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FROM GRAND ROUNDS AND OTHER CLINICAL CONFERENCES OF THE MGH PAIN CENTER, MASSACHUSETTS GENERAL HOSPITAL

Diabetic Neuropathy

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Pain is a common symptom of diabetic neuropathy. Of the various types of neuropathy, the most common is distal sensory polyneuropathy (DSPN). DSPN is also the most common cause of pain. Recent studies show that peripheral nerve dysfunction can be the first sign of diabetes and that it even occurs in pre-diabetes (impaired glucose tolerance). Elevated blood glucose and cardiovascular risk factors have been associated with the development of DSPN. The risk and severity of DSPN can be somewhat lessened by tight glucose control. In randomized controlled trials, 4 classes of medications have been proven safe and efficacious to treat pain in DSPN. This issue of *Pain Management Rounds* reviews the clinical features, methods of diagnosis, and treatment options for diabetic neuropathy.

BACKGROUND

Over 18 million people in the U.S. – or 6.3% of the population – have diabetes mellitus (DM) and the prevalence continues to increase dramatically across all age groups.[1] Diabetic neuropathy is more common in type 2 DM and its prevalence increases as the duration and severity of DM increases. In 10% of patients, neuropathic complaints are evident at diagnosis of DM. The risk of neuropathic dysfunction increases over time, so that >50% of diabetics are affected after 10 years.[2] Perhaps the most troubling symptom of diabetic neuropathy is pain, which may be the presenting symptom.[3]

CLINICAL FEATURES

Peripheral nerves are composed of large and small diameter nerve fibers. Symptoms associated with large fiber dysfunction include weakness, numbness, tingling, and loss of balance, while those associated with small fiber damage include pain, anesthesia to pin and temperature sensation, and autonomic dysfunction (eg, changes in local vasoregulation).

Among the forms of peripheral nervous system dysfunction associated with DM (Figures 1 and 2), by far the most common is DSPN.[2] In DSPN, the appearance and progression of symptoms depend on the length of the nerves so that it first affects the longest nerves in the feet. DSPN involves all fiber types, but small fiber dysfunction may predominate, especially in the early stages of neuropathy.[3] Early symptoms, which are more prominent at night, include bilateral symmetrical foot paresthesias and pain, often described as tingling, burning, prickling, shooting-pain, deep aching, pins and needles, tightness, or cold sensations. If not already present, evidence of large fiber dysfunction, such as sensory loss, numbness, tingling, and loss of coordination may appear as the neuropathy progresses. Motor symptoms and signs are generally minor and occur late. All symptoms migrate centrally over time to affect the proximal lower limbs and upper extremities. This classic pattern of sensory symptoms in DSPN is termed the "stocking-glove" distribution (Figure 1).

Symptoms of neuropathic pain are prominent early in DSPN and progress following the stocking-glove distribution. Typical symptoms include spontaneous pain, allodynia (pain due to a stimulus that does not normally provoke pain), hyperalgesia (an increased response to a stimulus that is normally painful), and sensitivity to cold temperatures. As these painful symptoms often result from small fiber dysfunction, patients may have accompanying abnormalities of autonomic function in

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the feet (eg, decreased sweating, dry skin, and impaired vasomotor control). This autonomic dysfunction may affect other organ systems (eg, sexual dysfunction). The discomfort of neuropathic pain can significantly impact quality of life and many patients complain of decreased physical activity, loss of libido, fatigue, and mood and sleep problems.[5]

A major concern in DSPN is the development of diabetic foot ulcers. Foot ulcers are multifactorial in origin with neuropathy, autonomic dysfunction, and vascular insufficiency all possibly contributing to this debilitating complication. Foot ulcers typically occur in areas under mechanical stress (eg, the weight-bearing areas of the foot) or as a result of poorly fitting shoes. It is important for diabetic patients to seek regular foot care as severe complications, such as an infection that requires amputation, can develop rapidly.[4]

Painful neuropathy and impaired glucose tolerance

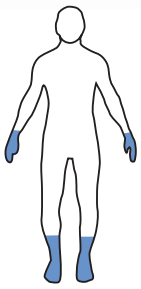
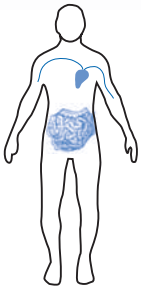
Although DM duration and blood sugar control correlate with the development of DSPN, recent studies reveal that a neuropathy with a predilection for small nerve fibers can appear with impaired glucose tolerance, a pre-diabetic state that does not meet the criteria for DM as defined by the American Diabetes Association.[3,6,7] Although this neuropathy is usually milder than the neuropathy seen in frank DM, impaired glucose tolerance has been associated with severe painful polyneuropathy without another known etiology.[3]

Clinical evaluation of DSPN

In taking a detailed history, the character, pattern, and timing of sensory symptoms are clues to the presence of DSPN and neuropathic pain. On physical exam, there may be sensory loss to all stimuli and a careful examination can help categorize sensory loss by nerve fiber type. Small fiber abnormalities can be mapped out with pinprick and temperature sensation testing. Pain may be induced by touch and areas of allodynia and hyperalgesia may be mapped out. The integrity of large fiber nerves can be assessed by applying a 128 Hz tuning fork (or an equivalent test of vibratory sensation) to the bony prominence of the dorsum of the big toe. Applying a monofilament pressure esthesiometer (4.21 – 5.07 U) to the foot tests thresholds for mechanosensation, a sensory modality also mediated by large fiber nerves. It is important to understand that sensory function is largely maintained during the degenerative process; therefore, a normal sensory exam does not exclude neuropathy.[5]

Decreased ankle reflexes often accompany early sensory changes in DSPN, followed by reflex changes in the patella and forearm as the neuropathy progresses. Evaluation of the feet and legs may reveal changes in skin color, abnormalities in sweating, scant hair growth, and dry skin. More severe complications of the foot that are associated with DM (eg, ulcers, calluses, and fissures) may be present early in DSPN.

FIGURE 1: Common generalized polyneuropathies

Syndrome	Distal sensory polyneuropathy (DSPN)	Autonomic neuropathy
Clinical findings	– Presentation is variable – A length-dependent disease – Symptoms in the stocking - glove distribution – Pain, numbness, and tingling in the feet – The most common type of neuropathy in DM	– Presentation is usually insidious – Affects multiple organ systems simultaneously (cardiovascular, GI, sexual, genitourinary, etc. – Underdiagnosed complication – Co-exists with other types of neuropathy
Pathology	Multifactorial	Multifactorial, small fiber damage
Diagnostic evaluation	Clinical findings, exclusion of other causes, screening tools, electrophysiology, punch skin biopsy, and QST	Clinical findings, lab and imaging studies tailored to organ system involved. Electrophysiology may be normal.
Treatment	See Figure 3	Tailored to organ system involved
Figure		

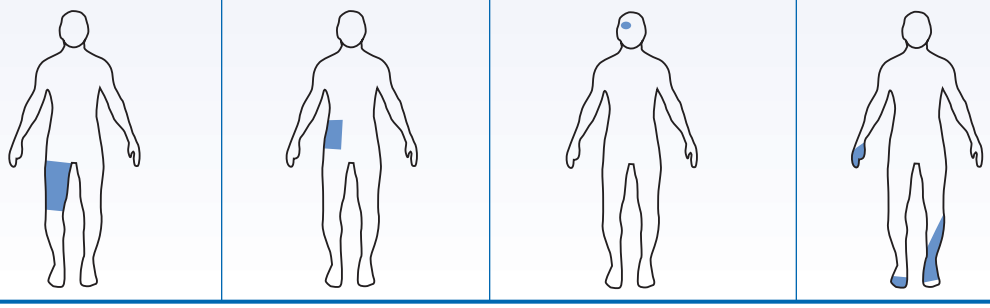
DM = diabetes mellitus; GI = gastro-intestinal
QST = quantitative sensory testing

Muscle weakness and atrophy are almost exclusively a late finding of severe neuropathy, with the intrinsic muscles of the foot being the first affected. Additionally, bony abnormalities of the foot such as neuropathic arthropathies (eg, Charcot joints) develop later in the disease process.

Differential diagnosis

Diagnosis of DSPN requires the presence of neuropathy consistent with DM, as well as exclusion of other common causes of neuropathy. Other potential causes include metabolic derangements (uremia, hypothyroidism), toxic exposure (alcohol, medication), infection (human immunodeficiency virus [HIV], leprosy), inflammatory disease (sarcoidosis), and connective tissue/autoimmune diseases (lupus). Additionally, there are several disease processes whose symptoms mimic those of neuropathy, such as traumatic injury or peripheral vascular disease. To further complicate the picture, many of these disease states may co-exist with DM. For a summary of recommended tests in the evaluation of

FIGURE 2: Focal pain syndromes from vasculitis

Syndrome	Lumbar polyradiculopathy/ diabetic amyotrophy	Thoracic radiculopathy	Mononeuropathy	Mononeuritis multiplex
Clinical findings	– Presentation is unilateral thigh pain and proximal weakness – Minimal sensory loss – Occurs with long duration DM – Patients typically report recent weight loss – Symptoms plateau at 6 months – Recovery can be expected within 2 years	– Presentation is abdominal pain in a band-like distribution – May present with bulging abdomen – Occurs with long duration DM – Patients with this neuropathy often undergo an extensive GI evaluation before arriving at the correct diagnosis.	– Presentation is dysfunction of a single nerve root – Occurs at any point in DM – Onset variable, can be insidious or acute – Often painful – Most common cranial nerve affected is the oculomotor nerve – Commonly causes carpal tunnel syndrome	– Presentation: there is consecutive or simultaneous onset of focal neurologic dysfunction in multiple areas – Common symptoms are pain, weakness, and numbness – In diabetics, symptoms often begin unilaterally in the legs – Differential diagnosis: HIV, hepatitis, lyme disease… etc.
Pathology	Vasculitis with resulting ischemia and infarction within individual nerves			
Diagnostic evaluation	Clinical findings and electrophysiology may aid diagnosis; when appropriate, imaging, serologic evaluation, and lumbar puncture may exclude other causes; nerve biopsy may be indicated in mononeuritis multiplex			
Treatment	Physical therapy, glycemic control, symptomatic therapy; unclear whether corticosteroids, immunosuppressive agents, or IVIg are efficacious			Immunosuppression with steroids, cyclophosphamide, or IVIg may be indicated
Figure				

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PATHOPHYSIOLOGY

Onset of pain in DSPN has been shown to be independent of damage to large myelinated fibers and to correlate with damage to small diameter nerves (A-delta and C fibers) that transmit pain sensation.[8] These small nerve fibers are often affected early and prominently.[3]

The molecular mechanisms of DSPN pain are multifactorial and incompletely defined. The distal axon is critically dependent upon oxidative metabolism to sustain axonal transport. Any disruption in the supply of blood, oxygen, glucose, ATP, or NADPH causes transport to falter, which can lead to distal axonal degeneration. Proposed mechanisms of disruption to normal nerve function include abnormal metabolic product formation as a result of glucose accumulation in the nerve, focal tissue ischemia in sensory and autonomic nerves as a result of endoneural hypoxia, abnormally functioning tissue repair mechanisms caused by excess glucose and oxidative stress, mitochondrial dysfunction in the dorsal root ganglia, aberrant neurofilament phosphorylation, and disruption of normal nerve growth factors. This is an area of continued investigation.[8,9]

DIAGNOSIS

Screening tools such as the United Kingdom Screening Test[10] that assess the symptoms and signs of neuropathy can be helpful in categorizing patients with questionable neuropathy.[2] However, there may be a high degree of variability, even among highly trained specialists when using neuropathy-screening tools.[11]

Electrophysiology tests, consisting of electromyography and nerve conduction studies, are the standard diagnostic tests for DSPN.[3] However, these studies only detect damage to large diameter nerves (characterized by slowing and reduced amplitude of sensory nerve action potentials) and do not detect isolated small fiber damage that often occurs early

FIGURE 3: The ABCs of diabetic neuropathy management

A	Antidepressants, anticonvulsants, topical anesthetics are the first-line treatments
B	Blood sugar management
C	Cardiovascular risk factor reduction
D	Diet and exercise for weight management
E	Emerging therapies for diabetes and neuralgia
F	Foot care to reduce infections and amputations

in the neuropathic process. Of the methods that have been developed to assess anatomical loss of small diameter nerves, neurodiagnostic skin biopsy is preferable to sural nerve biopsy because it is an easier, safer, and more sensitive diagnostic alternative.[12]

In 2003, the American Academy of Neurology concluded that quantitative somatosensory testing (QST) should not be used as the sole criteria to diagnose neuropathy, but it is a useful tool for measuring sensory impairment.[13] It may be particularly useful to monitor diminution of sensory function in established DSPN. The major limitation is that QST is entirely subjective and dependent on subject attention and cooperation.[14]

TREATMENT OPTIONS

Disease-modifying treatments

There are no treatments that can reliably reverse the damage associated with DSPN. Treatments that do exist are aimed at prevention or mitigation of progression (Figure 3). Multiple studies have established a causal relationship between glycemic control and the development and progression of the microvascular complications of DM.[11,15,16] The Diabetes Control and Complications Trial (DCCT) concluded that optimal insulin treatment of type 1 DM results in a 60%-70% reduction in the risk of developing neuropathy in patients without neuropathy and improvement in patients with established neuropathy.[11] The United Kingdom Prospective Diabetes Study (UKPDS) and other trials have suggested that the same relationship exists for type 2 DM.[15,16] Increased triglycerides, high body mass index (BMI), smoking, hypertension, and cardiovascular disease are among the newly identified independent risk factors for diabetic neuropathy.[17] Intensive treatment of these risk factors slows progression of autonomic neuropathy.[18] Weight loss, diet, and exercise improve both cardiovascular status and diabetic control.

There is some evidence that angiotensin-converting enzyme (ACE) inhibitors improve neuropathy, however, the mechanism is unclear.[19] The utility of aldose reductase inhibitors is unclear since they improve nerve conduction velocities, but do not clearly impact clinical symptoms.[20] A large trial of nerve growth factor failed to show efficacy, however, the trial was compromised methodologically and, therefore, the benefit of this therapeutic approach remains unresolved.[21]

TREATMENT OF PAIN IN DSPN

Antidepressants

Although DSPN is a commonly studied condition in trials for neuropathic pain medications, there are limited options. The tricyclic antidepressants (TCAs) are an inexpensive, safe, and effective first-line treatment supported by several placebo-controlled, double-blind, randomized controlled trials.[22,23] These well-studied medications have antihyperalgesic effects that occur more rapidly and at lower doses than in the treatment of depression. It is important to tell patients that they will not feel any response to an individual dose and maximum benefit may take up to 2 months to achieve.[22]

The limitation of TCA use is adverse effects that are often attributable to their anticholinergic properties. Some of the common side effects are constipation, dry mouth and eyes, sedation, cognitive changes, and nightmares. Additionally, some adverse events can mimic or worsen the symptoms of diabetic autonomic neuropathy (eg, orthostatic hypotension, sexual dysfunction). These medications must be prescribed with great caution in geriatric patients and in those with previous myocardial infarction or arrhythmia, cognitive decline, narrow angle glaucoma, or prostatic hypertrophy. Effective TCAs with the least side effects are desipramine and nortriptyline. Amitriptyline has the most side effects and should rarely be prescribed.

Cymbalta, a serotonin and norepinephrine reuptake inhibitor, was found efficacious in 2 randomized controlled trials and was approved for treating pain associated with diabetic neuropathy by the Food and Drug Administration (FDA) in September 2004. Subjects noted improvement as early as the first week and reported sustained effects during the day and night. Common side effects are nausea, vomiting, dizziness, somnolence, decreased appetite, and constipation.[24]

The selective serotonin reuptake inhibitors (SSRIs), another class of antidepressant, have been found effective for depression associated with DM, but not for treatment of pain in DSPN.[23]

Anticonvulsants

Several anticonvulsants have been found efficacious for treatment of DSPN in randomized controlled trials.

• Gabapentin is a first-line agent.[25] It is less effective than the TCAs, but has fewer serious adverse events and

medication interactions. Reversible adverse events include sedation and cognitive changes, so it should be initiated using low doses. Patients also may complain of peripheral edema.

• Pregabalin, a structural analog of gabapentin, is awaiting FDA approval. A randomized controlled trial revealed early and sustained improvement in pain compared with placebo.[26] Efficacy and adverse events appear similar to gabapentin. Its main advantage appears to be a longer half-life, which permits less frequent dosing.

• Carbamazepine is an inexpensive option.[25] Dose-escalation adverse events include nausea, vomiting, sedation, and confusion. Patients should be monitored for hyponatremia and rare side effects (ie, skin rash and bone marrow suppression).

• Oxcarbazepine, is an analog of carbamazepine that has less adverse events. It has been found efficacious in one open-label trial.[25]

• Lamotrigine is another anticonvulsant that has been found efficacious in the treatment of DSPN in one trial.[25]

• The efficacy of phenytoin and valproate is unclear. Both have trials that suggest a positive response, while other studies show no benefit with treatment. An additional reason to avoid phenytoin is that it causes peripheral neuropathy with prolonged use.[25]

Opioids

Opioids are efficacious for DSPN pain. Several trials support the use of controlled-release oxycodone and tramadol.[27-29] Common adverse events include drowsiness, sedation, dizziness, constipation, nausea, and vomiting. A point of concern for prescribing physicians is drug dependence and withdrawal symptoms that may occur upon discontinuation after prolonged opioid use. Nonetheless, in carefully selected patients, opioids remain an excellent treatment option.

Topical local anesthetics

Topical local anesthetics applied to the feet have been shown to significantly improve pain in diabetic neuropathy in an open-label trial.[30] Local anesthetics remain in the skin and have an excellent safety profile. There are several formulations, including creams, gels, sprays and a topical lidocaine patch, which has the additional benefit of providing a mechanical barrier to environmental insult.

Miscellaneous drugs

One study concluded that there is a moderate improvement in the pain of diabetic neuropathy with capsaicin use.[31] Capsaicin burns when applied to the skin and requires multiple applications. A concern is that it produces the same kind of axon degeneration as does DSPN.[32]

There are several agents that have been shown to be efficacious in limited studies, including venlafaxine extended-release[33] and isosorbide nitrate spray.[34] Some patients may benefit from transcutaneous electrotherapy.[35] The non-steroidal anti-inflammatory drugs (NSAIDs) have not been shown to be efficacious in the treatment of neuropathic pain.[36]

CONCLUSION

Neuropathic pain is a common symptom of diabetic neuropathy. Blood sugar and cardiovascular risk factors associated with the development of neuropathy should be treated aggressively to prevent the development and progression of neuropathy. Neuropathic pain should be managed pharmacologically using treatments that are proven safe and effective in strong clinical trials. More research is needed to define the pathophysiology of pain in DSPN and to develop and test medications to treat this common complication of diabetes.

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