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Case Report

The Treatment and Natural Course of "Insulin Neuritis" or Treatment-induced Neuropathy from the Perspective of 2 Cases

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"Insulin neuritis" or "treatment-induced neuropathy" is a relatively rare disease course after the adequate regulation of glucose levels by insulin in diabetes mellitus. In 1933 the syndrome was first described.

Typically, the onset of pain, presenting as polyneuropathy, is just after the start of the (adequate) treatment for diabetes mellitus. In this article we present 2 cases (both women, 15 and 22 years of age) with a course such as was described in 1933. They were treated with oral gabapentin, pregabalin, amitriptyline, duloxetine, tramadol and with transdermal capsaicin 8% patch. Simultaneously, glucose levels were carefully monitored and diabetes mellitus and comorbidities (mainly ocular and gastro-intestinal) were treated. Treatment effects were variable, and patients seemed to show some spontaneous/ natural recovery of complaints.

Furthermore, we describe the pathophysiology, diagnosis, therapy, and natural course.

"Insulin neuritis" or "treatment-induced neuropathy" is pain in polyneuropathy with a (sub)acute onset after adequate glycemic control of diabetes mellitus with insulin, whereby traditionally this is seen as one of the mainstays in the treatment for polyneuropathy in diabetes mellitus. Possibly this is due to ectopic generation of impulses in regenerating axons.

From the limited literature, it follows that the course is variable, but that spontaneous remission of pain is possible, especially after 18 months of adequate glycemic control.

There are no separate treatment strategies described in this form or genesis of pain in polyneuropathy, other than that which could be derived from the treatment of other forms of pain in polyneuropathy.

Key words: Insulin neuritis, treatment induced neuropathy, polyneuropathy, transdermal capsaicin, diabetes mellitus

We describe the case history of a 15-year-old and 22-year-old patient, who both presented with (sub) acute onset of bilateral pain in the context of neuropathy in the feet. This emerged after adequate treatment of diabetes mellitus type I. Antineuropathic medication (amitriptyline, gabapentin, duloxetine, pregabalin) and tramadol were started, to which pain and poor sleep improved marginally. Given that complaints were in particular limited to the dorsum of the foot and toes (initially unilaterally, later also contralateral), patients were treated with transversal capsaicin 8%, on which the pain in the first patient improved while in the second patient pain did not improve.

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CASE PRESENTATION

Patient A, a 15-year-old female, was referred to our outpatient clinic with severe pain in both feet, which

had emerged within the past few weeks. Her medical history was not contributing to 2-3 months before the reference. She had acute reduction in her vision in one eye after a trauma (volleyball against the eye), after which on further investigation a bilateral cataract was seen. Further metabolic evaluation showed fasting blood glucose of 36 mmol/L with an HbA1c to 167 mmol/mol, and the thus diagnosed type I diabetes mellitus was handled by the endocrinologist and pediatrician. Within a few weeks stable glucose values were achieved under 10 mmol/L. On both sides a cataract extraction with an intraocular lens placement was performed. Within 6 weeks after the start of the treatment for diabetes mellitus type I, a burning pain in both feet, mostly in the dorsum of the foot and ankle, and in addition, to the sole of the foot and toes, arose.

In her visit to our clinic, she described the symptoms as above, and concluded, “my feet are on fire.” Complaints are always present, with a Numeric Rating Scale (NRS) between 5 and 10 (on average around 8), where in addition to the burning sensation there were also tingling and pricking sensations. The pain was exacerbated by exercise and activity and improved with (frequent) cooling. Falling asleep and night rest were significantly disturbed. At the moment she did not attend school. On physical examination, there was a slight reddening (in keeping with the very frequent cooling) at the dorsum on both sides, without any tropic disorders or changes in the pattern of hair growth. There are signs of hyperesthesia and allodynia. There was no obvious atrophy and strength in both legs was essentially normal. Previously, 7.5 mg meloxicam and diclofenac twice daily were used without effect. Since week one she took gabapentin 300mg/d as prescribed by her pediatric neurologist.

To the clear signs of (poly)neuropathy, we started raising the gabapentin initially to 600 mg twice daily and add tramadol, if necessary, up to 50 mg twice daily, when peaks occurred. An initial treatment with capsaicin 8% patch was planned. We also referred the patient to a neurologic referral center for specific diagnostics related to polyneuropathy.

After further outpatient monitoring, amitriptyline 50 mg at bedtime was added, and after a few weeks a stable dose of 25 mg of tramadol up to 6 times a day was used. The pain was then marginally under control and sleep was somewhat improved. Treatment with capsaicin 8% patch was reported to be very painful with significant postoperative pain, despite pretreatment with 3% lidocaine cream. It eventually reduced the “known” pain to an NRS of 0 and cold packs were applied. After several days, this created a significant decrease in pain on the treated side. An electromyography (EMG) study showed a sensorimotor axonal polyneuropathy in diabetes mellitus type I, without a thin fiber component. Upon treatment with capsaicin on the contralateral side, the previously applied pretreatment was combined with oral 50 mg tramadol tablets and additional methods for diversion. Pain scores were less during and after treatment.

The amitriptyline and tramadol were reduced from several days after the second treatment with capsaicin. The NRS fell to an average of 3. Sleeping improved; social activities and school attendance were slowly restarted. However, after about 2 and a half months, as could be expected in treatment with capsaicin, the pain got worse, and the capsaicin treatment was reapplied with the same success.

Patient B, a 22-year-old woman was referred to our outpatient clinic with peripheral neuropathic pain for 6 months that had arisen within a few weeks. She used pregabalin, oxazepam and tramadol. Her medical history reported type I diabetes mellitus, chronic (> one year),and poor set glucose and HbA1c levels, partly due to noncompliance. As a result, gastroparesis proliferative retinopathy (with several laser treatments) macular edema, and 2 hospital admissions due to diabetic ketoacidosis developed. Especially in the months that her sugar levels were better controlled (HbA1c between 109-149 mmol/mol dropped to 52-67 mmol/mol), her pain rose. Her pain originally consisted of paresthesia and dysesthesia; later, burning pain on the dorsum of the foot and both shins occurred.

In her visit to our clinic, she described the symptoms as above. Complaints were always present in varying degrees, with walking on a cold floor and relaxation giving some relief. Falling asleep and night rest were disturbed by the pain, which woke her up 3-8 times a night. Her work (as a nurse) was suspended and she went on sick leave. On physical examination,

there were no tropic disorders or injuries visible on the lower legs and/ or feet, and she had a decreased perception of pinprick from the level of the knee down to the foot. Muscle force was essentially undisturbed and symmetrical. She took tramadol 100 mg 3 times a day, 1 g acetaminophen 3 times a day, and 150 mg pregabalin 4 times a day.

Duloxetine 30 mg once daily was started and later raised to 90 mg once a day at bedtime. Pregabalin was maintained at 150 mg twice a day. The dorsum of the feet were bilaterally treated with capsaicin 8% cream; no improvement in pain occurred. In the course of several months, her pain diminished considerably, in particular during the daytime. Medication was used as stated above, but in particular in the evening, wherein the tramadol was reduced to 100 mg once daily at bedime. Spinal cord stimulation was discussed with the patient, but with her pain (spontaneously) improving over months, we decided to wait and see its natural course before such steps were undertaken.

DISCUSSION

Pathophysiology:

Pain in the context of diabetic polyneuropathy is a relatively common problem, with an estimated prevalence of up to 3.6% for polyneuropathy; in 19% - 56% diabetes is the cause (1). However, the development of acute pain that arises just after appropriate adjustment of glucose levels, “insulin neuritis” or “treatment-induced neuropathy,” was first described in 1933 and is less often seen (2,3,4). The name “insulin neuritis” was given because it was seen that with the interruption of insulin, pain complaints disappeared within 3 days, but that these complaints came back again at any attempt to restart insulin therapy. The published case reports concern mostly elderly patients (2,3,5). Described case histories suggest regeneration as a result of the adequate control of blood sugars, in which pain would arise from ectopic generation of impulses in regenerating axons (6). A particular risk factor is the extent of the fall in HbA1c. An absolute risk of 20% with a decrease of 2% - 3% of the HbA1c over 3 months, compared to a risk of > 80% with a decrease of > 4% of the HbA1c for the development of neuropathy (7).

Diagnosis:

There was a broad differential diagnosis in these 2 patients, as to the cause of their polyneuropathy.

Causes of polyneuropathy include, but are not confined to: diabetes type I (13% - 17%); diabetes type II (5.5% - 35%); alcoholism (6% - 14%); hereditary (4% - 12%); inflammatory (4% - 8%); toxic (3-6%, mostly vincristine/ paclitaxel/ cisplatin); vitamin deficiency (1% - 4%); paraproteinemia (1% - 4%); chronic renal deficiency/ dialysis, chronic idiopathic axonal polyneuropathy ; Guillain-Barre syndrome; hereditary motoric and sensory neuropathy (Charcot-Marie-Tooth, 0.02% - 0.03%); paraprotein/ monoclonal gammopathies (0.05%); collagen diseases/ vasculitides (Sjögren disease, Systemic Erythematous Lupus, Wegener disease); human immunodeficiency virus in polyneuropathy “critical illness” (1).

Diseases that can mimic part of the presentation of these patients, and of polyneuropathy, are erythromelalgia, peripheral vascular disease, certain metabolic states or diseases (e.g., Fabry disease), lipodermatosclerosis, acrocyanosis, Raynaud phenomenon, and cellulitis.

In the “Directive Polyneuropathy” (Dutch societies for neurology and clinical neurophysiology, NVN/ NVKNF, 2005) a structured history (e.g., standardized questionnaire to sensory symptoms) and neurological physical examination (at least consisting of sensory research, reflexes, examination of the force) are considered to have a high sensitivity and specificity compared to an EMG examination. It is estimated that in 14% of patients with diabetes mellitus and electrophysiological abnormalities that suit polyneuropathy, no physical complaints or abnormalities in neurological physical examination exist (1). On the other hand, abnormalities on EMG examination have a high sensitivity of 84% but a low specificity (67%) when compared to a nerve biopsy (sural nerve) as a gold standard, especially in cases of small fiber neuropathies.

There are not many publications regarding the specific content of the EMG examination in the diagnosis of polyneuropathy. To assess the character and extent of damage, it is suggested that at least 3 extremities be tested, motor sensory nerves also be tested, proximal distal segments be tested, and

needle-testing be added for the diagnosis of axonal degeneration. To assess the character and extent of damage, it is suggested that at least 3 extremities be tested for the diagnosis of axonal degeneration: motor and sensory nerves; poximal and distal segments; and needle-testing. In combination, specificity and sensitivity of the examination improves, also with respect to identification of chronic idiopathic demyelinating polyneuropathy (CIDP) in diabetes versus diabetic polyneuropathy. In the diagnosis of demyelinating polyneuropathy, motor nerve testing of the arm(s) must be added.

The same directive states that an EMG examination is not necessary for the diagnosis of polyneuropathy if the clinical picture and the course fit to the underlying disease. However, it is recommended to further investigate any other possible cause of polyneuropathy as in the case of an acute onset, asymmetry, pain, a predominantly proximal disease, predominantly motor symptoms, or rapid progression of motor symptoms (1).

Therapy:

We could not find specific treatment strategies for pain in this form and cause of polyneuropathy in the literature. It therefore seems obvious that a treatment such as this also applies to other forms of painful neuropathies. Treatment would consist of anticonvulsants (phenytoin, carbamazepine, gabapentin) and antidepressants (e.g., amitriptyline, nortriptyline, fluoxetine, paroxetine). A tricyclic antidepressant may be chosen over a selective serotonin reuptake inhibitor , capsaicin cream, levodopa (with failed previous therapy), opioid preparations (oxycodone, tramadol) and transcutaneous electrical nerve stimulation. In choosing a specific agent, efficacy (number needed to treat), side effects (number needed to harm), patient-friendliness (route of administration, frequency of intake, need for the monitoring of blood levels), should be taken into account (1).

Natural course:

In the description of 16 cases of a “insulin neuritis”-like condition (diabetes mellitus type I: n = 9, mean age 25, diabetes mellitus type II: n = 7, mean age 47), pain scores , autonomic symptoms and “intra-epidermal nerve fiber density” improved after 18 months following good glycemic control, where it was more pronounced in patients with type I diabetes mellitus. Obviously, treatment was aimed at adequate glycemic control, but no other treatment strategies were applied, aimed at the mentioned improvement. In the description of 9 cases (ages ranging from 13 – 61 years old), 3 had ongoing complaints and 6 had significant improvement of complaints after 2, 7, 8, 9, 13 and 17 months respectively (8).

CONCLUSION

“Insulin neuritits” or “treatment-induced neuropathy” is pain in polyneuropathy with a (sub)acute onset, arising after adequate glycemic control of diabetes mellitus with insulin. Whereas traditionally, adequate glycemic control is seen as one of the mainstays in the treatment for polyneuropathy in diabetes mellitus.

From the limited literature, it follows that the course is variable, but that spontaneous remission of pain is possible, especially after 18 months of adequate glycemic control.

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Conflicts of Interest

None to report

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