Case Study: A 68-Year-Old Man With Diabetes and Peripheral Neuropathy

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Presentation

C.T. is a 68-year-old man with a 3-year history of impaired glucose tolerance. His only other medical problem is hypertension treated with a small dose of an angiotensin-converting enzyme (ACE) inhibitor. He quit smoking 20 years ago. He has no dyslipidemia and has had stress electrocardiograms every 2 years with normal results. He uses no alcohol.

He is retired from an office job with the government and presently teaches part-time at a local college. His glucose intolerance was discovered on routine laboratory testing. He was sent for diabetes education, learned home glucose monitoring, and followed a diet and exercise program suggested by our diabetes educator. He was not obese and led a physically active life, playing golf frequently and taking vigorous walks almost daily. He lost 10 lb and was able to normalize his blood glucose levels with this regimen.

Approximately 3 months ago, he noticed some burning and tingling in his feet. He admitted that he had not felt as well as usual and that his walking was becoming more of a chore. He denied chest pain or shortness of breath. He denied any other symptoms and had no fever or chills, cough, bloody stools, or hematuria. When seen in the office, he had gained 5 lb. His physical examination was normal except for some hyperesthesia of both feet as well as decreased vibratory sensation. His thyroid, reflexes, and pulses were normal. He was not depressed.

A review of his blood glucose log revealed fasting and premeal blood glucose levels generally <130 mg/dl. Postprandial glucose levels were almost always >150 mg/dl. Laboratory studies revealed normal chemistries except for a fasting blood glucose of 146 mg/dl. His HbA1c was 7.2% (normal 4.0–6.0%), up from 6.1% 6 months earlier. A complete blood count, lipid panel, liver screening, and a renal profile were all normal, as was a prostate-specific antigen (PSA) test.

C.T. was started on repaglinide (Prandin), 0.5 mg twice a day taken with breakfast and the evening meal. He continued his glucose monitoring and was asked to fax in his blood glucose levels every 2 weeks for the next 2 months. He was encouraged to restart his former exercise regimen.

Within a few weeks, C.T.’s blood glucose returned to near-normal levels. He reported no hypoglycemic events. At his next office visit 2 months later, he had lost the 5 lb he had gained plus an additional 4 lb. His HbA1c concentration was now 5.6%. He reported, however, that his fatigue was not much better and that his feet had become more painful. A slight ataxia was noted.

Questions

1. What is the differential diagnosis of C.T.’s neuropathy?
2. What is the next step in evaluating his symptoms?

Commentary

In the Western world, diabetes is the leading cause of peripheral neuropathy. It is estimated that 60–100% of the diabetic population has some form of neuropathy, ranging from barely detectable asymptomatic neuropathy to severe disabling painful disease to dense anesthesia.

Few doubt that duration and degree of hyperglycemia are the major culprits, although the mechanisms involved are complex, not adequately or completely understood, and currently are under intense investigation.

Sensory nerve dysfunction may produce no symptoms; symptoms of tingling, numbness, or burning; or a sense of “walking on eggshells” or a “funny sensation” under the ball of the foot. When motor nerves are affected, the prominent feature is foot deformities, particularly the claw-toe deformity. When autonomic nerves are affected, sweating is lost, and dry, cracked skin may result.

A careful history is particularly important when dealing with neuropathy because diabetes is only one cause of peripheral neuropathy (Table 1). The “exposure neuropathies” (alcohol abuse, toxins, HIV, etc.) can usually be eliminated in the history. Asking about similar symptoms in family members may help in distinguishing familial neuropathies.

In someone complaining of painful, burning feet, differential diagnoses in addition to diabetes would include alcohol toxicity, HIV infection, underlying malignant tumor, or amyloidosis. If carpal tunnel syndrome accompanies peripheral neuropathy, thyroid disease, rheumatoid arthritis, diabetes, and amyloidosis are more likely. Onset of symptoms is another clue to the etiology of different neuropathies, with "entrapment" causes having a more gradual, chronic nature and mononeuritis being sudden and acute.

A complete physical examination should be done to assess vibration, light touch, and temperature sensation, reflexes and to test for proprioception. A 10-g filament, which is widely available, dis-
possible, and easy to use, is very useful in assessing protective sensation.

Laboratory studies should include a complete blood count, general chemistries, and evaluation of glycemic control by measuring HbA1c. A thyroid-stimulating hormone (TSH) test should be included to rule out thyroid disease, and B12 and folate should be measured to rule out pernicious anemia. If suspicion regarding etiology still exists, other testing such as antinuclear antibodies, sedimentation rate, rheumatoid factor, and urine protein electrophoresis might be appropriate.

Nerve-conduction studies evaluate whether the myelin or nerve axon is affected and help pinpoint a specific diagnosis. Electromyography can distinguish if weakness is from a nerve or muscle disorder. Nerve biopsy is reserved for patients with severe and progressive disease and can identify vasculitis, amyloidosis, sarcoidosis, and several types of hereditary neuropathies.

After thorough evaluation, treatment is geared to the underlying etiology. When diabetic neuropathy is confirmed, treatment begins with glycemic control. The Diabetes Complications and Control Trial Research Group reported significant effects of intensive insulin treatment on prevention of neuropathy. The prevalence rates were reduced by 50% at 5 years in those receiving intensive therapy. Even patients whose blood glucose control is in the “good” range may see improvement or slowing of progression of their neuropathy symptoms with tighter control.

A vitamin B12 deficiency was discovered in C.T. No macrocytic anemia was found since he was taking a vitamin supplement containing folate. Because he had never had a colonoscopy, this was done as well as upper gastrointestinal X-rays to rule out any malignancy because of the increased incidence of gastric cancer in patients with pernicious anemia. These test results were normal.

C.T. was started on B12 treatments. After 4 months of treatment, he reported only minimal improvement in his neurological symptoms, but his fatigue had lessened.

**Clinical Pearls**

1. Diabetic peripheral neuropathy is a diagnosis of exclusion. A focused history, physical examination, and appropriate laboratory tests should be performed to rule out other potential causes. It is important to diagnose other causes so that they can be appropriately treated.

2. Glycemic control is key to the prevention and treatment of diabetic neuropathy and can result in significant improvements.

3. In B12 deficiency, neurological symptoms may be present even without anemia and may take up to 18 months to resolve.

**Suggested Readings**


### Table 1. Differential Diagnosis of Distal Symmetric Polyneuropathy

<table>
<thead>
<tr>
<th>Type</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congenital/familial</td>
<td>Charcot-Marie-Tooth</td>
</tr>
<tr>
<td>Traumatic</td>
<td>Entrapment syndromes</td>
</tr>
<tr>
<td>Inflammatory/infiltrative</td>
<td>Sarcoïdosis, leprosy, Lyme disease, HIV, Refsum’s disease, amyloidosis, periarteritis nordosa</td>
</tr>
<tr>
<td>Neoplastic</td>
<td>Carcinoma, paraneoplastic syndrome, myeloma, leukemias, lymphomas</td>
</tr>
<tr>
<td>Metabolic/endocrine</td>
<td>Diabetes, uremia, pernicious anemia, hypothyroidism, acute intermittent porphyria</td>
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<tr>
<td>Vascular</td>
<td>Diabetes, vasculitis</td>
</tr>
<tr>
<td>Toxic</td>
<td>Alcohol, heavy metals (lead, mercury, arsenic) hydrocarbons chemotherapeutics drugs (pyridoxine toxicity)</td>
</tr>
<tr>
<td>Autoimmune</td>
<td>Diabetes, phospholipid antibody syndrome, chronic inflammatory demyelinating polynephropathy (CIDP), multifocal motor neuropathy, Guillain-Barré syndrome</td>
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