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Nosocomial treatment-induced neuropathy of diabetes: An important cause of painful and autonomic neuropathy in hospitalized diabetes mellitus patients

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Abstract

Treatment-induced neuropathy of diabetes (TIND) is an acute painful autonomic small-fiber neuropathy that develops following an abrupt improvement in glycaemia control. Recent reports suggest TIND is a significant problem in tertiary neuropathy clinics. TIND in hospitalized patients with poor initial glycaemia control, that we refer to as nosocomial TIND, has not been well-studied. We describe the demographic, clinical features and indices of glycaemia control in 5 consecutive nosocomial TIND patients. TIND was defined using recently published criteria. Pre-meal capillary blood glucose recordings performed during the period of HbA1c decline was used to calculate glycaemic variability. All the nosocomial TIND patients were hospitalized for prolonged periods for serious medical conditions that warranted good glycaemia control, namely severe sepsis, diabetic ketoacidosis, stroke, heart failure and traumatic head injury. They had raised, double-digit, HbA1c levels at admission that subsequently dropped precipitously with tight in-patient glycaemia control protocols. These patients had multiple, largely asymptomatic, hypoglycaemic episodes. Glycaemic variability also appeared to be high in this cohort. TIND may be a significant cause of morbidity in hospitalized diabetic patients with poor glycaemia control. Not all patients developed both autonomic and painful neuropathies, raising the possibility of forme-fruste TIND.

Keywords: Treatment-induced neuropathy, insulin neuritis, TIND, diabetes mellitus, small-fiber neuropathy, autonomic dysfunction, neuropathic pain

INTRODUCTION

Treatment-induced neuropathy of diabetes (TIND), known previously as insulin neuritis[1], is a painful autonomic small-fibre neuropathy that develops after an abrupt improvement in glycaemia control in types 1 and 2 diabetes mellitus (DM) patients with a history of chronic hyperglycaemia. Previous study by Gibbons and Freeman[2] showed that TIND is not uncommon among patients referred to tertiary neuropathy outpatient clinics, with an estimated prevalence of 10.9%. The study established criteria for diagnosis of TIND and reported a strong correlation between the magnitude and rate of HbA1c decline with the severity of neuropathic pain and autonomic dysfunction. Other important microvascular complications such as nephropathy and sight-threatening maculopathy and retinopathy showed contemporaneous worsening with TIND[2,3], further emphasizing the importance of recognizing this entity.

On the other hand, our retrospective studies (unpublished) of unselected patients from general DM clinics of 2 local tertiary institutions found low TIND prevalence, suggesting that TIND prevalence may not be uniform across the various settings where DM patients are cared for; and other additional factors may be contributory. Current literature is devoid of studies on TIND in hospitalized patients with poorly-controlled DM. We describe the demographic, clinical features and two indices of glycaemic variability of 5 consecutive patients who developed TIND following prolonged hospitalization for serious

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illnesses during which the blood sugar level were tightly controlled. We refer to this phenomenon as nosocomial TIND.

METHODS

We retrospectively analysed the clinical, neurodiagnostic, medication and laboratory records of 5 consecutive patients diagnosed with TIND following hospitalization for serious illnesses.

We used pre-meal capillary blood glucose recordings performed during the period of HbA1c decline to calculate standard deviation (SD) and coefficient of variance, the two indices of glycaemic variability[4] used in our study.

TIND was diagnosed using previously established clinical and biochemical criteria[2]: i) Decrease in HbA1c ≥2% over 3 months or ≥4% over 6 months, ii) Presence of acute onset painful neuropathy and/or autonomic dysfunction over 2 weeks of sufficient severity to cause subjects to seek medical attention, iii) Symptoms begin within 8 weeks of documented HbA1c decline. These symptoms were defined using clinical assessments and questionnaires[2,3] which included, neuropathy impairment score, 11-point Likert scale for neuropathic pain and the Boston Autonomic Symptom Questionnaire. Almost all patients with TIND had normal Neuropathy Impairment Score (NIS), refractory neuropathic pain, orthostatic hypotension and near syncope or syncope. Nerve conduction studies (NCS) and autonomic function tests were not routinely performed but dictated by clinical indications. Majority of those who underwent NCS and electromyography (EMG) had a normal result. Autonomic function tests of these patients with TIND confirmed worsening of both sympathetic and parasympathetic systems.[2,3]

We excluded alternative causes of painful neuropathy and/or cardiovascular autonomic dysfunction based on clinical features, medication review and blood tests, dictated by clinical indications and performed at the discretion of the treating physician. The study was approved by institutional review board.

RESULTS

We describe 5 consecutive patients with nosocomial TIND. The mean age was 55 years (range 43-72 years). The 5 patients were admitted for serious medical conditions that warranted good glycaemic control. Median duration of hospitalization was 45 days (range 19-90 days). All had type 2 DM and were on oral hypoglycaemic agents and/or insulin therapy, with a median DM duration of 10 years (range 6-20 years). The clinical features, diabetes history, associated complications and glycaemic control indices of the 5 patients are shown in Table 1. Median admission HbA1c was 13.5% (13.5±1.3%) with a median decline of 4.7% (4.7±1.4%) over 47 days (range 28-98 days). None of these patients received blood transfusions and none them had haemolysis, anaemia or blood loss to account for the marked HbA1c decline. Median SD and coefficient of variance of capillary blood glucose were 3.3mmol/l (3.3±1.7 mmol/l) and 36.7% (36.7±5.1%) respectively. Remarkably, all except 1 patient had several episodes of asymptomatic hypoglycaemia during hospitalization. Two patients developed sight-threatening maculopathy while one patient had worsening of background proliferative diabetic retinopathy and maculopathy. Renal function remained stable in all patients.

Not all TIND patients developed both neuropathic pain and autonomic dysfunction. Two patients had both autonomic dysfunction and painful neuropathy, 2 patients had only autonomic dysfunction and 1 patient experienced only neuropathic pain without autonomic dysfunction (Table 1). One patient had features of diabetic lumbosacral plexoradiculoneuropathy. Orthostatic hypotension and sympathetic dysfunction were predominant manifestations of autonomic dysfunction.

Tests done to exclude other causes of neuropathic pain and autonomic dysfunction are shown in Table 1. None of these patients had causative medications, toxin exposure or significant alcohol history to account for their symptoms.

DISCUSSION

The circumstances of nosocomial TIND patients, namely poorly-controlled DM, serious medical illnesses that require admission for a prolonged duration when DM is appropriately controlled tightly, commiserate to the seriousness of the conditions, episodes of hypoglycaemia, conspire to make TIND relatively important among hospitalized patients.

All were debilitated by new onset, severe and refractory neuropathic pain and/or autonomic dysfunction. The autonomic dysfunction, unlike chronic diabetic dysautonomia, affected the sympathetic system preferentially. One patient had concomitant lumbosacral plexoradiculoneuropathy with pre-existing diabetic distal symmetrical

Table 1: Clinical features and glycaemic control markers of nosocomial TIND cohort

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	44	68	43	46	72
Gender	Male	Male	Male	Female	Female
Admission diagnosis	Traumatic brain injury (subdural haemorrhage)	Left middle cerebral artery ischaemic stroke	Diabetic ketoacidosis from Klebsiella liver abscess	Congestive cardiac failure	Staphylococcus aureus septicaemia from infective endocarditis
Duration of hospitalisation (days)	90	80	19	45	23
DM type	2	2	2	2	2
Pre-existing DM-associated complications	Non-proliferative diabetic retinopathy	None	DM polyneuropathy, nephropathy, non-proliferative diabetic retinopathy, diabetic macular edema	DM polynephropathy, proliferative diabetic retinopathy, diabetic macular edema, coronary artery disease	DM polyneuropathy, non-proliferative diabetic retinopathy, coronary artery disease
Type of DM treatment	OHGA	OHGA	OHGA	OHGA and insulin	OHGA
Initial HbA1c on admission (%)	13.5	14.3	13.0	11.5	14.9
Repeat HbA1c (Magnitude of HbA1c decline) (%)	9.3 (-4.2)	9.6 (-4.7)	5.8 (-7.2)	7.2 (-4.3)	9.2 (-5.7)
Duration over which HbA1c declined (days)	28	78	47	98	38
SD (mmol/l)	3.2	5.4	4.9	3.3	2.5
CV (%)	36.7	45.6	39.8	34.6	29.0
Number of hypoglycaemic episodes	5	4	0	2	4
Likely time of onset of TIND symptoms in relation to HbA1c decline (weeks)	2 weeks	2 weeks	6 weeks	8 weeks	4 weeks
TIND symptoms	Postural hypotension, urine retention	Postural hypotension	Painful neuropathy	Postural hypotension	Mild postural hypotension, urine retention, painful neuropathy

Autonomic function test results	Could not be done as patient was uncooperative	Severe orthostatic hypotension, normal heart rate variability with posture change. Unable to perform Valsalva manoeuvre, deep breathing or isometric exercise due to dysphasia	Not done	Severe orthostatic hypotension; relatively intact parasympathetic responses to Valsalva manoeuvre, deep breathing and posture change.	Not done
Nerve conduction study findings	Not done	Not done	Length-dependent axonal sensorimotor polyneuropathy	Length-dependent mixed axonal-demyelinating sensorimotor polyneuropathy	Lumbosacral plexoradiculoneuropathy
Accompanying complications	Proliferative diabetic retinopathy, maculopathy	None	Maculopathy with stable background non-proliferative diabetic retinopathy	Worsening of background proliferative diabetic retinopathy and maculopathy	None
Result of tests done by treating physician to exclude alternative diagnoses, dictated by clinical indication	Vitamin B12: Normal	Vitamin B12: Normal	Vitamin B12: Normal	Vitamin B12: Normal	Vitamin B12: Normal
	Renal function: Normal	Renal function: Normal	Renal function: No change from baseline	Renal function: Normal	Renal function: Normal
	Retroviral screen: Non-reactive		Retroviral screen: Non-reactive	Retroviral screen: Non-reactive	
	Syphilis IgG and rapid plasma regin: Non-reactive		Rapid plasma regin: Non-reactive		
	Serum and urine protein electrophoresis and immunofixation: No paraprotein band		Serum and urine protein electrophoresis and immunofixation: No paraprotein band		

DM: diabetes mellitus; OHGA: oral hypoglycaemic agent; HbA1c: Glycated haemoglobin A1c; SD: standard deviation; CV: Coefficient of variance; mmol/L: millimole per litre; TIND: treatment-induced neuropathy of diabetes

polyneuropathy, adding further to anecdotal and unpublished observations[5] on possible links between TIND and painful proximal diabetic neuropathies. Recent reports suggest involvement of the autonomic and sensory fibres in patients with lumbosacral plexoradiculoneuropathy, implicating some potential overlap with TIND.[6,7]Two of the 5 patients developed sight-threatening maculopathy concurrently while 1 patient had contemporaneous worsening of background proliferative diabetic retinopathy and maculopathy. We agree that these patients also have TIND, the features of which are indistinguishable from other cases of TIND. We however, feel that the circumstances conspiring to precipitate them are unique in that these patients have been admitted for serious illnesses, during which blood sugars have to be controlled tightly. In contrast, for other cases of TIND, it could be argued that over-zealous and sudden control of blood sugars in a well stable patient with chronic hyperglycemia is relatively unwise. We highlight this entity, not so much to stop the clinicians from controlling the blood sugars as per standard guidelines for these diseases but to be vigilant of the morbidity of TIND, namely severe postural hypotension and painful neuropathy in the convalescent stage.

We also raise the possibility of forme-fruste TIND. In our study, only 2 patients had both neuropathic pain and autonomic dysfunction. This has two important implications. One is the under-recognition of TIND. Orthostatic hypotension, without neuropathic pain in a patient who recovers from prolonged illness may be wrongly attributed to deconditioning if a marked decline in HbA1c was not considered. In such a circumstance, unintentionally perpetuating the HbA1c decline may further worsen the orthostatic hypotension. Secondly, as mentioned above, factors other than the magnitude of HbA1c decline may be responsible for the pattern and severity of TIND.

Compared to the SD and coefficient of variance of capillary blood glucose reported in healthy controls and well-controlled DM patients[8-10], the glycaemic variability in our nosocomial TIND patients- SD of 3.3mmol/l and coefficient of variance of 36.7% appeared to be high. Gibbons *et al*.[2] previously reported a correlation between the magnitude and rate of HbA1c decline with the severity of neuropathic pain and autonomic dysfunction. However, not all patients with marked HbA1c decline develop TIND, suggesting that other mechanisms may be contributory. The role of glycaemic variability in DM-related micro- and macro-vascular complications remains controversial.[11-16] We postulate that tight glycaemia control with fluctuations between hyper- and hypo-glycaemic states that increase glycaemic variability[17-20], may additionally predispose patients to develop TIND. Increased oxidative stress, inflammation, apoptosis, microvascular damage and endoneurial ischaemia[21-24] have all been implicated in TIND pathophysiology. It is conceivable that markedly fluctuating blood sugars in addition to rate and quantum of HbA1c decline may exacerbate the development of TIND through one of these mechanisms.

Our study is limited by its retrospective nature, referral bias, small numbers and lack of a control cohort comprising hospitalized DM cohort without TIND. Evaluation for alternative causes of neuropathic pain and dysautonomia was also not uniform as it was largely determined by the discretion of the managing physician and predicted by clinical circumstances. We also used pre-meal capillary blood glucose recordings for glycaemic variability calculation instead of the more accurate continuous glucose measurements. In addition, glycaemic variability of acutely ill patients will have to be interpreted with caution. Nonetheless, our study provides some interesting insights to TIND development in a hospitalized cohort with poorly controlled DM. We are currently seeking further confirmation of our findings with a prospective nested case-control study.

In summary, we highlight the phenomenon of nosocomial TIND occurring in patients with poorly-controlled DM, who are hospitalized for prolonged periods with major illness and the blood glucose are well-controlled. With an increased number of DM patients worldwide coupled with resources available to achieve rapid glucose lowering, TIND prevalence may rise. Delineation of pre-disposing factors will also help clinicians mitigate the risk of developing TIND by identifying individuals in whom extra caution is warranted when lowering chronically raised blood sugars. At present, there are no studies to guide the rate of HbA1c change recommended to safely attain a target glycaemic goal and insufficient evidence to suggest permissive hyperglycaemia in sick hospitalized patients.

DISCLOSURE

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REFERENCES

1. Caravati CM. Insulin neuritis : case report. *Va Med Mon* 1933;59:745-6.
2. Gibbons CH, Freeman R. Treatment induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. *Brain* 2015;138:43-52.
3. Gibbons CH, Freeman R. Treatment induced neuropathy of diabetes – a reversible painful autonomic neuropathy. *Ann Neurol* 2010;67:534-41.
4. Kovatchev BP. Metrics for glycaemic control- from HbA1c to continuous glucose monitoring. *Nat Rev Endocrinol* 2017;13:425-436
5. Dyck PJB, Pinto MV, Ng PS, Thapa P, Laughlin R, Dyck PJ. Risk factors for lumbosacral radiculoplexus neuropathy, Poster presentation (Poster 81, Page 89 of 2019 PNS Abstract Supplement Posters), Peripheral Nerve Society Meeting, 22-26 June 2019, Genoa, Italy. Accessible https://www.pnsociety.com/files/Meetings/2019%20Meeting%20Genoa/Abstracts/2019%20PNS%20Abstract%20Supplement%20Posters(2).pdf
6. Tracy JA, Engelstad JK, Dyck PJ. Microvasculitis in diabetic lumbosacral radiculoplexus neuropathy.*J Clin Neuromuscul Dis* 2009;11(1), 44-8.
7. Younger DS. Diabetic lumbosacral radiculoplexus neuropathy: A postmortem studied patient and review of the literature. *J Neurol* 2011;258(7),1364-7.
8. Xu F, Tavintharan S, Sum CF, Woon K, Lim SC, Ong CN. Metabolic signature shift in type 2 diabetes mellitus revealed by mass spectrometry-based metabolomics. *J Clin Endocrinol Metab* 2013;98: E1060-5.
9. Rodbard D. Clinical interpretation of indices of quality of glycaemic control and glycaemic variability. *Postgrad Med* 2015;123(4):107-18.
10. Hill NR, Oliver NS, Choudhary P, Levy JC, Hindmarsh P, Matthews DR. Normal reference range for mean tissue glucose and glycaemic variability derived from continuous glucose monitoring for subjects without diabetes in different ethnic group. *Diabetes Technol Ther* 2011;13(9):921-928.
11. Kilpatrick ES, Rigby AS, Atkin SL. A1C variability and the risk of microvascular complications in type 1diabetes (Data from the Diabetes Control and Complications Trial). *Diabetes Care* 2009;31:2198-202.
12. Ang L, Jaiswal M, Martin C, Pop-Busui R. Glucose control and diabetic neuropathy: Lessons from recent large clinical trials. *Curr Diab Rep* 2014;14(9):528.
13. Siegelaar SE, Kilpatrick ES, Rigby AS, Atkin SL, Hoekstra JBL, DeVries JH. Glucose variability does not contribute to the development of peripheral and autonomic neuropathy in type 1 diabetes: data from the DCCT. *Diabetologia* 2009;52:2229-2232
14. Xu W, Zhu Y, Yang X, *et al*. Glycaemic variability is an important risk factor for cardiovascular autonomic neuropathy in newly diagnosed type 2 diabetic patients. *Int J Cardiol*2016;215:263-8.
15. Jun JE, Jin SM, Baek J, *et al*. The association between glycaemic variability and diabetic cardiovascular autonomic neuropathy in patients with type 2 diabetes. *Cardiovasc Diabetol* 2015;14:70
16. Xu F, Zhao L, Su J, *et al*. The relationship between glycaemic variability and diabetic peripheral neuropathy in type 2 diabetes with well-controlled HbA1c. *Diabetol Metab Syndr* 2016;6:139.
17. Zhou J, Jia W, Bao Y, *et al*. Glycaemic variability and its responses to intensive insulin treatment in newly diagnosed type 2 diabetes. *Med Sci Monit* 2008;14(11):CR552-8.
18. Kovatchev B, Cobelli C. Glucose variability: Timing, risk analysis and relationship to hypoglycemia in diabetes. *Diabetes Care* 2016;39:502-10.
19. Su S, Kim JH. Glycemic Variability: How do we measure it and why is it important? *Diabetes Metab J* 2015;39(4):273-82.
20. Monnier L, Colette C, Owens DR. Glycemic variability: The third component of the dysglycemia in diabetes. Is it important? How to measure it. *J Diabetes Sci Tehnol* 2008;2(6):1094-100.
21. Tesfaye S, Malik R, Harris N, *et al*. Arterio-venous shunting and proliferating new vessels in acute painful neuropathy of rapid glycaemic control (insulin neuritis). *Diabetologia* 1996;39:329-35.
22. Ohshima J, Nukada H. Hypoglycaemic neuropathy: microvascular changes due to recurrent hypoglycaemic episodes in rat sciatic nerve. *Brain Res* 2002;947:84-9.
23. Razavi NL, Kitabchi AE, Stentz FB, *et al*. Proinflammatory cytokines in response to insulin-induced hypoglycemic stress in healthy subjects. *Metabolism* 2009;58:443-8.
24. Honma H, Podratz JL, Windebank AJ. Acute glucose deprivation leads to apoptosis in a cell model of acute diabetic neuropathy.*J Peripher Nerv Syst* 2003;8:65-74.