

Case Report

Treatment-Induced Neuropathy of Diabetes in Youth: Case Series of a Heterogeneous and Challenging Complication

Eirene G. Alexandrou,^{1,2} Sarah D. Corathers,^{3,4} Amit Lahoti,^{5,6} Jacob Redel,^{7,8} Siobhan Tellez,³ Nana-Hawa Yayah Jones,^{3,4} and Ahlee Kim^{5,6}

¹Division of Endocrinology, University of Iowa Stead Family Children's Hospital, Iowa City, Iowa 52242; ²Department of Pediatrics, University of Iowa, Iowa City, Iowa 52242; ³Division of Endocrinology, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 45229; ⁴Department of Pediatrics, University of Cincinnati, Cincinnati, Ohio 45229; ⁵Division of Endocrinology, Le Bonheur Children's Hospital, Memphis, Tennessee 38103; ⁶Department of Pediatrics, University of Tennessee Health Science Center, Memphis, Tennessee 38103; ⁷Division of Endocrinology, Children's Mercy Hospital, Kansas City, Missouri 64108; and ⁸Department of Pediatrics, University of Missouri-Kansas City School of Medicine, Kansas City, Missouri 64108

ORCID numbers: 0000-0003-0039-8701 (A. Lahoti); 0000-0003-3978-8491 (J. Redel); 0000-0002-3631-0313 (S. Tellez); 0000-0002-9988-6686 (N.-H. Yayah Jones); 0000-0002-2620-5501 (A. Kim).

Abbreviations: DKA, diabetic ketoacidosis; DPN, diabetic polyneuropathy; HbA1c, glycosylated hemoglobin A1c; MDI, multiple daily injection; MRI, magnetic resonance imaging; T1D, type 1 diabetes; T2D, type 2 diabetes; TIND, treatment-induced neuropathy of diabetes.

Received: 1 September 2020; Editorial Decision: 6 October 2020; First Published Online: 15 October 2020; Corrected and Typeset: 7 November 2020.

Abstract

Treatment-induced neuropathy of diabetes (TIND) is a small fiber neuropathy precipitated by rapid correction of hyperglycemia. Literature on TIND in pediatric diabetes is scarce. We present 7 cases of TIND in children and young adults, increasing awareness of this condition in pediatric diabetes and broadening the scope of published knowledge.

Key Words: pediatric diabetes, diabetes complications, pain, diabetic neuropathy, somatic pain

Treatment-induced neuropathy of diabetes (TIND), first described in 1933, is a painful somatosensory and autonomic neuropathy occurring with rapid improvement in glycemic control (>2% decline in glycosylated hemoglobin A1c [HbA1c] over 3 months) achieved by insulin, oral hypoglycemic agents, or severe dietary restriction in patients with recent or remote type 1 (T1D) and type 2 diabetes (T2D) [1–3]. Neuropathic

symptoms are described as either burning, freezing, tingling, stinging, or allodynia, follow a symmetric distribution, and are worse distally. Risk factors include higher baseline HbA1c (>10% or 86 mmol/mol), diabetic anorexia or weight loss, and female gender [3, 4]. TIND is distinct from diabetic polyneuropathy (DPN), given its acute onset and often reversible nature. TIND is also associated with autonomic dysfunction and

microvascular complications, underscoring the importance of an interdisciplinary approach to care [4, 5]. Current management, including gabapentinoids, tricyclics, or serotonin reuptake inhibitors, is limited by our understanding of TIND pathophysiology [4-6], of which there are a few postulated mechanisms. One theory relates to hyperglycemia-induced microcirculatory changes that cannot remodel at the same rate of decline in serum glucose, leading to ischemic conditions within the endoneurium. Another thought is that acute glucose deprivation leads to cellular apoptosis and, once a normoglycemic state is achieved, the subsequent firing of regenerating axons results in the development of neuropathic symptoms [4]. Treatment response in TIND is variable with a gradual (but sometimes incomplete) resolution of symptoms over 3 to 24 months [4-6]. Cases of TIND are well described in adult literature, and a recent report has shown that 11% of patients (n = 954) referred to a diabetic neuropathy clinic had presentations consistent with TIND [3]. The prevalence in children remains unclear, as pediatric literature is scarce, with only 2 cases reported [4, 7].

In this series, we describe 7 cases of TIND in children and young adults treated at 2 pediatric centers (Cincinnati Children's Hospital Medical Center and Le Bonheur Children's Hospital). We aim to promote recognition of this condition, especially within the pediatric community. Additionally, we look to broaden the scope of published knowledge regarding TIND, highlight its varied course and treatment challenges, and inspire continued research in the area to better define TIND so that novel prevention and treatment strategies can be developed.

Case Descriptions

Case 1

A 14-year-old African American male presented with diabetic ketoacidosis (DKA) and new-onset T1D with initial HbA1c >14% (>130 mmol/mol). With multiple daily injection (MDI) insulin therapy, his HbA1c declined to 5.6% (38 mmol/mol) after 3 months. Simultaneously, burning and allodynia developed in his chest, abdomen, and lower extremities as well as early satiety with a 4 kg weight loss. Evaluation for weight loss demonstrated normal adrenal, thyroid, liver, and renal function, and was negative for inflammatory bowel disease. Over the next few months, his appetite normalized, and he regained 8 kg. His pain was discussed with rheumatology and neurology, and presentation was deemed consistent with TIND. Low-dose gabapentin was offered, but not pursued. His symptoms

resolved over 4 months without treatment or worsening glycemic control.

Case 2

A 16-year-old Caucasian female presented with DKA and new-onset T1D with HbA1c >14% (>130 mmol/mol). MDI insulin therapy was initiated. Generalized insulin edema with pleural effusions developed within 1 week, marked by an 18 kg weight gain that improved with diuretics. Over 4 weeks, her HbA1c improved to 9.9% (85 mmol/mol), at which time she developed pain and paresthesia of her chest, abdomen, back, hands, and feet. She reported early satiety with an 11 kg weight loss over 3 months and palpitations. Bilateral, moderate nonproliferative retinopathy, macular edema, and cataracts were also noted at T1D diagnosis. Additional screening for microvascular complications revealed microalbuminuria. Her evaluation was negative for pancreatitis, urinary tract infection, nephrolithiasis, and celiac disease. She had normal iron studies and inflammatory markers, and no vitamin deficiencies. A gastric emptying study revealed gastroparesis. Her electrocardiogram was notable for sinus tachycardia and echocardiogram was normal. She had normal muscle strength, deep tendon reflexes, and sensation to touch, temperature, vibration, and proprioception. Neurology diagnosed her with TIND and initiated gabapentin. Situational tachycardia was suspected, but over the next several months she experienced palpitations that awakened her from sleep and occurred at rest. Due to concerns for dysautonomia she was referred back for cardiologic consultation, but she did not follow up. With improved glycemic control over the next 6 months her neuropathy, autonomic symptoms, and microvascular manifestations subsided, and medications were tapered off.

Case 3

A 19-year-old Caucasian male with a five-year history of poorly controlled T1D was motivated to improve glycemic control. In 1 month, his HbA1c declined from 12.1% (109 mmol/mol) to 8.6% (70 mmol/mol). He developed burning pain in his feet and early satiety with a 3 kg weight loss. His exam was notable for normal muscle strength, deep tendon reflexes, and sensation to light touch and proprioception. He had mildly decreased vibration sensation in his feet with tenderness of the plantar surfaces. Neurology diagnosed him with TIND and started gabapentin along with cognitive behavioral therapy. His pain was refractory to treatment and he was subsequently lost to follow-up.

One year later, he returned to the endocrine clinic with HbA1c 6.5% (48 mmol/mol) and no complaints of pain or early satiety off medication.

Case 4

A 22-year-old African American male with a 3-year history of poorly controlled T1D with HbA1c >14% (>130 mmol/mol) was transitioned to insulin pump therapy. Over 2 months, his HbA1c improved to 10.5% (91 mmol/mol). Pain in his lower extremities and genitalia developed without associated impotence or urinary symptoms. Evaluation was performed by urology, pain team, and neurology. A computed tomography scan of abdomen and pelvis, testicular ultrasound, and infectious and lymphoproliferative disease workup was unremarkable. Deep tendon reflexes were symmetrically depressed at his knees and ankles. His pain was refractory to gabapentin, but improved modestly with acupuncture. He experienced a 4.5 kg weight loss attributed to decreased appetite and intermittent emesis in setting of severe pain. Given the unremitting pain, he developed depression and was started on duloxetine. Over 5 months, his HbA1c rose to 13.5% (124 mmol/mol) and symptoms resolved. His glycemic control gradually improved, and he has maintained a HbA1c near 10% (86 mmol/mol) without return of symptoms.

Case 5

A 19-year-old Caucasian male with a 3-year history of poorly controlled T1D reinitiated consistent MDI insulin therapy. Over 2 months, his HbA1c decreased from >14% (>130 mmol/mol) to 8.3% (67 mmol/mol). He developed burning pain in his extremities, torso, and perineum, and profuse diarrhea with emesis. He lost 8 kg over 5.5 months, resulting in admission. Evaluation demonstrated normal esophagogastroduodenoscopy, colonoscopy, gastric emptying scan, and magnetic resonance imaging (MRI) of abdomen and pelvis. He had a negative celiac screen, nonelevated secretory diarrhea hormones, negative bacterial overgrowth test, negative infectious workup, normal inflammatory markers, normal thyroid testing, and negative rheumatologic markers. He was diagnosed with diabetic enteric neuropathy and TIND, and started on medical therapy (Table 1). He developed restrictive eating behaviors given concern for worsening diarrhea and body image issues, and he was later diagnosed with anorexia nervosa. Within 3 months of his neuropathic symptoms, he also developed microalbuminuria, which is ongoing. He has continued medications for symptom management since initiation

2 years prior. His HbA1c remains between 6% and 8.5% (42-69 mmol/mol).

Case 6

A 9-year-old Caucasian female was admitted with severe DKA and in a coma due to medical neglect 1 month post-T1D diagnosis. Her HbA1c was >14% (>130 mmol/mol). She reinitiated MDI insulin therapy upon discharge with her foster family. Over 1 month, her glycemic control improved to HbA1c 6% (42 mmol/mol), she developed paresthesia of her lower extremities, incontinence, and reported difficulties in walking as well as a 14 kg weight loss. Her exam was remarkable for pain to palpation of right lower extremity, decreased strength of right dorsiflexor and plantar flexor, and right foot drop. Deep tendon reflexes were intact. Spine MRI was normal. She was diagnosed with TIND and referred to physical medicine and rehabilitation, but did not follow up. All symptoms resolved without intervention over 3 months. Her HbA1c has ranged from 6% to 6.2% (42-44 mmol/mol).

Case 7

A 17-year-old Caucasian male with new-onset, antibody-negative T1D was started on MDI insulin therapy. His glycemic control improved from HbA1c >14% (>130 mmol/mol) to 10.7% (93 mmol/mol) over 4 weeks. He developed allodynia and paresthesia in his lower extremities and scrotum, and a decreased appetite with 10 kg weight loss. Microalbuminuria and mild, nonproliferative retinopathy developed. He had a normal spine MRI and a delayed gastric emptying scan. His presentation was consistent with TIND, and he was started on gabapentin and self-initiated cannabis. His symptoms persisted, so treatment was modified (Table 1). He had gradual resolution of all symptoms over 10 months, aside from unchanged retinopathy, and he discontinued all noninsulin medications. His HbA1c remains <6% (<42 mmol/mol).

Discussion

In this series we describe 7 cases of TIND in children and young adults treated at 2 pediatric centers, increasing recognition of TIND as a complication of pediatric diabetes. Prior to our report, only 2 pediatric cases had been published [4, 7], indicating that the occurrence of TIND is more than the paucity of literature suggests. By raising awareness, we hope to enhance detection and timely management of this distressing and potentially debilitating condition. TIND should be considered in patients with diabetes who present with acute neuropathy or autonomic

Table 1. Demographics, Anthropometrics, Diabetes History, Presentation of Pain With Associated Manifestations, and Treatments Utilized for Each Case

Cases	Age at T1ND onset (years)	Duration of diabetes at T1ND onset	Gender	Change in weight (kg)/ time	Antibodies	Change in HbA1c/time	Pain pattern	Management	T1ND resolution time	Autonomic symptoms	Microvascular complications
Case 1	14	3 months	Male	38.8 to 34/1.5 months	GAA	>14% (130 mmol/mol) to 5.6% (38 mmol/mol)/3 months	Burning sensation in chest, abdomen, and lower extremities	Self-resolved	3–4 months	Early satiety and weight loss	None to date
Case 2	16	4 weeks	Female	71.1 to 59.6/3 months	IA-2, ZnT8	>14% (130 mmol/mol) to 9.9% (85 mmol/mol)/1 month	Burning sensation, numbness, and tingling in chest, abdomen, lower back, hands, and feet	Gabapentin up to 300mg daily, cyproheptadine 4mg daily	6 months	Early satiety, delayed gastric emptying, weight loss, and sinus tachycardia	Microalbuminuria, bilateral moderate nonproliferative retinopathy with macular edema (OD > OS) and cataracts
Case 3	19	5 years	Male	76.2 to 73.1/2 months	IA-2, IAA	12.1% (109 mmol/mol) to 8.6% (70 mmol/mol)/1 month	Bilateral burning and tingling sensation in feet	Gabapentin up to 1200mg daily	12 months	Early satiety and weight loss	None to date
Case 4	22	3 years	Male	66 to 61.6/4.5 months	GAA, IA-2, ZnT8	>14% (130mmol/mol) to 10.5% (91mmol/mol)/2 months	Sharp pain in lower extremities, perineum, and scrotum	Gabapentin up to 900mg daily	5 months	Early satiety, recurrent emesis, and weight loss	None to date
Case 5	19	3 years	Male	56.7 to 48.6/5.5 months	GAA	>14% (130mmol/mol) to 8.3% (67mmol/mol)/2 months	Pain in extremities, hip, trunk, and perineum	Gabapentin up to 2400mg daily, clonidine 0.1 mg daily, methocarbamol 500mg 3 times daily, loperamide 6mg 3 times daily	N/A	Enteric neuropathy with diarrhea and weight loss	Microalbuminuria
Case 6	9	2 months	Female	48 to 33.9/1.5 months	GAA, IAA	>14% (130mmol/mol) to 6% (42mmol/mol)/1 month	Weakness, tingling, numbness, and sharp pain in lower extremities	Self-resolved	3 months	Fecal and urinary incontinence and weight loss	None to date
Case 7	17	4 weeks	Male	58 to 48.4/3 months	Negative	>14% (130mmol/mol) to 10.7% (93mmol/mol)/1 month	Hypersensitivity, burning, and tingling in scrotum, thighs, legs, and soles of feet	Gabapentin up to 1800mg daily; switched to pregabalin 300mg daily, erythromycin 100mg 3 times daily, and cyproheptadine 4mg twice daily	10 months	Early satiety and weight loss	Microalbuminuria, mild nonproliferative retinopathy

symptoms following rapid correction of hyperglycemia defined as >2% decline in HbA1c over 3 months. If TIND is suspected, interdisciplinary care comprised of an endocrinologist, neurologist, and pain management physician or physical therapist should be coordinated.

Our cases reinforce the inciting events in TIND development, its varied course, unique treatment challenges, and continued limitations. In accordance with previous reports [1-8], all of our patients with TIND had a significantly elevated baseline HbA1c ranging from 12.1% to >14% (109 mmol/mol to >130 mmol/mol) with a >2% decline over 1 to 3 months (Table 1). TIND impacted both those with recent and remote diabetes. Within our population, 57% had new-onset diabetes and the remaining had lived with diabetes for 3 to 5 years. Despite the preponderance of T1D within our group, clinicians should remain cognizant that this condition also impacts those with T2D. Our cases also underscore the medical complexity of TIND. All presentations were complicated by autonomic symptoms (gastrointestinal 100%; cardiovascular 14%; genitourinary 14%). Microvascular complications were also present in 43% of our patients; all had microalbuminuria and 2 out of the 3 had nonproliferative retinopathy. For those patients that were not due for microvascular screening per American Diabetes Association guidelines [9], testing was performed only if symptoms were expressed, such as retinal screening for those with vision changes. Patients with retinal changes subsequently had microalbuminuria screening, as the presence of one microvascular complication may indicate another. The early microvascular changes detected in our patients with new-onset diabetes highlights the importance of screening for these conditions in all TIND presentations, despite duration of diabetes. Another unique finding was the presence of motor symptoms in 2 patients (cases 4 and 6). The loss of motor axons associated with neurogenic muscle atrophy has been documented as a late consequence of DPN [10]; however, motor deficits have yet to be reported in TIND. Although case 4 had 3 years of poorly controlled diabetes, the acute onset and resolution of his neuropathic and sensorimotor symptoms is inconsistent with DPN. Given our limited understanding of TIND's pathophysiology, small sample size, and the challenge of performing neurological exams in young children, we are unable to definitively conclude if motor deficit is a new, underrecognized manifestation of pediatric TIND. Lastly, treatment response in this condition is varied, as shown here. Some of our patients experienced spontaneous resolution of symptoms without treatment or worsening glycemic control (29%), while others experienced resolution of pain within 5 to 12 months of starting medical therapy (57%) or unremitting pain despite intervention (14%) (Table 1). We are

unable to explain the variable and at times incomplete response to treatment. This may be driven by underlying genetic modifiers that have yet to be elucidated or could also be a reflection of the lower doses of gabapentin prescribed, in contrast to a maximum daily dose of 3600 mg [11]. Furthermore, the most severe and persistent presentation (case 5) also had anorexia nervosa, which may have played a role in stagnating his recovery.

Although our cases clearly describe characteristics of pediatric TIND, reporting on its prevalence is beyond the scope of this series, as cases were identified through individual providers as opposed to unbiased, retrospective chart review. We speculate that the condition may occur more commonly in those with new-onset diabetes, as initiation of insulin results in rapid improvements in glycemic control in contrast to a patient who has been on insulin for several years (unless adherence to therapy changes). Despite the estimated incidence of diabetes nearing 34.2 per 100 000 youths per year [12], reasons as to why TIND is not more commonly reported, especially in comparison to adults, demonstrates the need for further scientific exploration. Part of this could be driven by under-reporting of symptoms in a pediatric population. The detection of neuropathic symptoms may improve by standardized application of screening tools with age-appropriate language for those presenting with rapidly improved glycemic control. Additional studies are also needed to determine genetic predisposition to TIND as well as other modifiers that may endow protection in youth with diabetes.

At this time, we remain underpowered to define any additional risk factors in TIND development or propose novel prevention and treatment strategies. Gradual control of hyperglycemia was speculated as a potential preventive measure for TIND; however, this has never been studied. Therefore, patients with diabetes should continue to be approached according to guidelines, with aggressive insulin therapy to reduce the risk of development and progression of microvascular complications [9]. Secondly, in those that develop TIND, permissive hyperglycemia for symptomatic resolution is inadvisable, given the increased risk of permanent microvascular complications [6]. There remain no consensus guidelines for management of TIND and the approach to these patients, as evidenced by our cases, continues to be varied. Our cases demonstrate that extensive evaluation, including sophisticated imaging, may be pursued; however, nearly all these studies were negative. This brings to light the need for established guidelines to streamline diagnostic workup, while promoting timely identification of TIND and minimizing the burden placed on patients, providers, and the medical system by excessive diagnostics. Until future studies can further elucidate the mechanisms contributing to TIND, the mainstay of

treatment continues to be supportive care and stable glycemic control within recommended targets [4, 12].

Acknowledgments

Authors thank the patients and their families. Authors also thank Cincinnati Children's Hospital and Le Bonheur Children's Hospital for their support and Courtney Bricker-Anthony, PhD, a scientific editor at Le Bonheur Children's Hospital, for assistance in editing manuscript.

Additional Information

Correspondence: Ahlee Kim, MD, Le Bonheur Children's Hospital, University of Tennessee Health Science Center, 51 N. Dunlap Street, Memphis, TN 38104, USA. E-mail: akim20@uthsc.edu.

Disclosure Summary: The authors have no conflicts of interests or financial disclosures.

Data Availability: Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

References

1. Caravati C. Insulin neuritis: a case report. *Va Med Monthly*. 1933;59:745-746.
2. Gibbons CH. Treatment-Induced Neuropathy of Diabetes. *Curr Diab Rep*. 2017;17(12):127.
3. Gibbons CH, Freeman R. Treatment-induced neuropathy of diabetes: an acute, iatrogenic complication of diabetes. *Brain*. 2015;138(Pt 1):43-52.
4. Chandler E, Brown M, Wintergerst K, Doll E. Treatment-induced neuropathy of diabetes (TIND) in pediatrics: a case report and review of the literature. *J Clin Endocrinol Metab*. 2020;105(2):395-398.
5. Gibbons CH, Freeman R. Treatment-induced diabetic neuropathy: a reversible painful autonomic neuropathy. *Ann Neurol*. 2010;67(4):534-541.
6. Gibbons CH. Treatment induced neuropathy of diabetes-Long term implications in type 1 diabetes. *J Diabetes Complications*. 2017;31(4):715-720.
7. Varadharaju N, Jeevarathnam D, Rajan M, Ponnurangam Nagarajan V, James S. A case of treatment-induced neuropathy in an adolescent with type 1 diabetes. *Ann Pediatr Endocrinol Metab*. 2019;24(3):203-206.
8. Gibbons CH. Treatment induced neuropathy of diabetes. *Auton Neurosci*. 2020;226:102668.
9. Chiang JL, Maahs DM, Garvey KC, et al. Type 1 diabetes in children and adolescents: a position statement by the American Diabetes Association. *Diabetes Care*. 2018;41(9):2026-2044.
10. Allen MD, Doherty TJ, Rice CL, Kimpinski K. Physiology in Medicine: neuromuscular consequences of diabetic neuropathy. *J Appl Physiol (1985)*. 2016;121(1):1-6.
11. Friedrichsdorf SJ, Giordano J, Desai Dakoji K, Warmuth A, Daughtry C, Schulz CA. Chronic pain in children and adolescents: diagnosis and treatment of primary pain disorders in head, abdomen, muscles and joints. *Children*. 2016;3(4):42.
12. Mayer-Davis EJ, Dabelea D, Lawrence JM. Incidence trends of type 1 and type 2 diabetes among youths, 2002-2012. *N Engl J Med*. 2017;377(3):301.