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Diabetic Neuropathy

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Introduction

Peripheral neuropathy (PN) encompasses a broad range of clinical pathologies potentially presenting with peripheral nervous system dysfunction.[1] Patients with PN often present with varying degrees of numbness, tingling and/or burning in the extremities. While metabolic disorders represent the predominant etiology of extremity pain caused by an underlying PN clinical pathology, broad clinical consideration is given to a plethora of clinical conditions.

Although there are many possible causes of peripheral neuropathy, the most prevalent subtype, diabetic peripheral neuropathy, can lead to major complications. Early assessment of symptoms of peripheral polyneuropathy helps avoid neuropathic foot ulcers to ultimately combat potential morbidity and mortality resulting from the pathophysiologic poor wound healing potential which can lead to limb compromise, local to systemic infection and septicemia, and even death.

The exact cause of diabetic peripheral neuropathy is not known. Proposed theories include metabolic, neurovascular, and autoimmune pathways have been proposed. Mechanical compression (e.g., carpal tunnel), genetics, social and lifestyle factors such as chronic alcohol consumption and smoking all have been implicated. Perpetually high blood serum glucose appears to lead to damaged small blood vessels which compromise oxygen and nutrients to the nerves. First, the distal sensory and autonomic nerve fibers are damaged; the damage then continues with proximal progression leading to a gradual loss of protective sensation in both the skin and foot joints. Half of diabetic peripheral neuropathies may be asymmetric, and if they are not recognized, and preventative foot care is not implemented, patients have an increased risk of injury a to their insensate feet.[2][3][4]

Etiology

Metabolic disorders represent the most common clinical category of etiologies causing extremity pain from underlying PN conditions.

Several causes of PN exist, but diabetes mellitus (DM) is the most common etiology. Other underlying etiologies worth considering include:

- Chronic alcoholism
- Nutritional deficiencies (e.g., B12)
- Guillain-Barre syndrome
- Toxicities and overdose
- Hereditary or genetic conditions (e.g., Charcot Marie Tooth disease, amyloidosis, porphyria)
- Infection

- Inflammatory conditions
- Malignancy

Epidemiology

At the time of diagnostic DM onset in patients, the literature reports about 10% to 20% of patients being concomitantly diagnosed with PN. However, studies analyzing DM patients at an increasing duration of stages of the disease in terms of chronicity report increasing prevalence rates for the DM and PN association. After 5 years, 26% have peripheral neuropathy, and at ten years, 41% of diabetic patients have neuropathy. The literature reports from 50% to 66% of DM patients will eventually develop PN at some point during their lifetime.[5]

Clinically, about half of DM PN patients can present with asymmetric sensory changes.[6][7] Obesity and genetic factors increase the risk of developing diabetes. Peripheral and autonomic neuropathies are one of the leading causes of morbidity in diabetes mellitus. The risk of death at five years for patients with a diabetic foot ulcer is 2.5 times as high as the risk of death for a patient with diabetes who does not have a foot ulcer. The rate of emergency department visits for diabetic foot ulcers and associated infection exceeds the rates for congestive heart failure, renal disease, depression, and most forms of cancer.[8][9][10]

Pathophysiology

Diabetic peripheral neuropathy encompasses sensory, motor, and autonomic neuropathy. Implicated causes of peripheral nerve damage include oxidate stress damage, accumulation of sorbitol and advanced glycosylation end products as well as a disturbance of hexosamine, protein kinase C and polymerase pathways. Neurovascular impairment with poor repair processes and endothelial dysfunction also have been implicated.[7]

Toxicokinetics

Transient hyperglycemia is often tolerated by normal compensatory physiological function and homeostatic mechanisms of blood sugar control. However, in chronically elevated states, it can have toxic effects such as neuropathy. For patients diagnosed early with type 1 diabetes mellitus, tight glucose control can reduce the risk of diabetic peripheral neuropathy by 78%, while typically, with a later diagnosis of long-standing hyperglycemia or type 2 diabetes, tight glucose control only reduces the risk by 5% to 9%.

History and Physical

Symptoms of burning, numbness, or tingling in the feet that tend to be worse at night are characteristic. Patients with pedal paresthesias and dysesthesia often describe a nonspecific constellation of symptoms resulting in difficulty with ambulation and other basic activities of daily living (ADL). The characteristic polyneuropathy and distal sensory peripheral neuropathy are present in about 80% of DM PN patients. This is often described as a "stocking-glove distribution," and it can take several years to develop.

Since protective sensation is lost after sensory impairment, the standard Semmes-Weinstein 5.07 monofilament 10 grams of pressure protective sensation test may be accurately sensed even after a neurotrophic ulcer has developed. Simply timing the duration that a vibrating 128 Hz tuning fork is felt at the dorsal hallux interphalangeal joint (usually 18 seconds) can be used to detect sensory deficits earlier as well as quantify severity. Decreased light touch sensation or loss of ankle reflexes tend to occur earlier in the disease process, while the detectable loss of protective sensation tends to occur later in the disease, sometimes even after a neuropathic ulcer develops. Needle electromyography (EMG) and nerve conduction velocity testing can be both painful and expensive.

Evaluation

The medical history review of systems and medications captures most of the causes of peripheral neuropathy. Electromyography and/or nerve conduction studies are suggested if there are severe or rapidly progressive symptoms

or motor weakness. Minor symptoms may not need laboratory workup. Persistent unexplained symptoms may warrant laboratory investigation including serum glucose, glycohemoglobulin, complete blood count, erythrocyte sedimentation rate, rapid plasma reagin, serum electrophoresis, and vitamin B12 level. Measurement of intra-epidermal nerve fiber density (IENFD) by skin biopsy can be considered in patients with idiopathic cases. The number and morphology of axons within the epidermis can be evaluated, and intraepidermal nerve fiber density is compared to age-dependent normal values.[11][12]

Treatment / Management

Many neuropathy patients have mild to moderate numbness symptoms yet still retain protective sensation in their feet and may only need reassurance and education as to the cause of the numbness. Periodic follow up is important. With improved glycemic control, paresthesias and dysesthesias may diminish within one year. After peripheral arterial disease and radiculopathy are ruled out, painful symptoms that disturb sleep or activities of daily living can be treated with pregabalin, gabapentin, or anti-depressants. These medications have been shown to reduce the symptoms by 30% to 50% in many patients. Some patients also respond to the over-the-counter antioxidant alpha lipoic acid. Additionally, although classified as a medical food, the prescription containing L-methylfolate, pyridoxal 5'-phosphate, and methylcobalamin for the dietary management of endothelial dysfunction has been shown to improve nerve fiber density and monofilament sensation significantly. Depletion of substance P with topical capsaicin cream may help some patients who can tolerate the initially increased burning.[13][14][15]

Differential Diagnosis

- Alcohol-associated neuropathy
- Nutritional linked neuropathy
- Uremic neuropathy
- Vasculitic linked neuropathy
- Vitamin B-12 deficiency
- Toxic metal neuropathy

Pearls and Other Issues

The lower extremities are especially prone to the repetitive microtrauma-induced complications of polyneuropathy. There is an increased propensity to develop not only recurrent neuropathic ulcers but Charcot neuroarthropathy and, to a lesser extent, motor neuropathy. Additionally, as patients age their nails become dystrophic and the face of decreased protective sensation, the risk of subungual ulceration, gangrene, and osteomyelitis increases. Periodic focused examinations are essential. Professional foot care along with therapeutic shoes and insoles have helped to reduce the lower limb amputation rates in patients with diabetes mellitus.

Enhancing Healthcare Team Outcomes

Diabetic neuropathy affects many organ systems and is best managed by an interprofessional team. Because there is no cure for the disorder, the key is prevention. All people with diabetes should have a dietary consult and should be educated on what foods they should eat and what to avoid. The diet should be realistic and focused on lowering blood glucose levels. The diabetic patient should also enter a rehabilitation program or some exercise. Losing weight not only makes it easier to control the blood sugars, but it also lowers blood pressure and lipids. A podiatry consult is vital as protection of the foot is necessary. Further, all people with diabetes should be informed on avoiding trauma and undergoing any invasive procedure on the feet without prior clearance from the endocrinologist. In addition, the patient should be told to avoid cold or hot temperatures. Finally, all people with diabetes should be educated on the importance of blood glucose control. Patients should be taught how to monitor their blood glucose and how to use

portable glucose monitors. Compliance with diabetic medications is vital. Finally, patients who do develop neuropathy also tend to have nephropathy and retinopathy- hence, all people with diabetes should be referred to a nephrologist and ophthalmologist.[16][17] (Level V)

Outcomes

In general, diabetic patients who are not compliant with treatment or are under treated, usually tend to have a poorer outcome compared to patients who undergo treatment. The neuropathy frequently results in the breakdown of skin, ulceration and eventually to an infection. Amputation of the toes and limbs are not uncommon. However, the actual treatment of diabetic neuropathy is not perfect, and often most treatments do not work. Complete relief from symptoms of neuropathy is rare. Overall, the mortality rates are highest in diabetic patients with autonomic neuropathy, especially those who have cardiac dysfunction. The overall mortality rates are 15% to 30% over 10 years, but there is also significant morbidity from limb amputation. Other symptoms which make the quality of life poor include syncopal attacks, diarrhea, constipation, and continuous pain.[2][18] (Level V)

Questions

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