

Insulin Neuritis: an old, but still an unfamiliar and mysterious condition

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Abstract

Insulin neuritis is a historical term for an acute neuropathy affecting diabetic patients who achieve rapid re-establishment of previously poor glycaemic control. It presents with neuropathic pain, symptoms of autonomic dysfunction, or a combination of both. Recently it has been proposed that 'treatment induced neuropathy of diabetes' would be a more accurate name for this entity. The management focuses on controlling the symptoms while they gradually improve with time.

INTRODUCTION

Diabetes mellitus is a common cause of small fibre neuropathy. It typically presents with sensory alterations and neuropathic pain in a 'glove-and-stocking' distribution, beginning insidiously after many years of impaired glycaemic control. The symptoms of autonomic system involvement may also accompany neuropathic pain.

Rarely, however, diabetic patients can present with an acute onset of small fibre neuropathy with prominent autonomic features, neuropathic pain, or both, in association with the re-establishment of good glycaemic control. Often, these patients are referred to the neurologist's attention with a concern about a rapidly progressive neurological illness with prominent autonomic features after they present to the emergency department with postural hypotension and a rapidly evolving neuropathy. Usually, these patients have excellent glycaemic control and they are not necessarily flagged to the local endocrinology service before the neurology review is requested.

We present two cases that illustrate the range of presentations of the acute treatment induced small fibre neuropathy in diabetic patients, or 'insulin neuritis'.

CASE 1

A 22 year old woman presented to the emergency department after passing out in a shopping centre. She described multiple episodes of syncope in the preceding month, along with palpitations, reduced appetite without nausea and vomiting and painful pins and needles up to just above the ankles. She denied bowel and bladder dysfunction. Her past history was significant for type 1 diabetes mellitus diagnosed at the age of 6 years, reduced vision in her left eye due to corneal abrasions from a traumatic injury and a recent diagnosis of non-alcoholic steatohepatitis (NASH) attributed to poorly controlled diabetes, which prompted her to become more diligent about maintaining glycaemic control. There was no history of eating disorder or a mental illness.

Physical examination revealed blood pressure of 128/73 mmHg on lying and 90/62 mmHg on standing and sinus tachycardia of between 110 and 120 and beats per minute. The neurological examination revealed normal tone and power with symmetrically brisk reflexes and altered sensation up to just above the ankles to light touch and pinprick. Proprioception was preserved. There were no cerebellar signs. The rest of the general examination was normal.

Her glycosylated haemoglobin (HbA_{1c}) results were 101.1 mmol/mol (11.4%) 12 months prior to the presentation; it had dropped to 92.4 mmol/mol (10.6%) 4 months prior to admission and on admission was 80.3 mmol/mol (9.5%). Nerve conduction studies revealed a generalised axonal neuropathy affecting large fibres with autonomic involvement .

During the admission, her postural hypotension improved with increased fluid intake and she was commenced on gabapentin 300mg TDS for neuropathic pain. Other autonomic symptoms were mild and did not require specific therapy. She was discharged after 4 days in hospital to be followed up in the community by the local diabetes and the neurology service and her symptoms were persistent but milder at 4 weeks after discharge.

CASE 2

A 24 year old woman presented to the emergency department with syncope shortly after complaining of chest pain and palpitations, two weeks after she was a passenger in a minor motor vehicle accident. Her past history was significant for type 1 diabetes diagnosed at 8 years of age, although she had been lost to follow up for several years until 1 month prior to this presentation. There was no other medical or psychiatric history. She was hypotensive (98/62 mmHg lying) with a further drop on sitting up (74/46 mmHg) and tachycardic at 130 to 150 beats per minute. Aortic dissection and pulmonary embolism was ruled out in the emergency department and she was

admitted to the ward for cardiac monitoring. On the ward, she poorly tolerated sitting up with a highly variable heart rate between 70 beats per minute to 120 beats per minute. She also described a 2 week history of neuropathic pain in her feet, persistent nausea and vomiting after meals, irregular bowel movements and persistent but non-specific lower abdominal discomfort. Subsequent investigations confirmed gastroparesis and urinary retention as suggested by the history.

Her HbA_{1c} was not checked as it was deemed 'too soon' from the previous HbA_{1c} check of 12.2% (109.8 mmol/mol and suggesting average blood sugar of 16.8 mmol/l) 3 weeks ago but her serum blood sugar readings prior to the admission according to her logbook were between 5 mmol/l and 12 mmol/l, consistent with significantly improved glycaemic control.

She was commenced in ivabradine 5mg BD for tachycardia, domperidone 10 mg TDS and erythromycin 500 mg TDS for gastroparesis, fludrocortisone 150 micrograms daily for postural hypotension and pregabalin 150 mg BD for neuropathic pain. These symptoms gradually improved during a prolonged hospital stay. At 9 months post discharge, she had completely recovered with no symptoms off all medications with excellent glycaemic control.

DISCUSSION

Acute small fibre neuropathy related to an improvement in glycaemic control in diabetic patients was first described in 1933 by Caravati,[1] only 11 years after Banting and MacLeod first administered bovine insulin to humans. He called it 'insulin neuritis', although this is a slight misnomer as insulin is not thought to be directly implicated in the pathogenesis of this condition, and there are several cases beginning after the patients commenced oral hypoglycaemic agents or achieving glycaemic control purely with weight loss.[2,3] The common denominator in all the reported cases are clear improvements in glycaemic control preceding the onset of the symptoms,

and the term 'treatment induced neuropathy of diabetes', as proposed by Gibbons and Freeman,[2] may be a more appropriate term.

Two different pathological findings have been reported in these patients. Tesfaye et al found a proliferation of epineural vessels with evidence of arterio-venous shunting on sural nerve photography of five patients affected with this condition.[4] They proposed that the resulting vascular 'steal' effect leads to ischaemia of endoneurium and neuropathic pain. On the other hand Llewelyn et al reported a sural nerve biopsy of a single patient with insulin neuritis and found histopathological evidence of chronic neuropathy with prominent regeneration activity.[5] They did not find any evidence of vasa nervorum abnormalities and proposed that the normoglycaemic state promotes the regeneration of damaged axons which results in ectopic signal generation and neuropathic pain. While the latter theory is more consistent with the current understanding of neuropathic pain, neither of these findings has been replicated. The precise pathophysiology and the reasons for the development of clinical syndrome remain unclear.

Overall, insulin neuritis is a rare condition with no data on its prevalence or incidence and most of the literature since its initial description consists of only a handful of patients. The exception is the recent paper by Gibbons and Freeman that included 104 patients with insulin neuritis encountered over five years at a tertiary neurology centre in the United States.[6] This series confirmed that the symptoms of insulin neuritis improve over time, consistent with the past reports and our experience. While waiting for the symptoms to improve, symptomatic treatments, in consultation with other relevant specialties, should be offered to the patient. It is unclear at this stage whether relaxation of glycaemic control is warranted and whether this would lead to a more rapid resolution of insulin neuritis but the current consensus is that the good glycaemic control should not be relaxed. ~~If that were to be shown, any consideration of this would need to be weighed against the long term benefits of establishing good glycaemic control quickly.~~

It is likely that insulin neuritis will become more common as the overall prevalence of diabetes increases and as better treatments allow for tighter glycaemic control. From the clinical perspective, it is an important condition to recognise so that the diagnosis can be made rapidly, the symptoms treated, and the patients reassured that overall the prognosis is relatively benign.

KEY POINTS

- Insulin neuritis, or treatment induced neuropathy of diabetes, is seen in diabetic patients who achieve rapid re-establishment of previously poor glycaemic control
- ~~Insulin neuritis~~ Treatment induced neuropathy of diabetes can present with neuropathic pain, symptoms of autonomic dysfunction, or a combination of both.
- Treatment consists of symptom management, in conjunction with other specialties.
- ~~Overall prognosis is benign, with complete recovery expected.~~

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COMPETING INTERESTS

The authors have no competing interests to declare

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AUTHORSHIP STATEMENT

YH and GD prepared the drafts of the paper, reviewed, provided corrections and agree with the submitted version of the paper.

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