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Results of bilateral thoracoscopic splanchnicectomy in a patient with diabetic neuropathy of the coeliac plexus; reduction of 2,000 mg daily dose of morphine: a case report

Abstract

We report the case of a 32-year-old patient with a long history of diabetes mellitus Type I complicated by coeliac plexus neuropathy. A strong pain syndrome of neuropathic type led to an addiction to parenterally applied morphine. The patient consumed 2,000 mg of intravenous or subcutaneous morphine per day. Thanks to the cooperation of three centres, the Pain Clinic at the Department of Anaesthesiology and Intensive Therapy of The Medical Centre of Postgraduate Education (CMKP) in Warsaw, the Department of Surgery CMKP in Warsaw, and the Pain Clinic and Palliative Care Clinic of Jagiellonian University Medical College (CMUJ) in Cracow, it was possible to stop the opioid intake completely.

Key words: neuropathy, chronic pain, dependence on opioids

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Introduction

Diabetes mellitus Type I is a disease based on total or near-total lack of insulin, which is caused by the destruction of the pancreatic β cells in the islet of Langerhans by an autoimmune process and which requires continuous substitution of this hormone. Some role is also played by genetic factors: 20% of patients have a positive family history for this disease and over 90% of patients have proven to be carriers of antigen DR3 and/or DR4. Treatment of Type I diabetes is based on insulin intake in the manner most resembling its physiological production. However, there are difficulties in treating diabetes due to an inability to imitate fully the physiological fluctuations of serum insulin concentration. Late complications of diabetes are divided into two groups. The first group is associated with large ves-

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sels, such as coronary heart disease due to atherosclerosis, obliterative atherosclerosis of peripheral vessels, cerebral vascular disease and cerebral ischaemic stroke. The other group involves small vessels and includes retinopathy, nephropathy and neuropathy. Scientific research supports the view that long-term complications related to small vessels are due to chronic hyperglycaemia. Therefore, improper treatment of diabetes predisposes patients for these complications. Diabetic neuropathy is one of the most common late complications of diabetes mellitus. In some patients neuropathy may be associated with disturbances within the autonomic nervous system [1].

Case report

A 32-year-old female patient with a history of diabetes since the age of eight. The diabetes was complicated by bilateral proliferative retinopathy, nephropathy and neuropathy of the coeliac plexus — Group III on the Mogensen scale — with a strong pain syndrome. Glaucoma of the left eye with partial loss of vision in that eye due to optic nerve atrophy. Caesarean section delivery. Duodenal ulcer. Treated with very high doses of strong opioids without success.

The patient was referred by her internist to the Pain Clinic at the Department of Anaesthesiology and Intensive Care Medicine in Warsaw. The reason for the referral was very strong pain localized in the upper abdomen which was not responding to strong opioids. On the day of admission on 8 August 2006, she was suffering from strong pain and reported its level at 10 on an 11-point numerical rating score (NRS); the NRS is a self-reporting measure of pain intensity where 0 means no pain and 10 relates to the worst pain imaginable. The pain was constant and accompanied by paroxysmal nausea and vomiting. The pain first started in July of 2004. According to the patient the onset of pain was strictly associated with the beginning of pregnancy. Initially the pain was paroxysmal in nature. Each pain attack would last for a week and was accompanied by persistent nausea and vomiting, the gastric contents periodically stained with fresh blood. The intensity of pain at the time of the attacks was reaching a score of 10 on the NRS scale. Periods between the attacks and vomiting were 6 to 9 days long. Starting in the eighth month of pregnancy, the character of the pain changed to being constant but the nausea and vomiting stayed persistently paroxysmal. The pregnancy ended on 14 March 2005 with the delivery of a healthy son. Immediately after the Caesarian section delivery there was a 10-day cessation of pain attacks.

Prior to her admittance to the Pain Clinic the patient was treated without effect with NSAID, weak opioids such as tramadol 600 mg IM per day and buprenorphine patches at 130 μg/h. She was then treated with pethidine IM 400–500 mg a day for 4 months and transdermic fentanyl at maximum dose of 300 μg/h. Finally, parenteral morphine was first applied intravenously and later, due to problems with the intravenous method, subcutaneously in increasing in strength doses.

At the time of admittance to the Pain Clinic the patient was on 2,000 mg of morphine per day. The daily dose was estimated by analyzing data on the number of written and paid for prescriptions received from pharmaceutical monitoring. Morphine was prescribed to the patient by her husband, a specialist in internal medicine, who had been treating his wife himself for two years without any consultation with pain specialists. The patient admitted to a daily dose of morphine of 700 mg, applied 5 times at 140 mg doses. Her husband stated that his wife had not been exceeding a daily dose of 200 mg subcutaneously or 80 mg intravenously. No initiation of treatment with co-analgetics commonly applied in neuropathic pain treatment had been attempted.

Results of diagnostic tests carried out prior to the first visit at the pain clinic are as follows:

1. Ht — 35%, Hg — 11.5 g/dl, Na — 135 mmol/l, K — 3.6 mmol/l, Ca total — 2.4 mmol/l, coagulogram: APTT — 30.1 s, INR — 1.1, gasometry pH — 7.44, p O2 — 68.7 mm Hg, PCO_2 — 38.4 mm Hg, BE + 1.5, glycaemia at 42 j insulin/day: 61–180 mg%.
2. Electrogastrography (22.04.05) — advanced abnormalities on record in the character of dyskinesis with distinctive bradygastria.
3. Ultrasound of abdomen — liver not enlarged, of normal echogenicity. Wall thickening of gall bladder to about 4 mm. Normal pancreas and spleen. Kidneys of normal size, properly localized, of normal echogenicity. No dilatation of pelvis of calices. Normal thin-walled urinary bladder.

At the Pain Clinic the patient was commenced on the following: venlafaxine 75 mg/day, gabapentin (Neurontin) 3 × 100 — 3 × 300 mg, mebeverine HCl 2 × 1 tablet, lactulose 3 × 15 ml, omeprazol 2 × 20 mg, chlorpromazine 2.5 mg if vomiting persists. Additional advice included the following: prophylaxis of constipation, 6 easily-digest-

ible meals a day, control gastroscopy in order to exclude active peptic ulcer and gastro-oesophageal reflux and gynaecologist-endocrinologist consultation in order to diagnose menstruation problems. Gastro-esophageal reflux, active duodenal ulcer, oesophageal hiatal hernia, porphyria and thyroid hormonal imbalance were all excluded. Gastroscopic examination results: "Esophagus without pathologic changes. Ventricular mucus pale, atrophic. Prepyloric part congested. Pylorus narrow, permeable. Duodenal bulb and its distal part without pathological changes".

The patient was referred to the Department of Pain Treatment and Palliative Care of CMUJ in Cracow, where she stayed from 9 to 18 October 2006. On admittance to the hospital she was experiencing strong pain localized in the upper abdomen and, in order to settle, she required a constant intravenous infusion of morphine at the dose of 1,000 mg per day. Pain was accompanied by nausea and vomiting "coffee-ground" contents. Surgical consultation: patient suffering a great deal, lying on one side with aggravated vomit reflux.

On palpation abdomen soft, peristalsis present. Lack of bleeding in gastroscopy but presence of "coffee-ground" content; hysterical reaction to examination. Examination of duodenum was not possible. According to the surgeon's advice, null diet, drip infusion and antiemetics such as ondansetron, metoclopramide and haloperidol were administered. After 2 days, the vomiting stopped but the patient still required morphine infusion. On 16 October 2006, a diagnostic/prognostic coeliac plexus blockade was performed under X-ray control. The blockade was carried out under a local anaesthetic and steroid. Following the procedure the pain subsided and conversion to oral intake of morphine was attempted, unfortunately without success. One positive effect of the block was an indication of bilateral thoracoscopic splanchnicectomy. The previously recommended treatment was continued. It included the following: gabapentin, venlafaxine, omeprazol, lactulose and insulin, and additionally cisapride 3 × 10 mg 15 min before meals, pentoxifylline 3 × 100 mg, alpha-lipoic acid 2 × 600 mg added by a diabetologist. The procedure of the thoracoscopic splanchnicectomy was undertaken at the Department of Surgery at CMKP on 2 November 2006. The surgery was performed on the patient while she was face-down under general anaesthesia — TIVA with propofol. The face-down position allows for easy access to both pleural cavities and the patient does not need repositioning on the operating table during the procedure. The surgery itself and the perioperative period were free of complication. It was possible to achieve complete pain alleviation and a reduction in the frequency of vomiting to one or only a few episodes per day over the following three weeks. Following the surgery, the parenteral dose of morphine was reduced gradually over a few days to 100 mg a day. It was not possible to reduce the daily dose below 60 mg or to switch the patient to oral therapy, despite a number of consultations with the Addiction Clinic at the Institute of Psychiatry and Neurology in Warsaw and numerous consultations with a psychotherapist. The patient had been constantly demanding parenteral dosing of opioids. The difficulty in treating the patient was due to weak cooperation from the family; especially from the patient's husband. Since no ambulatory treatment was possible the patient was once again referred to the Department of Pain Medicine and Palliative Care in Cracow, where she stayed from 27 November 2007 to 11 January 2008. According to the psychiatric consultation: "Patient well-oriented with good but superficial verbal contact. She complains of anxiety and frequent awakenings at night. Addicted to morphine, currently reducing the dose". Treatment with methadone was implemented. The dose of methadone at the end of the hospitalization was 3 × 15 ml with the recommendation of gradual reduction, which was possible to achieve. In agreement with the psychiatrist, pharmacological treatment was changed to the chrono form of valproic acid 2 × 500 mg, pernazine 25 × 25 × 50 mg, atorvastatine 20 mg, ramipril 2.5 mg at night. Treatment in this form was continued. Recommendations for the future were a total ban on the parenteral intake of opioids.

Improper management of neuropathic pain may lead to addiction to opioids. Thanks to a proper diagnosis and the complete reduction of pain, it was possible to reduce the patient's addiction to high doses of morphine.

Discussion

Diabetes mellitus Type I is a disease caused by destruction of the pancreatic β cells in the islet of Langerhans by an autoimmune process, leading to a total lack of insulin which requires continuous hormonal substitution. Vascular complications of diabetes may be divided into non-specific macroangiopathy and microangiopathy, the latter being specific to diabetes and characterized by a thickening of the basement membrane of the capillaries. It

seems that hyperglycaemia leading to the glycation of proteins within the basement membrane plays some role in the process resulting in microangiopathy. This conclusion was drawn based on the fact that the thickness of the basement membrane correlates to the duration of the diabetes. Microangiopathy may lead to necrosis of peripheral tissues even in the presence of a peripherally-detected pulse. With both types of diabetes, diabetic nephropathy appears in approximately 35% of patients after 25 years of illness. It may lead to severe kidney failure requiring dialysis. DM I leads to glomerulosclerosis — Kimmelstiel-Wilson syndrome. Our patient had been diabetic for 24 years and had developed diabetic nephropathy. Diabetic retinopathy comes after 15 years of illness with Type I in 90% of patients and in 25% of those with Type II. Angiogenesis is a pathological process due to the production of growth factors on the basis of metabolic disturbances. The disease may take the course of simple retinopathy or proliferative retinopathy. The former is characterized by angiogenesis within the optic nerve head or in the adjacent retina. Angiogenesis may also take place in the corpus vitreum. Late complications include retinal separation and glaucoma [1]. The reported case had both disorders: proliferative retinopathy and glaucoma. Diabetic neuropathy is valued at 50% after 10 years of illness. Pathogenesis of neuropathy remains unclear. It is proposed that it is the result of a disorder in the microcirculation within nerves and the metabolic disturbances in diabetes. The most common type of polyneuropathy is peripheral sensory and motor neuropathy, which particularly affects the distal parts of the limbs. It manifests itself by symmetrical paresthesias, particularly of the lower limbs and feet — burning feet syndrome — and bilateral loss of Achilles tendon reflexes. The second-most common diabetic neuropathy is autonomic neuropathy. It is the consequence of lesions within the sympathetic and parasympathetic autonomic nervous system [1]. For instance, it may involve the coeliac plexus, which is of mixed type, built from both sympathetic and parasympathetic nerve fibres of the vagal nerve. This form of neuropathy was the most probable cause of pain in our patient. Neuropathy can also involve the digestive tract due to lesions within the parasympathetic system. It may lead to disturbances in motor function of the oesophagus, dysphagia as well as gastroparesis [1]. Impaired functioning of the digestive system was also described in the case of our patient. It seems that she suffered from neuropathic pain originating in the coeliac plexus. Neuropathic pain is the pathological type that is initiated or caused by primary damage to the central or peripheral nervous systems. The definition of neuropathic pain includes various pain syndromes which lack a common aetiology and do not result from the same kind of disorder within the autonomic system. Despite a different aetiology and variability in lesions, many of the neuropathic pain syndromes have common clinical features, such as a lack of easily-noticeable damage, a paradoxical combination of sensory depletion and hyperalgesia within the painful area, and paroxysmal pain which may become constant. Although there are common clinical features for various neuropathic pain syndromes, which could suggest similar pathogenic mechanisms resulting from hyperexcitability of peripheral and central neurons, the pathogenesis of this type of pain might be the result of many additional factors, such as a receptor component or sympathetic system dependency. All these factors are responsible for a highly variable success rate in the treatment of neuropathic pain [2, 4].

The treatment optimalization route chosen for patients with neuropathic pain is based on an understanding of the mechanisms responsible for inducing pain in an individual patient and the choice of treatment specific to a particular mechanism. The results of experimental research point to at least three components, which coexist as to which is responsible for the initiation of neuropathic pain. The first component involves changes in the electrical excitability of cellular membranes of the damaged axon or spinal ganglion of the first afferent neuron. The second involves changes in the processing of received signals in the posterior horn of the spinal cord. The third points to the higher floor of the central nervous system, where disintegration of programmed and coordinated responses to stimuli affects the system's integrity. Despite the similarities in pathogenesis and symptoms of neuropathic pain, regardless of the type of damage, the classification of neuropathic pain is most frequently based on the probable cause of pain in an individual patient. This approach allows implementation of optimal therapy; invasive techniques are as worth considering as treatment with pharmaceuticals with different action mechanisms [3-5]. The effectiveness of classical analgetics, including the most commonly-administered NSAID, is relatively small. These were not effective in the case of our patient. In the US over 50% of patients with neuropathic pain receive weak or strong opioids. The effectiveness of opioids in the treatment of neuropathic pain has been prov-

en but varies from being very high, even though applied in much higher doses than in nociceptive pain, to completely ineffective. In the case of a complete lack of noticeable therapeutic success after the implementation of opioid treatment, withdrawing from the treatment is advised. If unsuccessful opioid therapy is not abandoned soon enough, it can potentially, in only a short time, cause addiction to this group of pain medication [4]. In the case of our patient, tramadol, buprenorphine, pethidine and fentanyl appeared to be ineffective, and finally the administered morphine led to the necessity of a high parenteral dosage intake in a short period of time. Before her arrival at the Pain Clinic, no one had tried the other groups of medication which are recommended in the treatment of neuropathic pain and are characterized by low NNT (Number Needed to Treat). The NNT relates to the number of patients who are given a particular agent in order to achieve a 50% reduction in pain in one of them at the 95% confidence interval. The lowest NNT belongs to tricyclic antidepressant drugs with amitryptilline (NNT = 2.4), anticonvulsants (NNT = 2.2–3.8), carbazepine, oxycarbamazepine, phenytoin, gabapentin, pregabalin, lamotrigine, valproic acid, and local anaesthetics [4]. At the Pain Clinic our patient was started on gabapentin at 900 mg a day; later on, valproic acid chrono at 600 mg per day and venlafaxine at 75 mg a day were added. Amitryptilline was not administered due to the history of glaucoma. Unfortunately, this treatment has brought no success.

Neurophysiological and neuroimmunological tests for the mechanisms of pain have pointed to the important role of the autonomic system in the modulation of the nociceptive process and has laid new bases for the treatment of pain. Neurodestructive procedures on the sympathetic system turned out to be successful in treating many pain syndromes, especially in the case of the coeliac plexus [6]. In the case of the patient presented here, a diagnostic-prognostic blockade of the coeliac plexus with a local anaesthetic and steroid was first performed. Only after receiving a satisfactory result of the blockade was the decision made to perform bilateral thoracoscopic splanchnicectomy. The procedure is based on sectioning the coeliac nerves within the thorax. Two trocars are inserted into the thoracic cage: one just below the scapular angle, the other into the intercostal space below and closer to the spine. Under visual control, following earlier lung deflation using a harmonic knife, a cut in the visible nerve branches is made. It is usually possible to cut 4 to 7 branches on each side. The procedure is always started on the left-hand side since it is the more difficult side on which to operate and is more time-consuming because of the less transparent pleura. After the procedure on the left is finished the lung is expanded and left without drainage. Next, the procedure is carried out on the right-hand side. The time required for the procedure on each side is approximately 10–15 minutes. Following the surgery, the double-lumen endotracheal tube was replaced by a standard endotracheal tube and the patient was put on controlled pressure support ventilation in order to ensure proper lung expansion [7].

As a result of the procedure our patient was free of pain and it very quickly became possible to reduce her need for morphine from 2,000 mg to 100 mg a day. The minimal daily dose of morphine was reduced to 60 mg a day but complete elimination of the opioid from the treatment or the changing of its route to being parenteral or subcutaneous could not be achieved. Difficulties in managing the patient on an ambulatory basis resulted from the lack of cooperation from the patient's family, especially her husband who, despite being informed of the strategy behind the treatment, persisted in increasing the subcutaneous dosage of morphine.

In managing intense chronic non-cancer pain we can reach for strong opioids, but continuation of the opioid-based therapy is justified only in case they had been proven beneficial. The route of administration for the opioids should be either enteral or subcutaneous. Each doctor prescribing opioids should be aware of the risk factors and methods for diagnosing opioid dependency [8]. The patient's husband was not cautious enough and made a number of errors in managing her pain which, as a consequence, led to his wife's addiction to opioids. Finally, the plan to eliminate the intake of opioids by our patient completely was undertaken in the Department of Pain Medicine and Palliative Care of CMUJ in Cracow.

There are two major routes of treatment for opioid addiction: one based on drugs which reduce the discomfort due to the discontinuation of opioid intake; and the other based on agents that do not reduce addiction but lower opioid activity. Substitutive treatment is an oft-employed method of addiction therapy with the use of a substance having an opioid-like course of action and, thus, being the agonist of the opioid receptor. This agonist is administered to the addicted patient in order to transform the addiction to a more controllable form. The

managing of addiction with an agonist prevents abstinence syndrome, reduces the health and social consequences of addiction and, implemented in the proper dosage, lowers the psychological need for opiates. Methadone is one example of an opioid agonist. Conditions for methadone therapy have been established by the Ministry of Health in two sets of regulation in 1999 and 2004 [9]. Our patient underwent this therapy and positive results were achieved.

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