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VIEWS AND REVIEW

Treatment induced neuritis in diabetes (TIND) – Terra incognita in the spectrum of diabetic neuropathies

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Abstract

Treatment-induced neuropathy in diabetes (TIND), better known as insulin neuritis, is an uncommon, iatrogenic, small fibre neuropathy occurring with an abrupt betterment in glycaemic control in patients of chronic hyperglycaemia. TIND, as such, is a less reported entity often missed by clinicians on initial presentation, but is an important consideration in patients with rapid correction of their hyperglycaemic status. TIND is characterised by an acute onset length dependent or generalised neuropathic pain often accompanied by autonomic symptoms and signs. This mostly occur after 2-8 weeks of initiating glycaemic control with insulin and is associated with a decline in glycosylated haemoglobin (HbA1c) by ≥2% points over 3 months. In fact, these patients on presentation, have reasonably satisfactory glycosylated haemoglobin profiles, as this condition is seen with acute control of glycaemic status. We herein discuss details of this entity as a review of literature with an overview of its pathophysiology, clinical features, and management.

INTRODUCTION

Diabetes is a constellation of metabolic derangements of abnormal carbohydrate metabolism characterized by hyperglycaemia caused either due to deficient insulin production or a diminished insulin response. Type 1 (T1DM) and type 2 diabetes mellitus (T2DM) are most prevalent types, the latter type is the majority. Neuropathy is one of the most common long-term complications in diabetic patients, such that over their lifetime, 30% of diabetics develop chronic neuropathic pain.[1]

Amongst a variety of classes of diabetic neuropathies (Table 1)[2], the most common manifestation is a length dependent axonal polyneuropathy, proposed mechanisms being inflammation, oxidative stress and mitochondrial dysfunction resulting in impaired axonal transport, neuronal dysfunction, and eventually axonal damage.[3]

However, a distinct, acute, severely painful form of neuropathy is seen shortly after initiation of intensive glycaemic control in chronically unchecked diabetics. It was first described in 1933 by Caravati[4], and considered an uncommon iatrogenic neuropathy and was different in many

Table 1 Classification of diabetic neuropathies modified from the American Diabetes Association [6]

Diffuse neuropathy	Mononeuropathy	Radiculopathy	Other neropathies
DPN primarily small fiber	Isolated cranial or peripheral neuropathy	Thoracic radiculoneuropathy	Pressure neuropathies
DPN primarily large fiber	Mononeuritis multiplex	Radiculoplexus neuropathy	CIDP
DPN mixed small and large fiber			Acute treatment induced neuropathy
DPN and autonomic neuropathy			

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aspects from the more common distal sensory polyneuropathy (DSPN) (Table 2). This condition is also referred to as insulin neuritis or acute painful diabetic neuropathy of rapid glycaemic control, however, the most recent term is treatment-induced painful neuropathy of diabetes (TIND).[5] This possibility arises in individuals with type 1 or type 2 diabetes on insulin management, sometimes those on oral hypoglycaemic agents and, rarely with severe dietary restriction. The neuropathy is predominantly small fibre sensory subtype; however, severity of the neuropathy is related directly to the rate of change in the glycosylated haemoglobin A1C.[6] In fact, TIND has been found to be having an estimated prevalence of 10.9% in patients referred to tertiary outpatient clinics for neuropathy.[7] We herein attempt to uncover the significant details of this entity with this review article.

PATHOPHYSIOLOGY OF TIND

The underlying mechanism of TIND is not well understood, however, currently proposed mechanisms are:

- A state of "relative hypoglycaemia" follows intensive acute glycaemic control in subjects with chronic and sustained hyperglycaemia, in turn causing energy dependent failure of axonal transport. This leads to formation of epineural arterio-venous shunt and resulting "steal effect", consequentially producing enhanced epineural blood flow and endoneural hypoxia of small fibres.[5]
- Hypoglycaemic microvascular damage and cellular apoptosis due to glucose deprivation.
- Ectopic firing of regenerating axon sprouts.
- Controlled studies with an insulin clamp causing modest hypoglycaemia have previously documented the development of tactile hyperalgesia and transient dysautonomia in humans along with release of pro-inflammatory cytokines.[8]

Besides, there is evidence of co-existence of other microvascular complications in TIND patients.[9] The development of nephropathy and retinopathy simultaneously with TIND is suggestive of a systemic mechanism likely resulting in microvascular disease. Also, there have been prior reports of 'early worsening retinopathy'[10] which represents a higher risk of proliferation and neovascularisation with each point decrement in the glycosylated haemoglobin, a phenomenon that parallels the development of neuropathy in TIND. Both new developing sight threatening maculopathy as well as worsening of

Table 2: Major differences between treatment induced neuropathy in diabetes and distal sensory polyneuropathy

TIND	DSPN
Rare in incidence.	Most common form of diabetic neuropathy
Caused by endoneurial ischemia, and microvascular damage due to a relative hypoglycaemic state.	Chronic hyperglycaemia-induced inflammation, oxidative stress and mitochondrial dysfunction causes neuronal damage.
The neuropathic pain has an acute onset, appearing within 8 weeks of glycaemic change.	Insidious onset gradually progressive course.
The pain is more severe, and poorly responsive to medicatons including opioids.	Most patients respond to non-opioid interventions
Distribution of pain is length-dependent and far more extensive than distal sensory-motor polyneuropathy with commonly associated allodynia and hyperalgesia.	Pain mostly follows a glove stocking pattern.
Autonomic symptoms and signs are common, prominent and appear acutely	Relatively lower prevalence, gradual onset, and slow progression of autonomic involvement.
Electrodiagnostic studies may be normal (owing to small fibre involvement)	Nerve conduction studies mostly show sensorimotor axonal affection.
Reversibility of both the pain and autonomic features, may be incomplete in some patients.	Relentless progression with time.

background proliferative diabetic retinopathy has been described.[7]

TIND has also been linked to prior diabetic anorexia and weight loss, which might enlighten an insight into a possible mechanism. TIND has features akin to acute painful and autonomic neuropathy which occur following bariatric surgeries, attributable to inflammatory injury, vitamin deficiencies, and malnutrition.[11] Further mechanistic studies would however be the needed to unravel this underlying pathophysiology.

There exists a direct relationship between rate of change in Hba1c and development of neuropathic pain (Figure 1). Analysing the rate of change of HbA1C in association with development of neuropathy revealed that patients with a decline in their HbA1C levels by more than 2 points over 3 months had higher incidence of TIND as compared to those with smaller shifts in blood glucose. The risk of developing TIND in less than 10%. While modest changes in HbA1C predispose to <10% risk, tighter control of HbA1C achieved in a short period increases the risk of TIND to >50%. Accordingly, a 5 percentage points or more decrement in HbA1C in 3 months takes the absolute risk (of TIND) to >90%.[11]

Diabulimia, an eating disorder wherein individuals of type 1 diabetes deliberately withhold insulin to lose weight, is also a significant risk factor for TIND, carrying high morbidity and mortality.[12]

Epidemiologically, patients with type 1 diabetes are more affected (73%) with mean age of less than 25 with female predominance. while prevalence is less with no sex dominance in type 2 diabetes mellitus. As type 1 diabetics have long standing history of hyperglycaemia, a sudden control of blood sugar with insulin (e.g., recovering from diabetic ketoacidosis) may lead to appearance of this severe neuropathic pain, hence the name 'insulin neuritis'.[11]

MANIFESTATIONS OF TIND

TIND is characterised by an acute onset length dependent or generalised neuropathic pain commonly accompanied by autonomic symptoms and signs (Table 3). This mostly occur after 2-8 weeks of starting glycaemic control with insulin and associated with a decline in glycosylated haemoglobin (HbA1c) by ≥2% points per 3 months (e.g., a fall of HbA1c from 10% to 8% over 3 months, or from 14% to 10% in 6 months are both significant). Pain is moderate to severe in intensity, lancinating or burning quality, described in length dependent manner, and is frequently accompanied by both hyperalgesias, contact allodynia and skin changes. (Figure 2)

Hyporeflexia/Areflexia in form of reduced or lost ankle jerks, sensory loss (if present) with diminished / absent pinprick sensation at the great toe and/or reduced vibration sense are common findings on physical examination.

Symptoms related to autonomic dysfunction mostly appear in combination with, or shortly after the onset of neuropathic pain and include orthostatic intolerance, orthostatic hypotension with syncope, postprandial fullness, hyperhidrosis, anhidrosis, erectile dysfunction and bladder involvement.[11] Autonomic testing

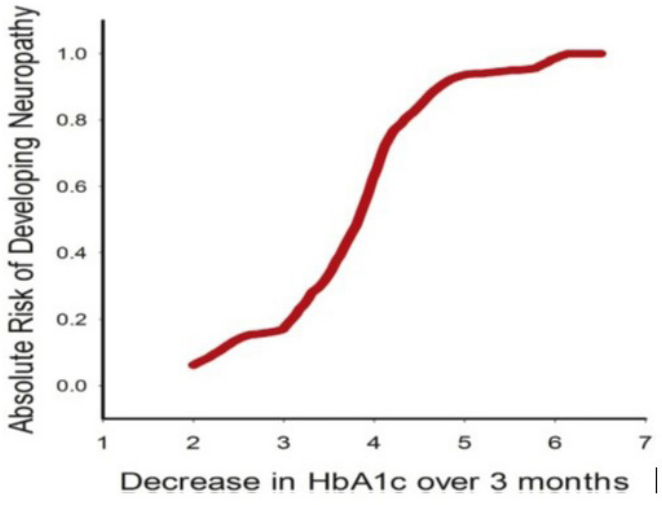

Figure 1: TIND risk with HbA1c changes

Table 3: The diagnostic criteria for Treatment Induced Neuropathy in Diabetes

The present criteria for diagnosis of TIND include[5]
• Onset of either neuropathic pain or autonomic dysfunction within 8 weeks of a decrease in average glucose values.
• Having neuropathic pain of at least 3 points on a 10-point Likert scale or autonomic dysfunction that was severe enough to require medical attention.
• The change in glucose control resulted in a decrease in haemoglobin A1C (HbA1c) of 2 points or more over a 3-month period.

quantitatively documents this dysfunction, and an established relationship exists between severity of autonomic failure and fall in HbA1c.[5] This autonomic dysfunction in TIND, unlike chronic diabetic dysautonomia, preferentially affects the sympathetic system. Moreover, lumbosacral plexoradiculoneuropathy with involvement of sensory and autonomic fibres has also been associated with TIND in rare cases.[7]

Differential diagnosis in such scenarios where patients exhibit subacute, symmetric, sensorimotor alterations in varying degrees, with associated autonomic dysfunction can be Guillain Barré variant, other causes of small fibre sensory neuropathy, systemic or non-systemic neural vasculitis, and uncommonly diabetic neuropathic cachexia.[12] While the pathophysiology of diabetic neuropathic cachexia is still not very clear, it is characterised by anorexia, involuntary, severe weight loss (usually >10% of baseline body weight) and emotional instability; these symptoms resolve completely with weight gain.[13]

MANAGEMENT OF TIND

Firstly, the diagnosis of aetiology is necessary in a patient of diabetic neuropathy, as mistreatment with intensive glycaemic treatment can lead to further worsening of pain. However, at present, permissive hyperglycaemia as a 'salvage treatment' is not considered an ideal management strategy for TIND.[14,15] The current standard of care remains supportive and includes avoidance of overly rapid glycemic correction at the outset of treatment, especially in high-risk situations like diabetes type 1 or a long-standing hyperglycemia,

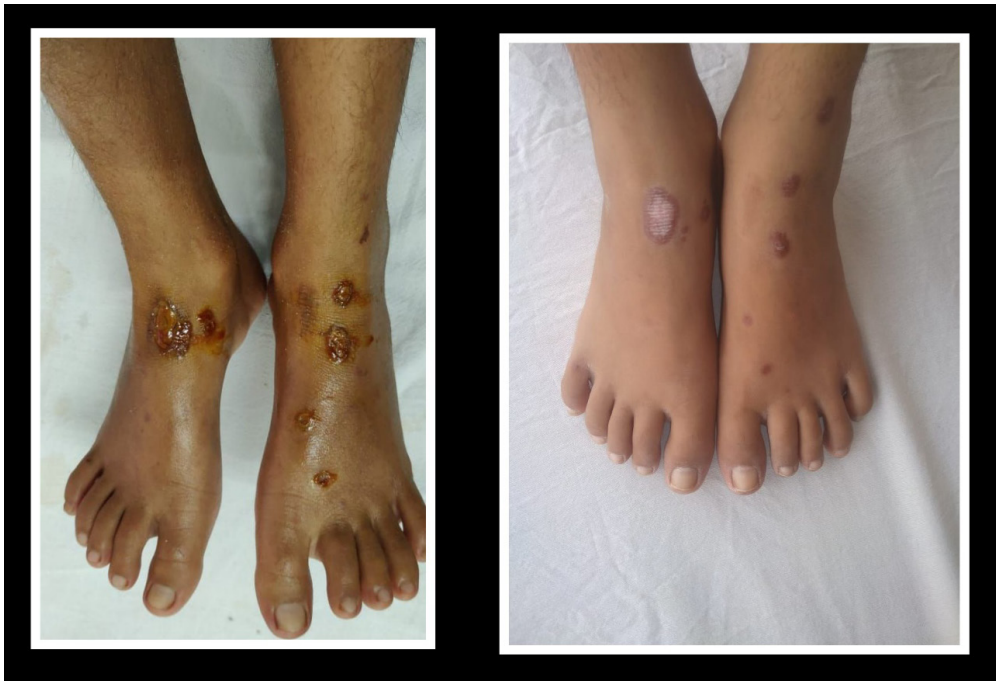

Figure 2. Autonomic changes, trophic ulcers on feet of a TIND patient, recovered later.

women, and people with eating disorders.[16]

Supportive care mostly includes symptomatic management for pain and autonomic dysfunction, both of which are initially refractory to therapeutic interventions (especially the pain), however, later improve over time, and mostly require administration of multiple classes of drugs.

The armamentarium includes tricyclic antidepressants (TCAs), such as amitriptyline and nortriptyline, serotonin–norepinephrine reuptake inhibitors (SNRIs), like duloxetine and venlafaxine. These act by potentiation of serotonergic and noradrenergic activity in the central nervous system (CNS). Norepinephrine reuptake inhibition, although known to have a beneficial effect on neuropathic pain, may deteriorate dysautonomia and enhance the probability of orthostatic hypotension (esp. TCA class of drugs), hence should be cautiously used.

Other drug modalities include anti-convulsant like pregabalin, gabapentin, valproate, and carbamazepine, and lastly opioid analogues like tramadol, dextromethorphan. Topical analgesic (capsaicin) usually used in neuropathies to desensitise afferent sensory nerves, may worsen skin made vulnerable by local cutaneous dysautonomia in TIND, and hence best avoided. Local anaesthetic agents (lignocaine) block neuronal sodium channels and blunt the sensitization of peripheral nociceptors, helping with pain relief.[17]

Regarding symptoms related to gastroparesis, all suspected patients require gastroenterology opinion for endoscopy and abdominal imaging to exclude gastric outlet obstruction.[18] Involvement of a nutritionist is also recommended, usual dietary modifications include a low-fat, low-fibre, and small-particle diet. Besides, promotility and antiemetic medications can be added to treatment regimens in patients with refractory symptoms.[18]

CONCLUSION

TIND presents as an acute neuropathy causing extreme burning or shooting pain in the extremities, autonomic symptoms, and worsening of retinopathy, or nephropathy in people with type 1 or type 2 diabetes, who undergo fairly intensive glycemic control with insulin or oral hypoglycemic agents after prolonged periods of hyperglycemia.

Treatment induced neuropathy in diabetic patients is more common than previously thought and is associated with rapid rates of blood glucose normalization. Misdiagnosis leads to progressive iatrogenic worsening of this condition by intensively controlling blood sugar. TIND is usually self-limiting and initially refractory to multiple analgesics.

DISCLOSURE

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