


# Sensorimotor Polyneuropathy in a Diabetic Patient After Rapid Overcorrection of Chronic Hyperglycemia

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## Abstract

The differential diagnosis for peripheral neuropathy of uncertain etiology is extensive, and the work-up presents a diagnostic challenge for the physician. Following initial clinical assessment, we recommend electrodiagnostic studies as the test of choice in the evaluation of peripheral neuropathy of unclear cause. Subsequent laboratory testing can then be better specified according to the results of the electrodiagnostic studies and clinical assessment. This case report presents a 66-year-old female with a history of uncontrolled type-II diabetes who developed prominent sensorimotor neuropathy after experiencing several hypoglycemic episodes. Due to difficulties with insulin titration, over the course of 4 weeks, the patient quickly and drastically lowered her chronically elevated average serum glucose concentration to the point of suffering multiple periods of hypoglycemia. Soon after, she developed paresthesia in her hands and feet, as well as significant weakness in both upper and lower extremities. Unfortunately, the patient was lost to follow-up before a definitive diagnosis could be established. Hypoglycemia and rapid correction of long-standing hyperglycemia are relatively under-recognized sources of neuropathy in diabetic patients. Physicians taking care of diabetic patients who develop peripheral neuropathy following rapidly improved glycemic control or hypoglycemia should be aware of the possibility of a diabetic neuropathy and begin prompt work-up to exclude other causes before making the diagnosis of treatment-induced diabetic neuropathy or hypoglycemic neuropathy.

## Keywords

peripheral neuropathy, electrodiagnostic testing, diabetes, treatment-induced diabetic neuropathy, hypoglycemic neuropathy

## Introduction

Peripheral neuropathy is a relatively common condition with a population prevalence of about 2.4%, increasing with age to around 8%.<sup>1</sup> The work-up of a patient presenting with generalized sensorimotor polyneuropathy of unclear etiology can be complex and time consuming due to the broad diagnostic differential. As with any chief complaint, many diagnoses can be ruled in or out based on a thorough history and physical exam findings. Beginning the initial investigation with electromyography (EMG) and nerve conduction studies (NCS) can be particularly useful to determine if the cause is due to a disease of the lower motor neuron, spinal root, nerve, neuromuscular junction, or muscle. If discovered to be neuropathy, electrodiagnostic testing can also reveal whether it be axonal or demyelinating. Subsequent laboratory assessment can then be directed at specific diseases based on the results of electrodiagnostic studies and the patient's history. This case report presents a diabetic patient who developed a prominent sensorimotor neuropathy after experiencing several hypoglycemic episodes due to

rapidly overcorrecting her severe hyperglycemia of many years duration. Unfortunately, the patient was lost to follow-up before a definitive etiology for her symptoms could be established. In the context of this case, the diagnoses of hypoglycemic neuropathy and/or treatment-induced neuropathy of diabetes (TIND) should be highly considered. As TIND and hypoglycemic neuropathy are diagnoses of exclusion, it is necessary to first exclude other potential causes of peripheral neuropathy, like acquired demyelinating polyneuropathies. Even though hypoglycemia is a well-known

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complication of several common diabetes treatments, hypoglycemia and TIND are relatively under-recognized sources of neuropathy in diabetic patients. There have been, however, several reports of hypoglycemic neuropathy associated with insulinoma.<sup>2-4</sup> Also of note are reports of painful peripheral neuropathy in diabetic patients with long-standing hyperglycemia following a swift and drastic decrease to normal blood glucose levels,<sup>5-7</sup> a phenomenon referred to as TIND.<sup>6</sup>

## Case Presentation

A 66-year-old female with a 9-year history of uncontrolled type-II diabetes mellitus presented to an outpatient family practice clinic for diabetes follow-up. For years, the patient had struggled to control her blood sugar, with hemoglobin A1c readings consistently above 14.0%. Three months prior to this visit, her physician was able to motivate her to begin consistently taking her medication as prescribed. However, due to difficulties with insulin titration despite proper education, she began experiencing blood sugar levels around 60 mg/dL, and even had one episode in which her blood sugar dropped to 23 mg/dL, and she became unresponsive. Emergency Medical Services were activated, and she was resuscitated, then evaluated and stabilized in the emergency department without the need for hospital admission. Soon after these hypoglycemic episodes began, the patient started experiencing numbness and tingling in her hands and feet, as well as significant weakness in both upper and lower extremities to the point that she was unable to ambulate without assistance. She previously had evidence of some cognitive slowing, and at this time, there was no change in her cognition. She did not report any chest pain, shortness of breath, peripheral edema, palpitations, vision changes, or pain in the extremities. She had not experienced any recent trauma, upper respiratory or gastrointestinal tract infections. The patient had never experienced symptoms of neuropathy previously. She denied alcohol, tobacco, and illicit drug use. The patient's past medical history is significant for hypertension, hyperlipidemia, and obstructive sleep apnea. At the time of this encounter, she was taking 850 mg of metformin twice per day, 64 units of insulin degludec injected once daily, atorvastatin 80 mg once per day, and lisinopril-hydrochlorothiazide 10-12.5 mg once daily. This medication regimen had brought her blood sugar level to around 100 mg/dL on average. On physical exam, the patient was alert and oriented with a normal thought process. There was no lymphadenopathy or thyromegaly. Neurologic exam demonstrated profound weakness (3/5 strength) in the lower extremities, most notably with extension, as well as significant weakness (3/5 strength) throughout the upper extremities. Deep tendon reflexes were absent in both upper and lower extremities. Cranial nerves II to XII were intact, as was finger-to-nose and rapid alternating movement. The Romberg test was difficult for the patient. Her gait was slow and labored. Sensation

to sharp and light touch, as well as 2-point discrimination was intact bilaterally on both hands and feet. An erythrocyte sedimentation rate, antinuclear antibody test, and a complete blood count with differential were found to be within normal limits. Consults were placed to endocrinology and neurology who recommended semiurgent evaluation by neuromuscular specialists for this patient's motor neuropathy. Because the rapid reduction in blood glucose and hypoglycemic episodes were thought to be contributing to the patient's symptoms, she was told to stop the metformin and to decrease the insulin degludec to 50 units daily to try to bring her average blood sugar up to around 200 mg/dL so that it could then be more gradually lowered to normal levels. The patient was advised to follow-up again in 1 week, which she was unable to do. Three weeks after the initial encounter she still had not been evaluated by the specialists; however, at this time, she reported over the phone subtle improvement in both her weakness and paresthesia. The patient was subsequently lost to follow-up.

## Discussion

Because the patient was lost to follow-up before expert evaluation including electrodiagnostic testing could be performed, and the full clinical course/natural history of her condition remains unknown, it is not possible to know for certain the cause of her symptoms. Since the onset of her symptoms corresponded chronologically with the rapid reduction of her chronically elevated blood sugar levels in conjunction with several hypoglycemic episodes, TIND and/or hypoglycemic neuropathy should be high on the differential diagnosis. However, as these are diagnoses of exclusion, it is necessary to rule out other conditions with similar clinical presentations, some of which can be excluded based on patient history, physical exam findings, and initial laboratory testing, while others require a more complex work-up.

As painless proximal and distal weakness with generalized areflexia could be suggestive of an acquired demyelinating polyneuropathy, the differential diagnosis for this patient should include entities like acute or chronic inflammatory demyelinating polyneuropathy, and multifocal motor neuropathy. Because our patient did not report symptoms suggestive of recent infection, autonomic neuropathy, pain, or an ascending or asymmetric nature of her weakness, we believe these causes to be less likely. Also, multifocal motor neuropathy is a pure motor neuropathy without sensory deficits.<sup>7</sup> Diagnostic testing with NCS, EMG, cerebral spinal fluid analysis, and serological screening for pathogens and antiganglioside antibodies would be necessary to definitively rule out inflammatory demyelinating polyneuropathy and multifocal motor neuropathy in this case.<sup>8</sup>

Plasma cell dyscrasias can also cause acquired demyelinating polyneuropathy<sup>9</sup> and should be considered especially given our patient's age. Peripheral neuropathy is not a common initial presentation of plasma cell dyscrasia except for

in POEMS syndrome.<sup>10</sup> However, our patient did not demonstrate signs of skin changes, osteosclerotic lesions, or Castleman disease, making the diagnosis of POEMS syndrome much less likely. Electrodiagnostic studies are further helpful in monoclonal gammopathies to differentiate the demyelinating neuropathy of plasma cell dyscrasias from axonal neuropathy caused by amyloidosis. Ultimately, evaluation with serum and urine protein electrophoresis with immunofixation would be needed to work-up a suspected monoclonal gammopathy.

An additional diagnostic consideration for this patient would be a lower motor neuron variant of amyotrophic lateral sclerosis (ALS) known as progressive muscular atrophy. Similarly, she could be experiencing an initial presentation of ALS limited to the lower motor neurons. Patients with lower motor neuron variants of ALS can also complain of tingling paresthesia with a completely normal sensory exam.<sup>11</sup> Electrodiagnostic studies would likewise be valuable in ruling out these conditions and could show evidence of muscle denervation and reinnervation,<sup>12</sup> as well as laboratory testing potentially revealing elevated levels of creatine kinase. Progressive muscular atrophy and ALS are asymmetric and progressive diseases, in our case the patient did not demonstrate asymmetric or progressive symptoms and reported mild improvement in both her weakness and paresthesia following medication adjustment. However, due to lack of formal follow-up it is not clear if her improvement was correlated with her medication changes or another explanation, or if the improvement was clinically significant.

Therefore, we suggest that electrodiagnostic testing with EMG and NCS be the initial step in evaluating a patient with suspected TIND or hypoglycemic neuropathy. Electrodiagnostic studies can help differentiate among axonal and demyelinating neuropathies as well as neuromuscular junction pathologies when considering the diagnosis of TIND or hypoglycemic neuropathy. It is important the patient be asked about family history of neuropathy, recent viral sickness, alcohol use, new medications, and exposure to heavy metals or toxins to rule out common causes of toxic and metabolic neuropathy. The recommended screening laboratory tests with the most utility in evaluating symmetric polyneuropathy are blood glucose, serum B12 with methylmalonic acid, and serum protein immunofixation electrophoresis.<sup>13</sup> Other screening tests include a complete blood count, erythrocyte sedimentation rate, folate, comprehensive metabolic panel, thyroid function tests, urinalysis, and urine protein immunofixation electrophoresis. Further testing can then be tailored based on the results of electrodiagnostic assessment in combination with patient history and physical examination findings to continue to narrow the differential diagnosis.

Clinical history of hypoglycemic episodes versus rapid reduction of average blood sugar is important in distinguishing between TIND and hypoglycemic neuropathy. There also

appears to be some difference in the neuropathy of TIND compared to that caused by hypoglycemia. Because the patient in this report experienced both a rapid reduction in her hemoglobin A1c, as well as episodes of hypoglycemia, it is more challenging to know for sure which of these, or perhaps both, may have caused her neuropathy. TIND typically results in neuropathic pain, autonomic dysfunction, and allodynia.<sup>5,6,14,15</sup> Whereas hypoglycemic neuropathy causes a generalized sensorimotor polyneuropathy, with the potential to preferentially affect motor axons.<sup>16</sup> Considering the neuropathy described by the patient in our case was predominantly motor, with only mild paresthesia and no burning pain, autonomic dysfunction, or allodynia, her symptoms seem to align more with sensorimotor neuropathy caused by absolute hypoglycemia, as has been well documented in animal models and some human cases of insulinoma.<sup>2-4,17-19</sup>

Clinicians should keep in mind the potential need for gradual reduction of blood sugar in patients with long-term poorly controlled diabetes to prevent the development of TIND, especially considering the true prevalence of TIND is still not known. Although regarded as a relatively rare disorder, there has been an increase in the number of reported cases of TIND over the last 10 years.<sup>20</sup> Some researchers have theorized this may be due to a progressively tight linkage between physician reimbursement and patient hemoglobin A1c scores, leading to enhanced pressure to quickly achieve glycemic control.<sup>20</sup> One study found that with a decrease in hemoglobin A1c of >4% points over 3 months, the absolute risk of developing TIND was greater than 80%.<sup>6</sup> This same study demonstrated a strong correlation between the magnitude of decrease in hemoglobin A1c and the severity of neuropathy.<sup>6</sup> Further studies are still needed to determine the rate at which serum glucose concentrations can be safely reduced to avoid nerve damage. In addition, it is of importance to increase clinician awareness of TIND and hypoglycemic neuropathy in diabetic patients as they are important diagnostic considerations in the work-up of peripheral neuropathy of unclear cause. Physicians who can recognize TIND and hypoglycemic neuropathy in diabetes, after ruling out other causes of neuropathy, can likely avoid more extensive testing like genetic studies or nerve/muscle biopsy.

Current descriptions of the pathogenesis of hypoglycemic peripheral neuropathy focus on the effects of low serum glucose concentrations as the cause of neuronal damage regardless of insulin levels.<sup>21</sup> This suggests the pathophysiology is not necessarily linked to the treatment modality. Animal experiments have demonstrated that the mechanism of damage in hypoglycemic neuropathy is axonal degeneration similar to Wallerian degeneration, with a tendency to affect large, myelinated nerve fibers.<sup>17,18</sup> There have been several proposed mechanisms for the nerve damage, including energy depletion in Schwann cells and neurons, and nerve ischemia secondary to changes in the microvessel endothelial cells of

the endoneurium.<sup>21</sup> While a definitive treatment protocol has not yet been established, there is some evidence the neuropathic symptoms experienced by patients following rapid glycaemic control can improve with the passage of time, continued glucose control, and supportive care.<sup>5,15</sup>

In conclusion, the diagnostic work-up of peripheral neuropathy of uncertain etiology can be a challenging task for any physician. We suggest a stepwise approach beginning with a thorough history and physical exam. In the absence of information favoring a single diagnosis, the next best tests with the most diagnostic utility are NCS and EMG. After characterizing the neuropathy with electrodiagnostic studies, the physician will then be able to order more specific testing to better pinpoint the exact etiology. In the context of a diabetic patient who develops peripheral neuropathy following rapidly improved glycaemic control or hypoglycemia, the diagnoses of hypoglycemic neuropathy and/or TIND should be highly considered after excluding other potential causes. To date, there are still very few studies analyzing the mechanism, treatment, prevention, or prognosis of hypoglycemic neuropathy or TIND. This may be a promising area for future study especially as guidelines from professional societies continue to advocate for strict glycaemic control in diabetic patients.

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### Ethics Approval

Ethical approval to report this case was obtained from the Rocky Vista University Institutional Review Board (IRB# 2021-0043).

### Informed Consent

Verbal informed consent was obtained from the patient for their anonymized information to be published in this article.

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