Charcot-Marie-Tooth Disease Complicating Type 2 Diabetes

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Although both conditions are relatively common, there are very few descriptions of type 2 diabetes mellitus coexisting with Charcot-Marie-Tooth disease (CMT). This case report and literature review describes a 53-year-old Irish man who presented with type 2 diabetes and significant neuropathy, and who was subsequently diagnosed with CMT type 1A. This case report will also discuss how to differentiate diabetic neuropathy from a progressive hereditary neuropathy and how coexistence aggravates the progression of neuropathy thus necessitating early diagnosis. (J Am Podiatr Med Assoc 101(4): 349-352, 2011)

Diabetes is the most common cause of acquired neuropathy in the western world. Diabetic neuropathy is defined as the presence of symptoms and/or signs of peripheral nerve dysfunction in diabetic individuals after exclusion of other potential causes of neuropathy. In clinical practice, diabetic patients with symptoms and signs of peripheral neuropathy are often assumed to have diabetic neuropathy and a screening to rule out other causes of neuropathy may not be performed.

Charcot-Marie-Tooth disease (CMT), known increasingly as hereditary motor sensory neuropathy, is the most common inherited peripheral neuropathy. As opposed to being a discrete disease entity, CMT encompasses an entire spectrum of inherited disorders caused by mutations affecting the synthesis, storage, or maintenance of myelin. CMT1A is the most common variant with a prevalence of 1 in 5000. CMT1A causes a combined motor and sensory neuropathy. Onset is usually in childhood; patients have distal weakness and sensory loss, develop foot deformities, are areflexic, but usually remain ambulant, and have a normal life expectancy. CMT1A occurs secondary to mutations in the gene for peripheral myelin protein 22 (PMP22). This leads to significant demyelination of large nerve fibers accompanied by a 40% reduction in nerve conduction velocity. Serum levels of PMP22 may be reduced, and sural nerve biopsy shows characteristic “onion bulbs,” which are formed by redundant Schwann cells following cycles of demyelination and remyelination.

Despite the relatively high prevalence rates of both diabetes and CMT, their coexistence is poorly described in the literature to date. The only prospective study in this area has suggested that when the two disease processes coexist, the resultant neuropathy is more severe than with either condition alone. Here we report the case of an Irish patient with both type 2 diabetes mellitus and CMT1A. This case highlights the importance of excluding other causes of neuropathy in diabetic patients, how to differentiate diabetic neuropathy from CMT, and reports ongoing neuropathic complications in this case despite multidisciplinary intervention.

Case Report

A 53-year-old male taxi driver was diagnosed with type 2 diabetes at age 53 by his general practitioner. He had presented with polyuria and his initial fasting plasma glucose was 167.4mg/dL (9.3 mmol/L). He had no family history of type 2 diabetes. Past history was relevant for recurrent episodes of lower-limb cellulitis that began in childhood and
continued to the present day. Treatment was started with a sulphonylurea, and the patient received no formal foot examination or education at time of diagnosis. Four years after diagnosis he was referred to Beaumont Hospital Diabetes Day Centre Diabetic Foot Clinic with an ulcer on his left first toe, and to the Beaumont Hospital Orthopedic Department with left knee pain. Examination revealed severe sensory neuropathy, hammertoe deformity, loss of pin-prick sensation in a glove and stocking distribution, impaired proprioception, and loss of vibration sensation up to his sternum. He had globally reduced reflexes especially in his lower limbs, and his ankle reflexes were completely absent. He also had distal muscle wasting, pes cavus bilaterally, and a high stepping gait. On questioning, it emerged that the patient’s grandmother, father, two siblings, and three of his sons had symptoms of foot drop.

Vasculitis antibody titres, vitamin B12/folate levels, and serum protein electrophoresis were all within normal ranges. Electromyelogram and nerve conduction studies identified a sensorimotor neuropathy that was demyelinating in nature with secondary axonal loss. Motor and sensory responses were absent in the right lower extremity tested. Sensory responses were absent in the right upper limb and motor conduction velocity was markedly reduced in the forearm and across the elbow (22–23 m/sec). In the context of the patient’s family history, the patient was diagnosed with CMT hereditary neuropathy type 1A.

The patient is currently a regular attendee of the diabetes specialist foot clinic and has excellent diabetes control with glycated hemoglobin of 6.5% on metformin only. He has been educated extensively on foot care and offloading, has new orthotic devices, and he receives regular debridement of calluses and podiatric review. Despite these efforts he has suffered osteomyelitis in his left first toe and recurrent ulcerations affecting both feet, particularly the right and left first toe (Fig. 1).

Discussion

The incidence of diabetes mellitus is increasing worldwide, and it is predicted that 366 million people will be diagnosed with the disease by year 2030. The high prevalence of diabetes and its well-recognized association with neuropathy can lead to clinicians failing to consider other causes of neuropathy in this patient population. This case illustrates how careful examination and evaluation is required in all patients with diabetes and neuropathy in order to ensure that a second disease process does not escape diagnosis (Table 1). The continuing complications experienced by this patient highlight the need for early diagnosis followed by appropriate education and multidisciplinary follow-up.

There are few publications on the coexistence of type 2 diabetes mellitus and CMT. In 2001, Celik et al published the first case series, describing a family of six individuals of whom four had proven CMT1A and type 2 diabetes mellitus, one had type 2 diabetes mellitus alone, and one had no evidence of either disease process, but was only 24 years of age at the time of reporting. The only other published case series was that of a large family in Turkey with 69 members, 22 of whom were diagnosed with CMT1A on gene testing, and six of these had type 2 diabetes. All of the diabetic patients were significantly overweight or obese. In both papers the authors queried a possible genetic linkage between the two conditions, but concluded that further study was necessary. In 2003, a 53-year-old Japanese man with CMT1A and poorly controlled type 2 diabetes mellitus was described. He had an unusual phenotype for type 2 diabetes mellitus in that his body mass index was 19kg/m², but he was insulin resistant on his homeostasis model insulin resistance index (HOMA-R). He demonstrated an excellent response to pioglitazone. The patient described in the present case does not meet the classic type 2 diabetes profile with a body mass

Figure 1. Photograph of the patient’s feet showing ulcerations of the pressure area in the sole and distal part of third toe of the right foot, and extensive ulcerations of his left first toe, despite excellent diabetic control and regular podiatric care. He also has pes cavus bilaterally, notably more in the left foot.
index of 24kg/m², but he is currently achieving excellent glucose control with metformin alone.

In 2008 Sheth et al⁵ compared the degree of neuropathy in ten patients with CMT1A and diabetes (seven patients on oral medications, three patients on insulin) against 48 patients (control group) with CMT1A alone. To compare the two groups they used the CMT neuropathy score (the higher the score, the greater the severity of neuropathy),¹⁰ a validated scoring system for the extent of peripheral neuropathy in CMT based on symptoms, signs, and electrophysiological measures. The authors showed that patients with both diabetes and CMT1A had significantly higher scores than patients with CMT1A only. Those with insulin-dependent diabetes scored the highest of all, and most of the additional neuropathic damage seen in the group with diabetes and CMT involved motor as opposed to sensory nerves. Severe neuropathy in the presence of both disease processes was also highlighted by Takakura et al¹¹ in their description of a 44-year-old woman with CMT1 and type 2 diabetes mellitus who developed bilateral phrenic nerve palsy. These authors went as far as recommending periodic evaluation of respiratory function when both diseases coexist.

In conclusion, the co-occurrence of diabetes and CMT can be a late diagnosis, and these patients may be at higher risk of neuropathic complications than those with CMT or diabetes alone. The coexistence of diabetes and neuropathy should always be assessed with a full differential for neuropathic processes in mind. Early diagnosis allows for intensive intervention aimed at reducing neuropathic complications, including optimal glycemic control and multidisciplinary assessment by diabetes, neurology, physiotherapy, and podiatric services.

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References

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