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Treatment induced neuropathy of diabetes—Long term implications in type 1 diabetes

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ABSTRACT

Aims/Hypothesis: Aggressive glucose control can result in treatment induced neuropathy of diabetes (TIND) if glycemic control is achieved too quickly. The aim of the present study is to describe the 8-year follow-up data on a cohort of individuals with type 1 diabetes who developed TIND.
Methods: Twenty-six individuals with type 1 diabetes and TIND were followed longitudinally for 8 years with regular quantitative measurement of pain, neurological examinations and evaluation of microvascular complications. Comprehensive neurological testing was performed after TIND and 7–8 years later.
Results: Among the 26 individuals with TIND, 19/26 had stable glycemic control and 7/26 had unstable glycemic control in long-term follow up. Those 19/26 with stable glycemic control had improvement in neuropathy, pain and microvascular complications while the 7/26 with unstable glycemic control had significant worsening of neuropathy, pain and microvascular complications ($P < 0.01$, all tests).
Conclusion/Interpretation: TIND is a poorly understood iatrogenic complication of aggressive glycemic control, although individuals with stable glycemic control tended to improve, while those with unstable glycemic control worsened. Additional studies of TIND are required to understand potential outcomes in an era of medical 'metrics' where physician reimbursement may be tied to achievement of excessively rapid glycemic control.

1. Introduction

Treatment induced neuropathy of diabetes (TIND) is considered a rare painful sensory and autonomic neuropathy seen in individuals with rapid changes in glycemic control (Archer, Watkins, Thomas, Sharma, & Payan, 1983; Dandona, Fonseca, Thomas, Llewellyn, & Bolger, 1985; Llewelyn, Thomas, Fonseca, King, & Dandona, 1986; Llewelyn, Thomas, Fonseca, & Dandona, 1988, Tesfaye et al., 1996). Previously reported as 'insulin neuritis' (Caravati, 1933; Tesfaye et al., 1996), the use of the term 'TIND' is preferred because the neuropathy can occur using insulin or oral hypoglycemic medications, or even by severe dietary restriction (Gibbons & Freeman, 2010). Originally considered a rare disorder, we recently reported that >10% of individuals seen for evaluation of diabetic neuropathy at a tertiary referral center developed their neuropathy as an iatrogenic complication of aggressive glycemic control (Gibbons & Freeman, 2015).

Clinically, individuals with TIND present with burning and shooting pains in a length dependent pattern that progresses over days to weeks. The reported pain is severe, continuous and often accompanied by allodynia and hyperalgesia. Neuropathy severity correlates with the magnitude of change in glycosylated hemoglobin (HbA1C) (Gibbons & Freeman, 2015). On examination, small fiber sensory modalities are impaired while large fiber modalities, motor function and deep tendon reflexes are relatively unaffected. Nerve conduction studies are typically normal (or unchanged if a pre-existing neuropathy has been noted). Structural examination of small nociceptive C-fibers by skin biopsy shows a length dependent loss of unmyelinated intra-epidermal nerve fibers with numerous morphologic changes within weeks of the onset of neuropathic pain (Gibbons & Freeman, 2010). Although autonomic symptoms occur, they are often overshadowed by the neuropathic pain. Autonomic testing may show mild to moderate sympathetic and parasympathetic dysfunction within a few weeks of the change in glycemic control (Gibbons & Freeman, 2015). Orthostatic hypotension and syncope may accompany more severe autonomic dysfunction and is more likely to bring the problem to medical attention.

Although originally reported in 1933 (Caravati, 1933), little progress has been made in understanding the natural history of the disorder although associated risks are now more clearly defined (Gibbons & Freeman, 2015). In the current manuscript, we provide long term follow-up data on individuals diagnosed with TIND.

2. Methods

2.1. Study participants

This study was approved by the institutional review board of Beth Israel Deaconess Medical Center. Twenty-six cases of treatment

Conflicts of interest: none.

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induced neuropathy with type 1 diabetes were followed longitudinally for 8 years after onset and diagnosis of TIND, with detailed historical records for an additional 6–12 years prior to onset of TIND. All subjects underwent a battery of autonomic tests at the time of presentation and the battery of tests was repeated again 7–8 years later. All subjects were followed at Joslin diabetes center for routine diabetes care. Spot urine tests for microalbuminuria were performed every 6–12 months and glomerular filtration rates (GFR) calculated at each visit. All subjects were evaluated for routine screening tests including complete blood count, erythrocyte sedimentation rate, thyroid function tests, serum B12, comprehensive metabolic panel (including renal and hepatic function) and serum and urine protein electrophoresis.

2.2. Glycosylated hemoglobin

Glycosylated hemoglobin (HbA1C) scores were monitored every 3–6 months for the duration of the follow-up.

2.3. Physical examination

Detailed neurologic examinations were performed every 6 months for the duration of follow-up. The physical examination was quantified via the neuropathy impairment score in the lower limb (NIS-LL) (Dyck, Davies, Litchy, & O'Brien, 1997; Bril, 1999). In brief, the NIS-LL is an 88 point system that grades neuropathy from 0 (no neuropathy) to 88 (total loss of sensation, reflexes and strength in the legs).

2.4. Retinal exams and renal function

Retinal exams, performed every 6–12 months were quantified as normal (0), mild non-proliferative retinopathy (1), moderate non-proliferative retinopathy (2), severe non-proliferative retinopathy (3), or proliferative retinopathy (4). Treatment interventions and outcomes were recorded.

Renal function was monitored during regular clinical visits. Renal glomerular filtration rate was measured using the chronic kidney disease epidemiology collaboration (CKD-EPI) formula (Levey et al., 2009).

2.5. Pain scores

All subjects rated their pain on an 11 point Likert scale at every neurologic examination (every 3–6 months); a score of 0 denoted no pain and a score of 10 denoted the worst pain imaginable. Subjects were treated with medications to reduce neuropathic pain, including anti-convulsants, anti-depressants and opioids, typically in combination. Pain scores were measured while on medication(s).

2.6. Skin biopsy evaluation of intra-epidermal nerve fiber density (IENFD)

All subjects underwent 3-mm punch skin biopsies 10 cm above the lateral malleolus of the distal leg within 6 months of the onset of TIND. Follow-up biopsies were taken 7–8 years later in the same subjects at the distal leg adjacent to the original biopsy sites using standard techniques. Specimens were fixed and stained with PGP 9.5 (ubiquitin hydrolase, Chemicon). All patients underwent IENFD counting by a blinded physician and results were expressed as a linear density for IENFD (number of fibers per millimeter) (McCarthy et al., 1995).

2.7. Autonomic testing

Subjects underwent cardiovascular parasympathetic function testing (the heart rate response to deep respiration and the Valsalva maneuver) and cardiovascular sympathetic function (the blood pressure response to a Valsalva maneuver and tilt-table testing to 60 degrees). Patients had continuous ECG monitoring, continuous beat-to-beat blood pressure recordings, and oscillometric blood pressure measurements every minute during tilt-table testing. Testing was performed within 6 months of the onset of TIND, and follow-up testing completed 7–8 years later.

2.8. Nerve conduction studies

Subjects underwent routine nerve conduction studies after the onset of TIND and 7–8 years later. Measurements included sural conduction velocity, sural amplitude, peroneal conduction velocity, peroneal amplitude and distal latency.

2.9. Statistics

Descriptive statistics are included for all data. Group data are presented as mean ± standard deviation. Test results were analyzed using analysis of variance and Student's *t* test where applicable. A P value <0.05 was considered significant. All analyses are performed using SPSS 17.0 (Systat software, SPSS, Richmond CA).

3. Results

All 26 individuals had type 1 diabetes (22 female, 4 male). No other causes of neuropathy were detected in any of these individuals. All individuals with treatment induced neuropathy fell into one of two categories: (1) stable glycemic control after development of TIND (19 individuals) or (2) unstable glycemic control with at least one additional episode of TIND (7 individuals). Demographic details by group are provided in Table 1.

3.1. Glycemic control

Of the 26 people included in the study, 19 individuals maintained adequate glycemic control (defined as HbA1C values ranging from 6% to 8.5%) for the 8 years after development of TIND. These individuals are described in Table 1 under 'stable glycemic control'.

The remaining 7 individuals had recurrent cycles of hyperglycemia and normoglycemia (that met criteria as additional episodes of TIND) for the 8 years after development of TIND as seen in Fig. 1. These subjects had long periods of poor glycemic control (HbA1C > 10%; >86 mmol/mol) followed by rapid improvements to glycemic control (HbA1C <8.0%; <64 mmol/mol). In all 7 cases these individuals discovered that pain related to TIND was diminished by relaxation of glycemic control. The intentional relaxation of glycemic control resulted in severe, prolonged periods of hyperglycemia. However, additional episodes of TIND recurred after hospitalization and treatment of the severe hyperglycemia. These 7 individuals are listed in Table 1 under 'unstable glycemic control'.

Both groups of individuals had long periods of hyperglycemia, with at least one time period of abrupt improvement (consistent with a diagnosis of TIND). Complete demographic information is provided in Table 1.

3.2. Neuropathic pain and neurological function

3.2.1. Stable glycemic control

The individuals with stable glycemic control had a gradual improvement in neuropathic pain and were able to decrease or discontinue most neuropathic pain medications over several years.