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Idiopathic neuropathy, prediabetes and the metabolic syndrome

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Abstract

Peripheral neuropathy is a common problem encountered by neurologists and primary care physicians. While there are many causes for peripheral neuropathy, none can be identified in a large percentage of patients ("idiopathic neuropathy"). Despite its high prevalence, idiopathic neuropathy is poorly studied and understood. There is evolving evidence that impaired glucose tolerance (prediabetes) is associated with idiopathic neuropathy. Preliminary data from a multicenter study of diet and exercise in prediabetes (the Impaired Glucose Tolerance Neuropathy Study) suggests a diet and exercise counseling regimen based on the Diabetes Prevention Program results in improved metabolic measures and small fiber function. Prediabetes is part of the Metabolic Syndrome, which also includes hypertension, hyperlipidemia and obesity. Individual aspects of the Metabolic Syndrome influence risk and progression of diabetic neuropathy and may play a causative role in neuropathy both for those with prediabetes, and those with otherwise idiopathic neuropathy. Thus, a multifactorial treatment approach to individual components of Metabolic Syndrome may slow prediabetic neuropathy progression or result in improvement.

Keywords: Peripheral neuropathy; Prediabetes; Diabetes; Metabolic syndrome; Idiopathic

1. Introduction

Peripheral neuropathy is one of the most common disorders seen in general neurology and neuromuscular specialty clinics, and foot numbness and pain is a frequent cause for referral for neurologic consultation. In our outpatient neuromuscular clinics, peripheral neuropathy is the most common diagnosis, accounting for over 20% of new patient visits. Despite its frequency, many neurologists approach the evaluation of peripheral neuropathy with ambivalence. While there are hundreds of causes for peripheral neuropathy, most patients present with symptoms of distal numbness and pain. Therefore, distinguishing one disorder from another can be challenging. Perhaps more discouraging is the mistaken perception that as many as two-thirds of neuropathy patients remain undiagnosed, relegated to the nebulous designation of "idiopathic" or "cryptogenic" neuropathy. Demonstration of familial, inflammatory, and toxic causes for neuropathy has chipped away at this large bloc of idiopathic patients, but in the past 25 years few novel causes of neuropathy have been recognized. However, recent work from our group and others suggests that impaired glucose tolerance (IGT or prediabetes) and other features of Metabolic Syndrome are important contributors to peripheral neuropathy [1–4]. In this paper, we review the epidemiology of idiopathic neuropathy, discuss the evidence implicating prediabetes and Metabolic Syndrome, and suggest a unifying hypothesis and a means of testing it.

2. The problem of idiopathic neuropathy

Little population-based epidemiological data is available regarding the prevalence of idiopathic neuropathy. The Italian General Practitioner Study Group interviewed 4191 elderly subjects in northern Italy and demonstrated possible neuropathy in up to 8% [5]. The National Health and Nutrition Examination Survey (NHANES) demonstrated a 14% prevalence of peripheral neuropathy among 2873 individuals over 39 years of age. The risk among diabetics was approximately twice that of non-diabetic individuals

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Table 1
The ATP III criteria for Metabolic Syndrome require fulfillment of at least 3 of 5 criteria [9]

Obesity	Waist circumference of <112 cm for men, >88 cm for women
Triglycerides	≥150 mg/dl
High density lipoprotein	>40 mg/dl for men, >50 mg/dl for woman
Blood pressure	>130/85 mm Hg
Insulin resistance	Prediabetes or diabetes (refer to Table 2 for specific criteria)

(28.5%) [6]. Based on this sample, if one assumes 10% prevalence in those 40 or older, approximately 15–20 million Americans suffer from peripheral neuropathy. One third may have idiopathic neuropathy.

Despite this apparently high prevalence, there has been little research focused on understanding idiopathic neuropathy. This paucity of interest may reflect perceptual barriers to the systematic study of idiopathic neuropathy. A first barrier to interest is what might reasonably be termed the "mundane factor." In general, diseases that are dramatic, either because of rarity or severity, pique our interest. Thus, a Pub-Med literature search reveals less than 100 papers addressing idiopathic or cryptogenic peripheral neuropathy. In contrast, there are in excess of 4000 papers written on the Guillain–Barré Syndrome, a peripheral nerve disease with a much lower incidence than idiopathic neuropathy, but distinctive clinical, laboratory and electrodiagnostic features.

Second, idiopathic neuropathy has been perceived as a relatively mild condition that progresses slowly, if at all, and causes minimal disability. In fact, while idiopathic neuropathy rarely leads to enough sensory or motor loss to significantly impact ambulation, patients are often disabled by neuropathic pain.

A third significant barrier to our understanding is the discouraging presumption that idiopathic neuropathy represents a large monolithic bloc that cannot be dissected by examining clinical or physiologic features. The first step towards a more comprehensive understanding of idiopathic neuropathy was taken by Dyck et al. in 1981, when they determined the diagnostic yield of an intensive evaluation of patients referred to the Mayo Clinic with undiagnosed peripheral neuropathy. They found that a diagnosis could be identified in 76% of subjects, with inflammatory demyelinating (21%) and inherited (42%) etiologies being most common [7]. This and subsequent work also helped to refine the current clinical phenotype of idiopathic neuropathy. We now recognize that most patients with idiopathic neuropathy have a slowly progressive, sensory predominant, distal symmetric neuropathy that is often painful. Atypical features such as prominent weakness, proximal involvement, or a rapidly progressive course almost always lead to a definable cause [8].

Until distinct subtypes or categories within this painful sensory-predominant idiopathic neuropathy group can be recognized, research focusing on mechanisms and therapy will be difficult. In the past two decades, few new causes of sensory-predominant neuropathy have been recognized. Various neuropathies associated with autoantibodies to axonal or glial targets (e.g. myelin associated glycoprotein, anti-gliadin antibody in celiac disease) have been defined. However, these neuropathies are uncommon and usually associated with a distinctive phenotype. Our work has focused on a potential role for hyperlipidemia, obesity and prediabetes in the pathogenesis of sensory neuropathy. These very common conditions occur most often in the context of insulin resistance, which begins in the prediabetic period and continues into early diabetes. The combination of insulin resistance, hypertension, hyperlipidemia and obesity has been referred to as "the Metabolic Syndrome" (Table 1) [9]. These are common disorders. Prediabetes is present in 11–15% of Americans older than 50, and Metabolic Syndrome is present in 8%. Thus, implication of these disorders in neuropathy pathogenesis would dramatically reduce the number of patients diagnosed with completely idiopathic neuropathy. Below, we lay out evidence to support our hypothesis that prediabetes, and perhaps other features of Metabolic Syndrome are sufficient to cause distal sensory neuropathy.

3. Prediabetes and peripheral neuropathy

Diabetes is the most common cause of peripheral neuropathy worldwide. Diabetes affects over 14 million people in the United States alone and the number of diabetic patients is increasing by 5% each year. Half of diabetic patients develop peripheral neuropathy. Traditional view has held that diabetes only results in neuropathy after many years of sustained hyperglycemia. However, there is evidence that neuropathy occurs earlier in the course of hyperglycemia than other microvascular diabetic complications. In a large survey, more than 20% of patients with early diabetes had physical examination or electrophysiological evidence of neuropathy, while almost none had proteinuria, or retinopathy [10].

Prediabetes is defined as either impaired fasting glucose or impaired glucose tolerance (IGT) following a 2-h oral glucose tolerance test (OGTT). Table 2 summarizes the diagnostic criteria for diabetes and prediabetes. Several lines

Table 2
The revised criteria for interpretation of oral glucose tolerance testing consisting of a fasting early morning plasma glucose, followed by a 75-g oral anhydrous dextrose load and a repeat glucose measurement 2 h later

Diagnosis	Fasting glucose	Two-hour glucose
Normal	<110 mg/dl	<140 mg/dl
Impaired fasting glucose (IFG)	110–125 mg/dl	<140 mg/dl
Impaired glucose tolerance	<126 mg/dl	140–199 mg/dl
Diabetes (may meet either fasting or 2-h criterion)	>125 mg/dl	>199 mg/dl