Case report

Aggressive and devastating neuropathy: the consequence of untreated slow-onset type 1 diabetes

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Summary

Though type 1 diabetes (T1D) is described to be a disease of acute onset, there is strong evidence for a period of subclinical hyperglycaemia leading up to diagnosis. We describe two clinical cases with a prolonged and insidious onset of T1D, where neurological complications were present at the time of diagnosis. In both, there was an initial rapid and debilitating progression in neurological as well as other microvascular complications, but with a subsequent stabilization in complications over the next few years. These rare and unusual cases illustrate the variable nature of the natural history of T1D as well as its microvascular complications.

Introduction

While it is traditionally believed that newly diagnosed patients with type 1 diabetes (T1D) present to medical care acutely, a careful history reveals this is not always the case. Children describe an average of 2 weeks of osmotic symptoms at the time of diagnosis, and adults up to 5 weeks.¹² In individual cases, 24 weeks of symptoms have been reported prior to diagnosis.² Though these reports rely on the accuracy of the patient’s history, they are supported by studies following up relatives of patients with T1D who themselves develop diabetes. Here, sequential oral glucose tolerance testing can detect significant hyperglycaemia up to 36 months before insulin treatment is initiated.³ Our current understanding of the natural history of T1D supports these studies. Pancreatic islet autoimmunity, as evidenced by the presence of islet specific autoantibodies and T cells, predate and predict the onset of T1D,⁴⁵ and the gradual loss of β-cell function is evidenced by a loss of insulin secretion many years before T1D is diagnosed⁶⁷ (Figure 1).

Given the gradual onset of T1D, can the hyperglycaemia that precedes diagnosis precipitate the complications of diabetes, and if so what is the natural history of these complications? We present two unusual cases who presented with a gradual onset of T1D and with neurological complications at the time of diagnosis. In both cases, there was an initial rapid and rampant progression of microvascular complications, but which subsequently stabilized.

Case 1

L.N. is a 32-year-old male insurance claims manager of white British ancestry, who smoked between...
20 and 30 cigarettes per day and consumed 16 units of alcohol per week. He describes a curious 4-month episode in his past during which he lost three-stone in weight, suffered severe thirst and polyurea, and developed thrush. These symptoms resolved spontaneously and he did not seek medical attention, attributing them to the stress associated with separating from his wife. These symptoms recurred more severely 5 years later, and this time L.N. presented to his doctor. Investigations revealed hyperglycaemia and ketonurea clinically confirming a diagnosis of T1D, and he was started on insulin replacement therapy. At the time of presentation, he complained of burning and shooting pains in his feet as well as marked allodynia (Figure 2), symptoms that were not investigated further at the time and which were managed adequately with non-prescription analgesic medication.

Two months following the diagnosis with T1D, L.N. was admitted to hospital with urinary retention and severe burning pain around his upper abdomen. On close questioning, L.N. also described a history of erectile dysfunction. Examination revealed a slim gentleman with a body mass index (BMI) of 19 kg/m², bilateral necrobiosis lipoidica, a resting tachycardia and a postural drop in blood pressure. He exhibited a glove and stocking loss of sensation up to the level of his mid-calves, absent ankle reflexes and pain to light touch across his lower abdomen and lower limbs.

Intriguing symptoms included a destructive neuropathic Charcot foot deformity. Investigations were conducted to exclude vitamin deficiency, connective tissue diseases, porphyria, syphilis and HIV immunodeficiency. Nerve-conduction studies showed moderate-severe mixed axonal and demyelinating sensory-motor neuropathy typical of diabetic neuropathy. A sural-nerve biopsy confirmed severe neuropathy and excluded amyloid and vasculitis as contributing causes.

A diagnosis of T1D complicated by severe painful distal peripheral neuropathy (DPN) and autonomic dysfunction was made. He was treated with

Figure 1. The natural history of T1D. (a) β-Cell function increases with growth into young adulthood. (b) Onset of autoimmunity (the triggers for which still remain illusive). (c) Gradual and progressive decline in β-cell function. (d) Adequate β-cell function ensures that good glucose control is maintained. (e) Glucose levels start to rise as beta cell function becomes insufficient to control blood glucose. (f) Diabetes is diagnosed and insulin therapy is initiated.

Figure 2. Figure illustrating the rapid onset and time course of microvascular complications in the two cases. Note the presence of complications at the time of diagnosis with T1D in both cases.
analgesia and anti-epileptic medication for his neuropathy, and taught to manage his urinary retention through intermittent self-catheterization.

Four months following his diagnosis of T1D, L.N. developed symptoms of diarrhoea and occasional fecal incontinence, as well as post-prandial nausea. A technetium-labelled gastric-emptying study demonstrated delayed gastric emptying consistent with diabetic gastroparesis. Fundal examination revealed evidence of background diabetic retinopathy, and he had a raised urinary microalbuminuria indicative of diabetic nephropathy. His glycated haemoglobin at this time indicated good glucose control at 6.8%, having come down from 8.5% at diagnosis. His lipids and blood pressure were under good control, and his weight remained appropriate for his height.

A significant reduction in the frequency of self-catheterization was noted 9 months following diagnosis, reducing from three–four times a day to twice a week. There was also a reduction in analgesic requirement for his painful DPN. Two and a half years following initial presentation, his retinopathy, microalbuminuria and neuropathy remained stable.

**Case 2**

B.H. was a 26-year-old man, also of white British ancestry when he presented to his general practitioner with a 2-month history of thirst, weight loss, lethargy and a feeling of heaviness in his legs. He was a non-smoker who consumed alcohol in moderation. Examination revealed poor dentition, oedema to the level of his knees, reduced vibration and nociception in his feet and absent ankle reflexes.

He had a BMI of 15 kg/m², and his urine tested positive for glucose (4+) and ketones (2+). Blood glucose was 17.7 mmol/l. Serum protein, electrolytes and urea were all normal and he had no proteinuria. A diagnosis of T1D with DPN and probable neuropathic oedema was made (Figure 2) and he started insulin replacement therapy. His HbA1c 4 months after diagnosis was 12.0%, and largely remained over 10% for the next 10 years.

Five months following his initial presentation, he continued to have lower limb oedema, and was also noted to have a postural drop in his blood pressure as well as background diabetic retinopathy. Around this time he developed swelling of his left foot that progressed rapidly to deformity. A radiograph revealed collapse of the left sub-talar joint—changes consistent with neuropathic Charcot foot. His lipids and blood pressure were both well controlled.

Six years later, he developed microalbuminuria and was initiated on angiotensin-converting enzyme inhibitor therapy. His blood pressure and lipids were otherwise well controlled and he had an appropriate weight for his height.

Twenty years later, however, the microvascular complications that had developed aggressively and so acutely were stable. His diabetic retinopathy and postural drop in blood pressure had resolved. His Charcot foot, peripheral neuropathy and microalbuminuria were stable. B.H. passed away at the age of 49 years from cardiovascular disease, having survived T1D for 23 years.

**Discussion**

We describe two cases of T1D where a period of undiagnosed and untreated hyperglycaemia resulted in the aggressive onset of microvascular complications. These cases support our previous understanding that T1D can present with preceding prolonged hyperglycaemia but go on to illustrate for the first time that this hyperglycaemia can result in diabetic complications. The phenomenon of undiagnosed diabetes resulting in complications is well recognized in type 2 diabetes (T2D), where a significant proportion of patients have a complication at the time of diagnosis, but as far as we are aware this has not been described in T1D.

We do not believe the aggressive microvascular complications can be attributed to ‘insulin neuritis’, a condition resulting from the rapid correction of glycaemia, because the HbA1c in Case 1 improved by <2% over a 4-month period, and that of Case 2 did not really improve at all. Though we were not able to confirm the presence of islet autoimmunity through antibody testing in these cases, there was clinical evidence of insulin deficiency (weight loss, ketonuria) and they satisfy the clinical criteria for T1D. We do not believe they were a monogenic form of diabetes because they lack a family history of diabetes, and their race and absence of features characterizing insulin resistance precludes them fulfilling the criteria for ketosis-prone T2D.

There are clear similarities between these cases (young white Caucasian adult males, insidious presentation of T1D, initial aggressive development of neurological and other microvascular complications with a subsequent stabilization), and they may form a distinct variant of T1D.

**Conflict of interest:** None declared
References


