

**PERIPHERAL DIABETIC NEUROPATHY: ETIOPATHOGENESIS OF PDN,
ITS COMPLICATIONS AND MANAGEMENT**

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Abstract

Peripheral neuropathy is a broad range of clinical pathologies that can cause dysfunction in the peripheral nervous system. Symptoms of PN often include varying degrees of numbness, tingling, and/or burning in the extremities. The objectives of this article include reviewing the pathophysiology of diabetic neuropathy, summarizing its treatment, describing its potential complications, and outlining the management of diabetic neuropathy

Introduction

PN refers to a wide range of clinical conditions that may cause dysfunction in the peripheral nervous system, and patients with PN typically experience various degrees of numbness, tingling, and/or burning sensations in their extremities.[1] While metabolic disorders are the most common cause of extremity pain resulting from PN, other clinical conditions should also be taken into consideration. Diabetic peripheral neuropathy is the most prevalent subtype of PN and can lead to significant complications. Therefore, early detection and assessment of peripheral polyneuropathy symptoms are crucial to prevent neuropathic foot ulcers and avoid potential morbidity and mortality resulting from poor wound healing. The exact cause of diabetic peripheral neuropathy is unknown, and various theories, including metabolic, neurovascular, and autoimmune pathways, have been proposed. Additionally, mechanical compression, genetics, chronic alcohol consumption, and smoking are also potential risk factors. High blood serum glucose levels are believed to damage small blood vessels, reducing oxygen and nutrients to the nerves. This damage typically starts with the distal sensory and autonomic nerve fibers and progresses proximally, leading to a gradual loss of protective sensation in the skin and foot joints. Diabetic peripheral neuropathies may also be asymmetric, and if they go unrecognized and untreated, patients are at an increased risk of foot injuries due to their insensate feet.[2], [3], [4]

Etiology

The most common cause of extremity pain resulting from underlying PN conditions is metabolic disorders. However, there are several potential underlying etiologies of PN, and diabetes mellitus is the most prevalent. Other possible causes worth considering include alcohol use disorder, nutritional deficiencies, Guillain-Barre syndrome, toxins or overdose, hereditary or genetic conditions, infection, and

inflammatory conditions. Risk factors that may increase the likelihood of PN include advanced age, hypertension, peripheral vascular disease, smoking, dyslipidemia, poor glucose control, a long duration of diabetes, heavy alcohol consumption, and a positive HLA-DR3/4 genotype.

Epidemiology

According to literature, around 10% to 20% of patients are diagnosed with peripheral neuropathy (PN) at the time of being diagnosed with diabetes mellitus (DM). However, studies examining patients with DM at various stages of the disease show an increasing prevalence of the association between DM and PN with chronicity. After five years, the prevalence of peripheral neuropathy is 26%, and at ten years, 41% of patients with diabetes have neuropathy. It is reported that during their lifetime, 50% to 66% of patients with DM will eventually develop PN. [5]

Clinically, about half of patients with diabetic PN may have asymmetric sensory changes. [6], [7] Obesity and genetic factors can increase the risk of developing diabetes, and peripheral and autonomic neuropathies are a leading cause of morbidity in diabetes mellitus. The risk of death for patients with a diabetic foot ulcer is 2.5 times higher than for a patient with diabetes who does not have a foot ulcer after five years. Furthermore, the rate of emergency department visits for diabetic foot ulcers and associated infections is higher than the rates for congestive heart failure, renal disease, depression, and most forms of cancer. [8], [9], [10]

Pathophysiology

Sensory, motor, and autonomic neuropathy are all included in diabetic peripheral neuropathy. The causes of damage to the peripheral nerves include the accumulation of sorbitol, oxidative stress damage, advanced glycosylation end products, and disturbances of hexosamine, protein kinase C, and polymerase pathways. Additionally, neurovascular impairment with poor repair processes and endothelial dysfunction have been suggested as factors contributing to the condition. [7]

Toxicokinetics

Short-term elevation of blood glucose levels is usually well-tolerated by the body's compensatory mechanisms and homeostatic functions to regulate blood sugar. However, chronic hyperglycemia can be harmful and contribute to the development of neuropathy. Tight glucose control can significantly reduce the risk of diabetic peripheral neuropathy in individuals diagnosed early with type 1 diabetes mellitus, with a reduction rate of 78%. [11] In contrast, for individuals with a later diagnosis of long-standing hyperglycemia or type 2 diabetes, tight glucose control only reduces the risk by 5% to 9%. [11]

History and physical

The typical signs of burning, tingling, or numbness in the feet become more severe during the night. People who suffer from pedal paresthesias and dysesthesia often have a range of vague symptoms that make it challenging to walk or perform routine daily tasks. Nearly 80% of patients with diabetic peripheral neuropathy (DM PN) have a recognizable polyneuropathy and distal sensory condition. The symptoms of this condition appear gradually over several years and affect the feet and hands in a "stocking-glove" pattern. [12]

After losing protective sensation due to sensory impairment, the Semmes-Weinstein 5.07 monofilament 10-gram pressure test can still accurately detect a neurotrophic ulcer. Sensory deficits can be detected earlier and their severity quantified by timing how long a 128 Hz tuning fork is felt at the dorsal hallux interphalangeal joint (usually 18 seconds). In the early stages of the disease, decreased light touch sensation or loss of ankle reflexes are more likely to occur than detectable loss of protective sensation, which may not happen until after a neuropathic ulcer has developed. Although needle electromyography (EMG) and nerve conduction velocity tests are expensive and painful and mainly test large myelinated fibers, epidermal nerve fiber density testing can be performed to assess small unmyelinated fibers. [13]

Diabetes also commonly causes autonomic neuropathy, which can affect various organs such as the gastrointestinal, cardiovascular, and genitourinary systems. Symptoms of autonomic neuropathy include abdominal discomfort, dysphagia, nausea, fecal incontinence, constipation, diarrhea, hypotension, sinus tachycardia, variable heart rate, syncope, weak urinary stream, straining to void, incomplete bladder emptying, heat intolerance, gustatory sweating, extreme diaphoresis, carpal tunnel syndrome, radiculopathy, lumbosacral, and cervical neuropathy. Additionally, cranial nerves 3, 4, 6, and 7 may be affected.

Staging

1. NO: No neuropathy
2. N1a: Signs but no symptoms of neuropathy
3. N2a: Mild polyneuropathy or autonomic neuropathy, patient able to walk on heels
4. N2b: Severe polyneuropathy and patient unable to walk on heels
5. N3: Disabling polyneuropathy

Evaluation

Most of the causes of peripheral neuropathy can be identified through a review of medical history and medication use. Electromyography and nerve conduction studies may be necessary if symptoms are severe, rapidly progressive, or include motor weakness. However, minor symptoms may not require a laboratory workup. If unexplained symptoms persist, further laboratory investigation may be necessary,

including tests for serum glucose, hemoglobin A1c, complete blood count, erythrocyte sedimentation rate, rapid plasma reagin, serum electrophoresis, and vitamin B1, B6, and B12 levels. A neurological exam should also be conducted, evaluating muscle strength, reflexes, and sensation (light touch with a monofilament, vibratory sensation, and proprioception). Autonomic neuropathy can be indicated by a dermatological exam revealing dry/cracked skin, while pedal deformities like hammertoes may suggest motor neuropathy. [12]

In idiopathic cases, epidermal nerve fiber density (ENFD) can be measured through skin biopsy. This test evaluates the number and morphology of axons within the epidermis and compares intraepidermal nerve fiber density to age-dependent normal values. [14], [15]

Treatment / Management

It is common for patients with neuropathy to experience mild to moderate numbness but still have protective sensations in their feet. These patients may require reassurance and education about the cause of their numbness, as well as periodic follow-up. Improving glycemic control may lead to a decrease in symptoms within a year. Patients with painful symptoms that interfere with sleep or daily activities may benefit from pregabalin, gabapentin, or antidepressants, which have been shown to reduce symptoms by 30% to 50%. [16] Some patients may also respond to over-the-counter antioxidants such as alpha-lipoic acid. Prescription medications containing L-methyl folate, pyridoxal 5'-phosphate, and methylcobalamin have also been shown to improve nerve fiber density and monofilament sensation. [17]

Topical capsaicin cream, which depletes substance P, may help some patients, although it can cause initial burning. [18], [19], [20] A capsaicin 8% patch may also provide modest improvements in pain and sleep quality for patients with painful diabetic peripheral neuropathy. [21], [16] Diabetic gastroparesis can be managed with erythromycin and metoclopramide, while erectile dysfunction can be managed with phosphodiesterase inhibitors or a penile prosthesis.

Orthostatic hypotension may be managed with increased salt and fluid intake and compression stockings, and steroids may be required in some cases. Glycopyrrolate is used to manage sweating but is not always effective. Infected diabetic foot ulcers require debridement or amputation. Gastroparesis may be managed with a jejunostomy tube, and a pancreas transplant may be an option to stabilize autonomic function. Physical therapy is important for patients with muscle pain and weakness, while occupational therapy may be necessary for functional loss. Speech therapy is needed for patients with

Prognosis

Patients with poorly managed diabetes are more likely to experience morbidity and complications related to peripheral neuropathy (PN) compared to those with well-controlled diabetes. PN can result in skin breakdown, infections, ulcers, and ultimately, amputation. Unfortunately, the treatment of PN is often inadequate, and cardiac complications are prevalent. Additionally, less than one-third of patients with PN experience effective pain control, leading to a generally poor quality of life for most patients with this condition.

Complications

Amputations of the toes, foot, or leg; infections of the foot; dizziness falls; diarrhea, failure to thrive, dehydration; pain; cardiovascular neuropathy can cause death

Outcomes

Patients with diabetes mellitus (DM) who are non-compliant with or undertreated for their condition generally experience worse outcomes compared to those who receive proper treatment. Peripheral neuropathy often leads to skin breakdown, ulceration, and infection, which may result in amputation of the affected toes or limbs. However, the available treatments for diabetic neuropathy are not always effective, and complete relief from symptoms is rare. Patients with autonomic neuropathy, particularly those with cardiac dysfunction, have the highest mortality rates, which range from 15% to 30% over ten years. In addition to the risk of limb amputation, other symptoms such as syncopal attacks, diarrhea, constipation, and continuous pain significantly impact patients' quality of life. [2], [22]

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