

## CLINICAL VIGNETTE

# A Case Report: Idiopathic Peripheral Neuropathy Preceding Frank Diabetes by Seven Years

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### *Introduction*

Peripheral neuropathy, characterized by burning feet and other distal limb sensory complaints, is a relatively common diagnosis; however even with extensive evaluation, the underlying cause is identified in only 7-30% of cases.<sup>1</sup> The remaining undiagnosed cases fall under the umbrella of chronic idiopathic axonal polyneuropathy (CIAP). Patients in this group have a two-fold higher frequency of undiagnosed diabetes mellitus and impaired fasting glucose.<sup>1</sup>

### *Case Report*

A 61-year-old obese, Caucasian male presented with a five year history of peripheral neuropathy. This was initially characterized by numbness and a burning sensation involving bilateral feet, beginning in the soles and progressing to involve both the dorsal and plantar surfaces. An underlying etiology had never been identified. He now noted a new intermittent burning pain in his palms, occurring 3-4 times a day and lasting up to an hour. Of note, he also had symmetric lower extremity edema, which was managed with furosemide. He had no family history of neuropathy or diabetes. He experienced mild improvement with low-dose amitriptyline (25 mg three times a day).

On physical examination, the patient was obese with normal blood pressure. The lower extremities had 2+ edema with venous stasis changes. Neurologic exam showed normal cranial nerves, 4+/5 strength in the intrinsic foot muscles bilaterally, decreased sensation to light touch, and absent to pinprick below both ankles, bilateral hyporeflexia at the patella and Achilles, and difficulty with tandem gait.

A broad array of laboratory studies to evaluate peripheral neuropathy had failed to uncover a cause. A peripheral smear was unremarkable; HIV serology, viral hepatitis serologies, rapid plasma reagin for syphilis, anti-nuclear antibodies, serum/urine protein electrophoresis, and cryoglobulin were all negative; thyroid stimulating hormone, vitamin B12, folate, methylmalonic acid, and homocysteine levels were all normal; and the hemoglobin A1c level (HbA1c) of 5.8% was not suggestive of overt diabetes. A nerve conduction study

performed four years prior was interpreted as bilateral sural neuropathy versus possible early peripheral neuropathy.

The patient was referred to Neurology who noted that while the HbA1c did not suggest overt diabetes, the patient did have a single random glucose value of 200 mg/dL in the past. They recommended a three-hour oral glucose tolerance test (OGTT) to definitively rule out diabetes. Unfortunately, the patient did not follow through with this test and was lost to follow-up.

When he showed up at primary care again two years later, his neuropathy had worsened. Furthermore, he had been experiencing classic symptoms of polyuria, polydipsia, fatigue, and a 25-pound weight loss over the preceding few months. His glucose level had jumped up to 468 mg/dL, and his HbA1c level was now 13.4%, confirming the diagnosis of diabetes mellitus.

### *Discussion*

It has long been held that peripheral neuropathy is a chronic complication of long-standing, poorly controlled diabetes. However, studies document many cases where the neuropathy is present well before the diagnosis of frank diabetes. Over 60% of patients with CIAP have pre-diabetes (defined by a fasting glucose between 100-125 mg/dL, an OGTT with 2-hour glucose between 140-199 mg/dL, or a HbA1c value between 5.7-6.4%).<sup>1</sup> Among individuals with pre-diabetes, 11-25% are thought to have peripheral neuropathy and neuropathic pain.<sup>2</sup> The likelihood of CIAP increases with the severity of abnormal glucose metabolism and is least likely in patients with only impaired fasting glucose.<sup>2</sup>

The neuropathy in pre-diabetics is generally milder than diabetic neuropathy and mainly affects small fibers mediating sensory function.<sup>3</sup> One study compared sural nerve conduction studies (NCS) in asymptomatic patients with impaired glucose tolerance (IGT) to NCS in asymptomatic diabetics and their normal counterparts. Patients with IGT mainly demonstrated abnormal conduction velocity limited to the distal segment of the sural nerve, suggesting that myelin dysfunction of the distal sensory fibers represents the earliest detectable nerve response to the hyperglycemia. Diabetic patients showed more advanced stages of nerve disease while the normal

controls had normal conduction velocities.<sup>4</sup> The neuropathy associated with IGT caused preferential injury to small nerve fibers resulting in decreased pain, temperature sensation, and autonomic dysfunction more than motor modalities, which are carried by large nerve fibers.<sup>3,5</sup>

Neuropathy in IGT and diabetes follows a common pathway. Hyperglycemia causes direct nerve toxicity by increasing oxidative stress, accumulating advanced glycation end-products, and impairing axonal transport. There also appears to be impaired microvascular function due to defects in endothelial function, which may lead to hypoxia and ischemia of the nerve.<sup>5</sup>

Diagnosis of pre-diabetic neuropathy will depend on a careful physical examination, appropriate laboratory evaluation, and increased clinical index of suspicion to look beyond the standard guidelines for the diagnosis of diabetes. Oftentimes, neuropathy can be the presenting symptom of either diabetes or pre-diabetes.<sup>6</sup> Though the most common test for diagnosing diabetes in the clinic is a fasting blood glucose and a HbA1c, these tests may not catch all cases of abnormal glucose metabolism. One study examined high-risk patients and found the diagnostic criteria recommended by the American Diabetes Association (ADA) of a normal fasting blood glucose <109 mg/dL (prior to the routine use of HbA1c) missed those high-risk patients with isolated post prandial hyperglycemia.<sup>7</sup> Another study, conducted by the Endocrinology group at the Minneapolis VA, looked at how well HgA1c correlated with mean blood glucose values and found that the correlation was not as direct as we may assume. In fact, patients with HbA1c values of 5% (normal) ranged in their mean glucose values from 80-120 mg/dL, and those with HbA1c values of 7% (well-controlled diabetics) ranged from 120-180mg/dL. The higher the HbA1c, the broader the range for mean glucose values.<sup>8</sup> So a “normal” fasting glucose or HgA1c does not necessarily preclude a diagnosis of abnormal glucose metabolism or pre-diabetes. Patients with unexplained peripheral neuropathy that have normal fasting blood sugars and HgbA1c, the 3 hour OGTT, the gold standard for diabetes mellitus screening, should be considered.

It is important also not to miss the early signs of small fiber dysfunction, namely loss of pain and/or temperature perception. Skin biopsy is the most sensitive way to diagnose small fiber neuropathy but is not feasible for routine use in a clinical setting.<sup>2</sup> Nerve conduction studies can help confirm the diagnosis.

The only known means of slowing the progression of diabetic neuropathy is good glycemic control. The Diabetes Prevention Program (DPP) looked at the effects of metformin versus aggressive diet and exercise counseling versus placebo, and found that the diet and exercise arm was almost twice as effective (58% versus 31%) in reducing progression risk to diabetes as the metformin group.<sup>9</sup> The Impaired Glucose

Tolerance Neuropathy (IGTN) study found that the same lifestyle interventions based on the DPP resulted in significant improvement in measures of small-fiber function and reduction in neuropathic pain.<sup>10</sup>

In conclusion, peripheral neuropathy is very common in clinical practice. Though it can frequently be idiopathic, a significant percentage may be attributed to dysfunctional glucose metabolism in pre-diabetes. In these cases, patient education and encouragement of healthy diet and exercise with tighter glycemic control should be stressed to slow disease progression.

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