

Diabetic Polyneuropathy, A Review of the Need for Early Diagnosis and Treatment

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Abstract

Diabetic neuropathies include polyneuropathies and mononeuropathies such as cranial neuropathies, limb and trunk mononeuropathies, and plexopathies caused by multiple processes including vascular, mechanical, and metabolic. Early diagnosis, which may be difficult, allows for early and intensive intervention. History, neurologic examination, and electrodiagnostic studies are standard in evaluation, with other studies dependent on the initial findings. Narcotics, antidepressants, clonidine, anticonvulsants, electrotherapy, and acupuncture may be effective in therapy. Careful control of glucose levels is important in prevention and slowing the progress of diabetic neuropathy.

Introduction

Diabetes has developed to epidemic proportions along with a population that is now overweight and obese as reported by the 2000 survey of the Center for Disease Control and Prevention.¹ The 2000 survey reveals a prevalence by self reporting of diabetes as 7.3% compared to 4.9% in 1990. This increase has been directly proportional to 56.4% of the population becoming overweight (body mass index over 25kg/m²), compared to 45% in 1991. Diabetes is the leading cause of peripheral neuropathy in the developed countries. In 1993, Dyck³ identified as many as 1.3% of the community population of Rochester, Minnesota to have diabetes mellitus. Among the diabetic inhabitants, approximately 66% could be determined to have a diabetic neuropathy; of these individuals, 20% were considered to be symptomatic. Previously, diabetic neuropathy has been attributed to affect 15% of all persons with diabetes and 37% of those older than 18 years of age. Clinically, any neuropathy has been defined by the presence of sensory, motor, or autonomic deficits on examination. A detailed classification and staging has been proposed by Dyck³ based on the degree that these three components are involved.

Diabetic neuropathies include polyneuropathies and mononeuropathies such as cranial neuropathies, limb and trunk mononeuropathies, and plexopathies.⁴ (Table 1). The development of a length-dependent sensory or sensorimotor polyneuropathy has been the hallmark of diabetes. Unfortunately, those with

this type diabetic neuropathy may suffer dysesthesias and paresthesias depending on the neural fiber type size, often with neuralgia.^{5,6} Another length-dependent polyneuropathy is diabetic autonomic neuropathy. The majority of individuals who have developed autonomic neuropathy have an associated sensory or sensorimotor polyneuropathy. Together, these neuropathies are frequently associated with the development of adverse autonomic symptoms (i.e. orthostatic hypotension) and of painful neuralgias with an increased morbidity and mortality that are a dilemma for both patients and their physicians.

Table 1
Classification of Diabetic Neuropathy⁴

Symmetrical polyneuropathies
Sensory or sensorimotor polyneuropathy
Acute or subacute motor neuropathy
Autonomic neuropathy
Focal and multifocal neuropathies
Cranial neuropathy
Trunk and limb mononeuropathy
Proximal motor neuropathy

Pathophysiology

The pathophysiology of diabetic neuropathy includes multiple processes causing injury of varying degrees to large myelinated and small myelinated and nonmyelinated nerve fibers.⁶ These have included vascular, mechanical, and metabolic theories.

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The vascular considerations have included atherosclerosis, microangiopathic, and intraluminal fibrin deposition. Atherosclerotic disease was considered relatively early in medical history with the inspection of the larger vasculature of amputated limbs. Large vessel occlusive disease has subsequently, for the most part, been dismissed as an etiology of peripheral polyneuropathy. In contrast, microangiopathy, though not a total explanation for the development of polyneuropathy, is still considered a significant component to the development of mononeuropathies such as oculomotor palsies as well as motor neuropathies as diabetic amyotrophy. In 1993, Reichard, et al⁷ demonstrated that intensive insulin therapy of a cohort of patients could retard the microvascular complications of retinopathy, nephropathy and neuropathy. Additionally, intraluminal fibrin deposition may represent additional vascular pathology sensitive to endoneurial pressure leading to intraluminal plugging with fibrin deposits.⁴

Mechanical factors are of concern due to an apparent increased sensitivity and poor recovery from external pressure as is noted by the increased frequency of entrapment syndromes.⁴ This situation is perhaps well exemplified by a large population based study, among whom the frequency of asymptomatic and symptomatic carpal tunnel syndrome developed in approximately a third of the diabetic patients.²

Metabolic factors being explored include vitamin deficiencies, lipid abnormalities, sorbital accumulation, myo-inositol deficiency, abnormal protein metabolism including abnormal glycosylation and impaired synthesis of structural proteins, and experimental diketone toxicity.^{4,8} Immune-mediated inflammation is also being evaluated as a potential inciting event in specific complications.⁹ Unfortunately, many metabolic trials including high myo-inositol diets, aldose reductase inhibitor therapy, supplementary gamma-linolenic acid therapy, ganglioside, and nerve growth factor have had only limited benefit.¹⁰ Intensified insulin treatment therapy has had the most beneficial results.^{7,11}

Diagnosis

Currently, early diagnosis that allows for early and intensive intervention is the mainstay of reducing the complications of diabetic neuropathy.^{5,7} Early diagnosis, however, can be

difficult. Since the individual may be otherwise healthy, symptoms of early neuropathy such as “numb feet” may be dismissed or attributed to incidental mechanical, radicular or circulatory factors. Not infrequently, when the physician encounters the question of a neuropathy, a fasting glucose may be obtained. When the result returns normal and the individual is believed to have a nonspecific peripheral polyneuropathy the physician may begin an exhaustive evaluation utilizing many of the elegant tests available today to analyze for common and infrequent metabolic and genetic disorders.

In a retrospective evaluation in 1999, Lubec and others,¹² reviewed the medical records of 171 of their patients. All had an erythrocyte sedimentation rate, serum glucose, glycosylated hemoglobin, C-reactive protein, blood cell count, lipid studies, liver functions, thyroid function, serum electrophoresis, renal function and urine analysis, as well as studies for sexually transmitted diseases as VDRL, FTA-ABS, and HIV. Many had still more invasive examinations including electrophysiologic examinations, spinal fluid analysis, and nerve/muscle biopsies. Evaluations of vitamin levels of B1, B6, B12, and folate as well as Schilling tests were performed. Immunologic studies included immunoelectrophoresis, antinuclear antibodies, antineutrocyte-cytoplasm antibodies, circulating immune complexes, rheumatoid factor, anti-GM1 antibodies, and several tumor markers were obtained. Despite these extensive studies only 81% could be characterized. However, noninvasive studies, including the history and physical/neurologic exam, identified 83% (114 pts.) of those that were able to be characterized. Of these, diabetic neuropathy was the most common (26pts) and alcohol related neuropathy was the next most common (20pts).

As an effort to provide a rationale and cost effective approach to the evaluation of a peripheral neuropathy, Pourmand¹³ recently provides an initial approach to the patient suspected of having a peripheral polyneuropathy. This includes the history, including family history, and physical/neurologic examinations, and electrodiagnostic studies (EDX, Table2) which are recognized as the standard in the evaluation of a peripheral neuropathy. Initial and basic laboratory tests include a complete blood count, chemistry profile, erythrocyte sedimentation rate, serum B12 level, serum protein electrophoresis (SPE) and immunoelectrophoresis (IME). A chest X-ray

should be considered in the elderly patient. Additional testing to be performed depending on the initial results, such as methylmalonic acid and homocysteine levels, if an elderly patient has a low B12 level. A bone scan and hematology/oncology evaluation if an M-protein is identified on the SPE. Only in further selective situations is testing for “Anti-nerve” tests (such as GM1, Myelin-associated glycoprotein ‘MAG’ antibodies, GQ1b and Anti-Hu antibodies), genetic testing, skin biopsy, spinal fluid analysis, and a nerve biopsy, worthwhile. Despite these efforts, though the majority of etiologies may be identified, many will remain idiopathic.

**Table 2
Electrodiagnostic testing for Diabetic Peripheral Polyneuropathy¹⁸**

<p>Motor nerve – conduction studies (including an upper and lower limb). Unilateral studies of either ulnar or median nerve including F waves in the upper limb. Unilateral studies of peroneal nerve including F wave in the lower limb. Measurement of muscle-action potential amplitude and latency at each site of stimulation and calculation of segmental conduction velocity</p>
<p>Sensory nerve – conduction studies (including an upper and lower limb). Unilateral studies of either ulnar or median nerve in the upper limb. Unilateral studies of either medial plantar or sural nerve in the lower limb</p>
<p>Measurement of muscle – action potential amplitude and latency at each site of stimulation and calculation of segmental conduction velocity.</p>
<p>Studies of additional nerves may be necessary to characterize abnormalities based on the distribution of clinical symptoms or signs. In addition to nerve conduction studies of two limbs recording the latency, amplitude, duration, configuration, and conduction velocities; the needle EMG exam should include at least one distal muscle in each leg and one distal muscle in one arm. Demonstration of a proximal-to-distal gradient of increasing neuropathic abnormality augments the nerve conduction study demonstration of a peripheral polyneuropathy.²⁸</p>

Since diabetic sensorimotor polyneuropathy is the most common neuropathy in the developed countries, its presence should be excluded first. In a retrospective evaluation, Singleton et al¹⁴ reviewed the 1997 American Diabetes Association recommendations and identified 198 patients with EDX supported polyneuropathy. Initially 121 cases were considered idiopathic polyneuropathy at the time of EDX. Eighty-nine of the 121 cases had an identifiable single abnormal measurement of glucose handling (fasting glucose, hemoglobin A1c, or a 2-hour glucose test). Thirty-one percent (28 patients) met criteria for diabetes mellitus. Of the remaining 61 cases, 13 were identified to have impaired glucose tolerance by an abnormal oral glucose tolerance test (OGTT) and 2 had

impaired fasting glucose. Subsequently, by utilizing a 2-hour glucose tolerance test, the authors identified diabetic related neuropathy in two-thirds of patients with an impaired glucose tolerance and more than half with diabetes mellitus would have been missed if fasting plasma glucose or hemoglobin A1c alone had been used for screening. Others have also suggested that the standard 2-hour oral glucose tolerance test be considered early in the investigation of a peripheral neuropathy. When evaluating the patient presenting with a peripheral neuropathy or the known patient with diabetes, the physician needs to be aware that 10% have a peripheral neuropathy at the time of the diagnosis.¹⁵ The OGTT may be more sensitive than the fasting glucose and HbA1c¹⁶ and provide characterization to almost half of those neuropathies that might otherwise be considered idiopathic.¹⁷

In 1988 a Consensus statement¹⁸ identified the recommendation of establishing the presence of an autonomic neuropathy due to the potential manifestation of multiple organ dysfunction including cardiovascular, gastrointestinal, genitourinary, sudomotor, and ocular. (Table 3) Of these tests, measurement of heart-rate variability may reflect the earliest stage, abnormality of Valsalva response an intermediate stage, and postural hypotension a more severe stage. The presence of autonomic neuropathy has also been identified as an independent risk factor for stroke.¹⁹ That symptomatic autonomic neuropathy has a high associated mortality has been well described.^{20,21} The mortality ranging from a calculated mortality of 44% in two and a half years to more than 50% in 5 to 10 years.

**Table 3
Autonomic Neuropathy¹⁸**

<p>Tests of heart-rate control (primarily parasympathetic) Heart-rate response to: Valsalva maneuver Deep breathing Standing</p>
<p>Tests of blood pressure control (primarily sympathetic) Blood pressure response to: Standing or tilting Sustained handgrip</p>
<p>Tests of Sudomotor control Temperature-induced sweating Chemically induced sweating (acetylcholine or pilocarpine)</p>

Treatment of chronic painful peripheral polyneuropathy

Approximately 5% of patients with diabetes may experience a painful neuropathy. Providing symptomatic relief for these patients has represented a major challenge. These have included pharmacologic and nonpharmacologic trials including the following:

Opioid narcotics have been an obvious choice except for the concern of tolerance and abuse.

Nonnarcotic nonsteroidal anti-inflammatory drugs have not been effective. Tricyclic antidepressants as amitriptyline and nortriptyline, have been utilized and have been modestly beneficial though limited by prolonged titration and adverse side effects.

Alpha-agonist, clonidine, has been beneficial but limited by orthostatic hypotension.

Anticonvulsants have been beneficial though their use may be limited on an individual basis by specific side effects, including ataxia, rash, lethargy, and blood dyscrasias. These include carbamazepine, valproate, lamotrigine, and gabapentin.²² Of these, lamotrigine, gabapentin, and topiramate are more recent. Lamotrigine was demonstrated in a double-blinded controlled trial to have efficacy over placebo in doses up to 400mg/day.²³ Compared to amitriptyline (at 90mg/day) which has commonly been used for neuralgia, gabapentin (at a maximum of 2400mg/day) was found by Dalocchio, et al²⁴ to demonstrate improved pain control with fewer adverse effects in an open limited pilot study of 25 patients. Recently, Connor²⁵ studied twenty patients refractory to previous medical intervention with topiramate. Using a mean dosage of 260mg/day, seventeen had a good or better response.

Recent novel nonpharmacologic interventions include the introduction of electrotherapy and acupuncture. As an adjunct to medical therapy, Kumar, et al, have tried electrotherapy as an adjunct to amitriptyline with some additional modest benefit.²⁶ As acupuncture has been introduced into western medicine, Abuaisha, et al,²⁷ in 1998 demonstrated that 77% of forty-six patients (34 cases) improved with acupuncture, including many already tried on standard medical treatment.

Treatment of autonomic neuropathy

The most important concern for the patient with autonomic neuropathy is the early recognition of its presence, as aggressive diabetic control has been found to delay and reduce the degree of neuropathy.⁵ Once developed, the problems experienced are multiple, including cardiovascular, orthostatic hypotension, gastroparesis, diarrhea, erectile dysfunction, and cystopathy.²⁰

Cardiovascular symptoms may occur in 17% of type I diabetics and 22% of type 2 diabetics. Resting tachycardia may be an early sign of cardiac autonomic neuropathy, though blunted symptoms including painless ischemia are frequent. Asymptomatic myocardial infarction (MI) may be associated with a mortality rate of 47% compared to 35% mortality of an MI with painful symptoms. As noted previously, most individuals with autonomic neuropathy also have a sensory or sensorimotor polyneuropathy.⁴ Therapeutic interventions are extensively reviewed by Vinik and Erbas.²⁰ Orthostatic hypotension may be benefited by nonpharmacologic means as supportive stockings, caution with posture changes, and avoiding hot showers. Pharmacologic intervention may include alpha-fluorohydrocortisone 0.5-2mg/day. Vasomodulator medications include an alpha 1-adrenergic agonist, midodrine, and the alpha 2-adrenergic agonist, clonidine. Gastroparesis may be commonly benefited by metoclopramide 30-60 minutes before meals and bedtime. Diarrhea may respond to metronidazole 250 mg three times daily for at least three weeks. Erectile dysfunction may be responsive to sildenafil 50 mg prior to sexual activity, once only per day. Cystopathy can be improved by bethanechol 10mg four times a day.²⁰

Summary

Diabetes is a common, and increasing, disorder of epidemic proportions frequently associated with a symptomatic length-dependent polyneuropathy. Autonomic neuropathy is associated with a significant increased morbidity and mortality. Due to the extensive nature of the sympathetic and parasympathetic pathways, the problems created by this neuropathy present in several organ systems in succession or in unison.

The sensory and sensorimotor

polyneuropathy as the hallmarks of diabetic neuropathy may precede the diagnosis of diabetes. Therefore, the physician evaluating for an idiopathic peripheral neuropathy needs to identify the impaired glucose tolerant patient as well as the patient who is clearly diabetic. An oral glucose tolerance test must be included in the evaluation should the patient's initial search not reveal diagnostic criteria for diabetes. Intensive medical therapy, including weight and exercise, of the diabetic individual will help to decrease the occurrence and severity of the neuropathy as well as other associated end-organ injury.^{5,7,11} The mainstay of therapy for the individual experiencing neuralgia continues to be pharmacologic, though due to modest response rates, other nonpharmacologic methods are being explored. Unfortunately, the pathophysiology of diabetic neuropathy is complex and multiple and continues to be incompletely understood.

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