarkably. Dosing follows the guidelines for that which is administered seizure patients.

Opioid therapy is the most controversial pharmacologic approach in the management of chronic neuropathic pain. Traditionally, this approach has not been used because of concerns with the development of tolerance, the potential for side effects, and most importantly, drug addiction. Research findings are neither supportive nor contradictive to opioid drug therapy in management of neuropathic pain. Controlled clinical trials are needed to confirm the efficacy and safety of this approach.

Although not discussed in this paper, other pharmacologic approaches include the use of neuroepileptics, benzodiazepines, calcium-channel blockers, and aldose-reductase inhibitors, which are all under present investigation. Finally, it should be mentioned that the most experimental approach, when all other conservative and pharmacologic means have failed, is surgical management.

Painful diabetic neuropathy has many treatment options. The podiatric physician must be familiar with the treatment alternatives and the associated physiologic risk/benefit ratio to the patient.

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