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CASE REPORT

# Treatment-induced neuropathy of diabetes in an adolescent with rapid reduction in HbA1c and weight loss: Persistent neuropathic findings at follow-up after 1.5 years

**Vinni Faber Rasmussen**[1,2] | **Mathilde Thrysøe**[1] | **Hatice Tankisi**[3] | **Páll Karlsson**[1,4] | **Esben Thyssen Vestergaard**[2,5] | **Kurt Kristensen**[5] | **Jens Randel Nyengaard**[4,6] | **Klaus Krogh**[5,7] | **Christina Brock**[8] | **Astrid Juhl Terkelsen**[1,9]

[1]Danish Pain Research Center, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[2]Department of Pediatrics and Adolescents, Randers Regional Hospital, Randers, Denmark

[3]Department of Neurophysiology, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[4]Core Centre for Molecular Morphology, Section for Stereology and Microscopy, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark

[5]Steno Diabetes Center Aarhus, Aarhus University Hospital, Aarhus, Denmark

[6]Department of Pathology, Aarhus University Hospital, Aarhus, Denmark

[7]Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark

[8]Department of Gastroenterology, Aalborg University Hospital, Aalborg, Denmark

[9]Department of Neurology, Aarhus University Hospital, Aarhus, Denmark

**Correspondence**
Vinni Faber Rasmussen, Danish Pain Research Center, Department of Clinical Medicine, Aarhus University, Aarhus, Denmark.
Email: vfr@clin.au.dk

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## Abstract

Treatment-induced neuropathy of diabetes (TIND) is a condition occurring within weeks after a rapid decline in blood glucose. This case report illustrates consequences in an adolescent with TIND. Gold standard methods diagnosing large fiber, small fiber, and autonomic neuropathy were abnormal at 1.5 years of follow-up. Awareness of TIND is important.

**KEYWORDS**
adolescent, neuropathy, pediatric, treatment-induced neuropathy of diabetes, type 1 diabetes

## 1 | INTRODUCTION

Treatment-induced neuropathy of diabetes (TIND), previously reported as insulin neuritis, is a rarely recognized painful sensory and/or autonomic neuropathy occurring within eight weeks after a rapid decline in blood glucose levels following chronic hyperglycemia. The prevalence is unknown; however, it is seen in up to

10% of tertiary cases referred for evaluation of diabetic neuropathy.[1]

TIND is iatrogenic and may develop subsequent to insulin administration, oral hypoglycemic medications, or even diet or weight loss to control diabetes. The underlying pathogenic mechanisms are, however, still incompletely understood.[2]

Gibbons et al. reported that approximately 11% of individuals with diabetes, who over a three-month period, experienced a decrease in hemoglobin A1c (HbA1c) of >22 mmol/mol (>2 percentages points) developed TIND. In addition, they found a relationship between the magnitude of change in HbA1c and the severity of neuropathic pain and autonomic dysfunction.[3] Risk factors of TIND include higher baseline HbA1c, anorexia or weight loss, and female gender.[4]

TIND may have debilitating consequences. Clinically, patients with TIND present with neuropathic pain in a length-dependent pattern that progresses over days to weeks. Common autonomic symptoms include orthostatic intolerance (syncope), gastrointestinal dysfunction (early satiety, constipation), sudomotor dysfunction (sweating abnormalities), and sexual challenges (decreased vaginal lubrication and erectile dysfunction).[5,6]

Simple bedside neurologic examination (e.g., deep segmental tendon reflexes, sensation, and vibration) and gold standard diagnostic method tests (e.g., nerve conduction studies (NCS), skin biopsies measuring intraepidermal nerve fiber density (IENFD), and cardiovascular reflex tests (CARTs)) can be used to distinguish pathology.

TIND has been reported in children, adolescents, and adults,[2,4,7–10] however, measurable consequences are rarely described. Here, we describe a case of an adolescent with TIND and her neurological deficits after 1.5 years. We aim to promote awareness of this condition, especially within young individuals with diabetes. In addition, we want to contribute to the existing knowledge regarding development and persistence of symptoms and signs in the first 1.5 years with TIND.

## 2 | CASE PRESENTATION

A sixteen-year-old girl was referred to the Pediatric and Adolescents Department in 2019 with a history of thirst, polydipsia, polyuria, stomach pain, and vomiting events within the last weeks and a weight loss from 57.5 to 48.1 kg. She was diagnosed with type 1 diabetes, and her HbA1c was 168 mmol/mol (17.5%). Sixteen days after initiating insulin treatment, the HbA1c was 131 mmol/mol (14.1%), and after 3 months, it was 61 mmol/mol (7.7%).

The patient received fluid therapy and intravenously insulin 5 IU/h followed by 3.5 IU/h when diagnosed. The next day, injection therapy was started: Estimated total daily insulin dose was 0.8 IU/kg, of which 50% was given as basal insulin (detemir 10 IE bid.) Within the first week, basal insulin was increased to 18 IU bid.

Eleven days after initiation of anti-diabetic treatment stomach pain returned. She also felt that the food was growing in her mouth (possible sign of oral dysphagia) and approximately 30 days later she developed pain and restlessness in her legs. She was hospitalized due to worsening of symptoms and a considerable weight loss. Additionally, she had developed pain in the toes, dizziness, burning pain in the legs especially when touching, affected mood, suicidal thoughts, and insomnia and interrupted sleep because of pain. In this period, a functional disorder was suspected and collaboration with the Centre for Child and Adolescent Psychiatry was initiated.

NCS showed large fiber polyneuropathy and analgesic treatment was initiated, first with pregabalin, then gabapentin and finally amitriptyline were added. In addition, she was treated with melatonin and promethazine for her sleeping disorder.

In the following year, the disabling symptoms (pain in the leg, abdominal pain, sleep disorders, and gastrointestinal symptoms including diarrhea and intermittent constipation) continued and caused school absence. Abdominal ultrasonography and magnetic resonance imaging were normal. Colonic transit time, assessed with radiopaque markers, was 74–96 h (normal <70 h) indicating slow transit constipation. However, no signs of gastroparesis were found.

### 2.1 | Follow-up about 1.5 years after the diagnosis of diabetes

She was in contact to a tertiary center 1.5 years after the diagnosis of diabetes, because she still had severe gastrointestinal symptoms and occasionally pain in her leg. She weighed 67 kg and was treated with insulin (total insulin dose 0.9 IU/kg, basal/total 40%) and with pregabalin (Lyrica 25 mg +50 mg per day).

### 2.2 | Symptoms and quality of life scored in questionnaires

She had a WHO-5 well-being raw score at 14 indicating affected quality of life (raw score ranges from 0 to 25, 0 representing worst possible and 25 best possible quality of life).

The patient assessment of upper gastrointestinal symptom severity index (PAGI-SYM)[11] and Gastrointestinal Symptom Rating Scale (GSRS)[12] score indicates slight to moderate discomfort (a score of 2.0 on a 6-point Likert scale from 0 to 5, and a score of 2.1 on a 7-point Likert scale from

1 to 7, respectively, where highest numbers reflect the most severe symptoms). Composite Autonomic Symptom Score 31 (COMPASS-31)[13] assesses symptoms of autonomic dysfunction in six domains: orthostatic, vasomotor, secretomotor, gastrointestinal, bladder, and pupillomotor functions. The total COMPASS-31 score was 25.4 indicating autonomic diabetic neuropathy, due to a score above 16.[13] The reported symptoms included abdominal pain, bloating, visibly larger abdominal circumference, satiety, diarrhea, sometimes mild constipation, sleeping problems, and dizziness.

## 2.3 | Large and small fiber neuropathy

The patient was diagnosed with a large fiber sensory-motor and small fiber neuropathy. She still had positive symptoms (stabbing and shooting pains) with a length-dependent neuropathy distribution, and signs with a slight reduction of vibration were shown (8 seconds). Other examinations in the Utah Early Neuropathy Scale score were normal.[14] She had normal sensation for cold, warm, touch (cotton wool, the sharp wood end of a broken cotton swab) and monofilament 10 g. and NeuroTip at the first toes, normal proprioception, and normal deep segmental reflexes.

## 2.4 | Sensory-motor large fiber neuropathy

Sensory and motor NCS were performed using standard neurophysiological methods and surface electrodes to evaluate conduction velocity (CV), sensory and motor action potential amplitudes, distal motor latencies (DML) and minimum F-wave latencies,[15] and compared with our own laboratory reference. Sensory NCS of the superficial peroneal (CV = 40.0 m/s, amplitude = 1.7 μV), sural (CV = 42.8 m/s, amplitude = 9.2 μV), and dorsal sural (CV = 39.1 m/s, amplitude = 2.3 μV) nerves showed decreased CVs and reduced amplitudes. Motor NCS of the peroneal (CV = 38.8, F-wave = 51.2) and tibial (CV = 41.9, F-wave = 51.8) nerves showed decreased CVs and prolonged minimum F-wave latencies (tibial nerve Figure 1A) whereas DMLs and motor amplitudes were normal.

## 2.5 | Small fiber neuropathy

Intra-epidermal nerve fiber density (IENFD)[16] assessed with skin biopsy was 4.71 n/mm$^2$. No normative data for adolescents exit, however, this value is under the normal range for adults between 20 and 29 years (0.05 quantile IENFD value: 8.4 n/mm$^2$),[17] suggesting decreased nerve fiber density (Image of nerves in skin Figure 1B).

Corneal nerve fiber length (CNFL), corneal nerve fiber density (CNFD), corneal nerve branch density (CNBD), corneal fiber total branch density (CTBD), and corneal fiber fractal dimension (CNFrD) were measured by corneal confocal microscopy (CCM) in vivo and automatically analyzed by Accmetrics.[18] Values were CNFL 9.86 mm/mm$^2$, CNFD 16.7 n/mm$^2$, CNBD 10.4 n/mm$^2$, CTBD 16.7 n/mm$^2$, and CNFrD 1.44, respectively (Image of nerves in cornea Figure 1C). Compared to healthy controls, these values are low[19] indicating small fiber neuropathy.

## 2.6 | Autonomic neuropathy

Cardiovascular autonomic reflex tests (CARTs)[20] were performed, and overall, a normal response was found. Heart rate variability to deep breathing was 24, and the Valsalva ratio was 2.13 indicating a normal cardiovagal activity. Blood pressure changes to tilt table testing and Valsalva maneuver were normal without orthostatic hypotension but with an almost absent blood pressure rise during phase II late in the Valsalva maneuver suggesting a mild cardiovascular adrenergic dysfunction.[21]

Gastrointestinal transit times, assessed with the wireless motility capsule (SmartPill™ Motility Testing System, Medtronic), showed gastroparesis evident as prolonged gastric emptying time. At the time of 7.5 h, the pH increased either because pH was buffered by a meal or the capsule was moved retrogradely from the duodenum to the stomach. Regardless of the cause, the capsule resided in the stomach for 28 h. The contractility pattern in the stomach indicated enteric neuropathy (Figure 1D). The small bowel transit time was 5 h (normal <6.5 h) and colon transit time at about 2.5 h (normal <59 h). Despite the retrograde movement, the whole gut transit time at 35 h was within normal range (normal <70 h).

The Quantitative sudomotor reflex tests (QSART)[22] were abnormal with a total sweat volume for the four recording sites of 0.47 (forearm), 0.61 (proximal leg), 0.18 (distal leg), and 0.00 (foot) (Figure 1E). These results indicate distal diabetic neuropathy, due to absent sweat response in the foot (most distal), and reduced signal in the distal leg (Figure 1E).

## 2.7 | Test for other microvascular complications

Due to her young age, no eye examination controlling for retinopathy was done, and the last value for urinary

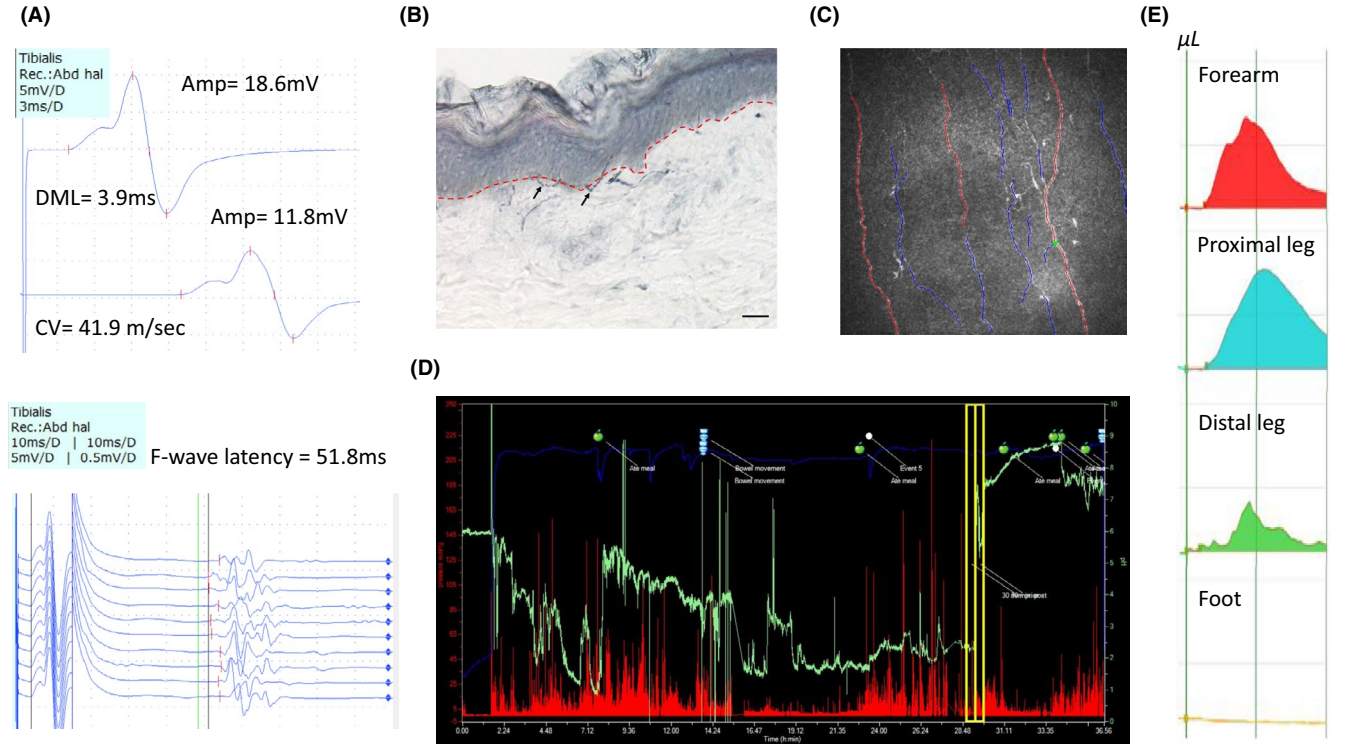


**FIGURE 1** Results of selected nerve tests obtained on a seventeen-year-old girl 1.5 years after debut of type 1 diabetes. All test results indicating nerve dysfunction or damage; (A) nerve conduction study of the tibial nerves with conduction velocity (CV) of 41.9 m/s and distal motor latency (DML) of 3.9 ms. Amplitude (Amp) = 18.6 mV and 11.8 mV, respectively. (B) Two PGP 9.5-positive nerve fibers (arrows) crossing the epidermal-dermal junction (stippled red line). (C) Automatically quantified corneal confocal microscopy image. The red lines represent main nerve fibers, blue lines are branches, and green spots indicate branch points. (D) Recording from Wireless motility capsule. The red lines represent the contractility pattern, the green line the pH value, and the yellow lines the time point after 28 h, where the capsule enters the small intestine. (E) Results from quantitative sudomotor reflex tests. The patients had no Q-sweat response (volume, µl) in the foot

albumin (µg/ml)-to-creatinine (mg/ml) ratio was 14 (normal < 30).

## 3 | DISCUSSION

Severe TIND is reported in a sixteen-year-old girl, after a rapid decline in blood glucose after the diagnosis of type 1 diabetes. After only 16 days, the HbA1c value was reduced by 37 mmol/mol (3.3 percentage points). This fast reduction led to long-term disabling symptoms for the patient, and after 1.5 years, the diagnostic tests revealed definite neuropathies. The diagnostic tests include NCS, CCM, IENFD, QSART, CARTs, and wireless motility capsule for detection of large fiber, small fiber, and autonomic neuropathy.

Recently, a review about TIND was published by Chandler et al.[22] Our case report supports that TIND is associated with autonomic dysfunction with gastroparesis, enteric neuropathy, cardiovascular adrenergic dysfunction, and sweat loss in addition to the length-dependent polyneuropathy. In addition, our case report adds to the discussion whether the condition is fully reversible or not and highlights a possible characteristic factor namely weight loss, and debates how inulin administration should be given initially to avoid TIND.

To our knowledge, no other published cases on TIND in pediatrics have reported a likewise extensive follow-up program and diagnostic testing for neuropathies. Remarkably, in our case, both nerve dysfunction and altered nerve structures were revealed. All the measurable abnormal findings at follow-up question whether the condition is reversible, despite TIND often is descripted as a condition that reverses over months.[2] Subclinical neuropathy, a condition with no obvious symptoms, but with abnormal diagnostic tests for neuropathy, may continue in patients with TIND and could have unknown long-term consequences. Previously, a follow-up study re-tested adult with TIND after 7–8 years, and it showed that the glucose control has impact on whether the patients showed neuropathic improvement or worsening in IENFD, NCS, and cardiovascular reflex tests and other microvascular complications.[5] This study supports the importance of keeping stable glucose control after diagnosing TIND, although prevention is first choice.

The best strategies avoiding TIND are debatable, but it seems that especially patients with a very high pretreatment HbA1c (>86 mmol/mol(10%)) not should obtain glycemic control too quickly. Future investigations in how a slower process over several months (>3 months and up to 12 months) in achieving the HbA1c goal (<53 mmol/mol(7%)) could reduce the risk of TIND, and other diabetic complications are needed.

In our case report, we also observed a significant weight loss, which is well-known also to be associated with TIND. This factor is interesting also because of the known condition denoted diabetic neuropathic cachexia, characterized with neuropathic pain and severe weight loss.[23] An increased focus on newly diagnosed patients with type 1 diabetes and a huge weight loss should be given due to a possible increase risk for developing TIND, theoretically because of increased metabolic disturbances.

In our case report, the adolescent had severe symptoms from the gastrointestinal tract, similar to previously described cases.[24] Gastrointestinal symptoms in youth with TIND seem to be the most present symptoms due to autonomic dysfunction following by cardiovascular and genitourinary symptoms.[4] Awareness that stomach pain, constipation, regurgitation, satiety, bloating, and diarrhea can be due to enteric neuropathy is important. In general, it is unacceptable if patients are categorized having a functional disorder like in our case report, because of insufficient knowledge about TIND.

There are no evidence-based strategies for management of TIND, but maintaining glycemic stability and treating symptoms of neuropathy until symptoms eventually disappear is a possible strategy.[25] Multidisciplinary collaboration between relevant specialists, for example, pediatrician, endocrinologist, neurologist, gastroenterologist, and psychiatrist and hospitals with neurologic test facilitates are considered necessary, and comorbid condition (e.g., vitamin deficiencies) might be excluded by biochemical testing and imaging modalities.

## 4 | CONCLUSION

TIND remains complex, and clinical awareness of TIND is important both in the step of preventing, detecting, treating, and avoiding long-term consequences. Disseminating knowledge about TIND is important, because these patients often have a severe clinical presentation, and it seems that the neurological deficits can persist for long time and even become chronic. Future investigations in how to prevent and manage TIND for best outcome for these patients are still needed.

## CONFLICT OF INTEREST

No conflict of interest.

## AUTHOR CONTRIBUTIONS

V.F.R.: is the main author and did the research about the case. V.F.R. and M.T.: performed the tests at follow-up. A.J.T., H.T., P.K., Kl.K., Ku.K., C.B., E.T.V., and J.R.N.: contributed to the analysis of the tests and reviewed and edited the manuscript.

## ETHICAL APPROVAL

The Danish Ethical Committee System has approved all included tests. The tests carry no substantial risks to the participant.

## CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this case report are available on request from the corresponding author, V.F.R. The data are not publicly available due to ethical restrictions and the General Data Protection Regulation.

## ORCID

*Vinni Faber Rasmussen* https://orcid.org/0000-0002-1356-2833
*Mathilde Thrysøe* https://orcid.org/0000-0002-3557-6566

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