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Chronic use of opioids in a patient with Ehlers-Danlos syndrome — a case report

Abstract

Ehlers-Danlos syndrome is not a well-known condition and often remains undiagnosed. Causal treatment does not exist, but there are numerous symptoms requiring symptomatic therapy. One of these, a particularly nagging one, is chronic pain. A lack or insufficiency of treatment can greatly disturb the everyday functioning of patients. Currently chronic pain is considered a disease in itself requiring treatment. Recommendations to use opioid painkillers for chronic non-cancerous pain have already been developed. This paper presents the case of a patient suffering from Ehlers-Danlos syndrome, who was administered opioid treatment due to nagging pain.

Key words: Ehlers-Danlos syndrome, chronic pain, opioids

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Introduction

Ehlers-Danlos syndrome (EDS) includes a group of diseases caused by genetically predisposed defects of collagen and metabolic disorders of connective tissue. Lesions concern mostly joints, skin and walls of blood vessels [1]. Heredity is most often autosomally dominant and the syndrome appears in approx. 1 in 5000 live births [2].

The clinical image is dominated by symptoms of excessive joint mobility. The skin is very flexible, prone to damage. Some patients suffer from vessel brittleness and related breakage of large vessels (mostly of the vascular type), heart defects and vision problems.

A total of six main types of EDS have been distinguished, defined by the dominant symptoms [1]:

— classic type — excessive mobility of joints, subluxations, increased flexibility of skin, "velvet skin";
— type with excessive joint mobility — joint symptoms are dominant;
— vascular type - vessel brittleness, ecchymoses, thinner skin;
— type with kyphoscoliosis — excessive joint mobility, thinner skin, innate, progressing kyphoscoliosis, ruptures of the eye-ball;
— type with joint flaccidity- excessive mobility of joints, subluxations, increased flexibility of skin;
— type with decreased joint flexibility — loss of skin flexibility, ecchymoses, proneness to hernias.

The appearance of a patient with EDS is characterised by decreased muscle tension, flat feet, knee valgosity, winged scapula, spine curvature, and chest deformation.

The most frequent problems include pain, decreased physical fitness, injuries difficult to heal. Ophthalmological problems and symptoms related to the alimentary or urinary system can occur. Vas-

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cular symptoms are dominated by problems of the cardiovascular system, such as mitral valve prolapse and aortic aneurysms. Abnormal bleeding may cause periprocedural complications.

In the case of pregnancy we may expect obstetrical complications, such as uterus rupture during birth, injuries of the vagina and perineum, haemorrhage and ruptures of blood vessels and large intestine during puerperium. A C-section is recommended in this situation.

The patients require multi-specialist medical care throughout their lives.

The prognosis in EDS patients depends on the type of syndrome. Increased risk of life-threatening complications is related to the vascular form. These types of complications are rare in childhood, they occur in 25% of patients before the age of 20, and 80% before the age of 40. The median survival time in the vascular type is 48 years, while in other EDS types no significantly shortened survival time is observed [2]. The degree of symptoms intensity is very individual, from barely noticeable to seriously limiting functioning in everyday life.

People suffering from EDS often encounter various social obstacles resulting from the lack of knowledge of the disease as well as a lack of its recognisability. This may cause isolation, lead to frustration, stress and depression.

Case description

A patient, 26, with a diagnosed classic type of EDS was sent to the Clinic of Palliative Medicine on 1st October 2008 due to pain in the lumbar part of the spine radiating mostly to the left lower limb. The pain was dull, constant, on average 7/10 in the numerical rating scale (NRS). Additionally fits of pain occurred, described by the patient as "drilling, acute", 10/10 in the NRS. The cause of pain fits is difficult to determine; most frequently it was long-lasting immobility. The pain occurred 1–2 times a day, but there were also painless days. The pain usually lasted the entire day, but its intensity largely depended on the motor activity. The ailment intensified when standing or sitting, and at the end of the day. Moreover, stressful situations, weather conditions (cold, damp), as well as menstruation increased the pain. The pain was accompanied by numbness of the left lower limb, increasing when remaining for long periods in the sitting position. Relief was achieved by decompressing positions. The patient slept well at night; sometimes not feeling pain for a short period of time after waking up. Moreover, the patient experienced minor pain of the knee joints, numbness of the 4th and 5th fingers of both hands, and vertigo.

The physical evaluation indicated good general condition, the patient being cardiovascularly and respiratorily stable. Flaccidity of all joints, with increased movement range, and flat and valgus feet with deformations of the 4th toe of both feet (pulled back, overlaying others) were diagnosed. The examination showed lateromedial instability of the knee joints. During passive movements the patient reported increased pain, mostly in knee, shoulder and elbow joints. Moreover, characteristics of pectus excavatum and pain of the thoracic spine while bending and deflecting to the left were observed (straightening and deflecting to the right not painful). The skin on the back was flaccid, flexible, with a healed, post-procedural scar. Laseque Sign bilaterally negative. Movement in the shoulder joint limited due to pain. Moreover, hyperextension in wrist and knee joints, pain and sensory disorders on the lateral surface of thigh, frontolateral surface of shin and back of left foot were observed.

The magnetic resonance imaging of the lumbar spine performed earlier (7th December 2004 and 23rd May 2006) showed a significant S-shaped curvature of the imaged part of the spine. In the lower part of the lumbar spine the roots of cauda equina were modelled on the curved lateral wall of the spinal canal. An MR image of the lumbar spine performed 6 weeks before referring the patient to the Clinic of Palliative Medicine (of 14th August 2008) showed more visible protrusions of intervertebral disc L5–S1 and its indentation into the spinal canal. The disc pressed on the front wall of the thecal sac, but not on the neural roots.

The patient had been diagnosed with EDS by the age of 8 months. Until the age of 4 she was treated by Centrum Zdrowia Dziecka (Children's Health Institute) in Warsaw, and since she was 5, that is since 1987, she has been under the care of the Orthopaedics Chair and Clinic of the Medical Academy in Poznań. Her health and physical fitness have deteriorated gradually.

At the age of 14 (1996) a spondylodesis of Th-10 to L-5, and then 3 years later (1999) a procedure for removing implants and revision of the spondylodesis were performed. Since approx. 1997 the pain in the lumbar part of spine, radiating mostly to the left lower limb, have been intensifying.

At the age of 20 (2002) the patient was hospitalised due to severe pain of the knee joints making it impossible for her to move on her own. The use of elbow crutches was impossible due to the over-

loading of the upper limbs joints. The patient moved using a wheelchair and partially with a walker. However, due to the spinal pain, she was mostly lying. She was equipped with a standing frame, orthosis, orthopaedic jacket and stabilisers for the wrist joints; she was mostly using the jacket. It was found that the stabilisers and orthoses could not be used due to limb oedemas.

During this period (2002), the patient experienced symptoms of depression, which were relieved after the inclusion of paroxetine.

For several years until this point, the problems with micturition and eye fixation had been intensifying. Progressing loss of vision, despite glass correction and special prismatic lenses, left the patient unable to read.

Moreover, internal chronic hydrocephalus, osteoporosis and mitral valve disease were diagnosed.

At the moment of referral to a specialist of palliative medicine, the patient was under constant care of the Neurological, Pain Treatment, Orthopaedic and Rehabilitation Clinics.

The patient had so far used various forms of pain treatment: regular rehabilitation, including annual rehabilitation camps, psychotherapy, acupuncture and TENS (the effects of the last two methods were evaluated especially well). At the same time pharmacological treatment was given. The medicine the patient was administered included: glucosamine sulphate, alendronic acid, ketoprofen in gel, morphine, codeine, tramadol, ibuprofen, ketoprofen, meloxicam, and paracetamol with codeine. Moreover, the patient received doxazosin and, due to the mitral valve disease, metoprolol and magnesium.

From the beginning no response to tramadol was observed. Previously for a long period she used non-steroidal anti-inflammatory drugs; however, they were discontinued, probably due to the possibility of complications. Morphine was introduced, but as the attending physician wanted to avoid dependence, the patient was instructed to use it only extemporaneously in case of very strong pain. As, in reality, it required administering 10 mg of morphine several (3–6) times a day in an immediate-release preparation, she was referred to the Clinic of Palliative Medicine. Apart from 10 mg immediate-release morphine, she was at the same time taking 20 mg paroxetine in the morning, 300 mg valproic acid, alendronic acid, vitamin D_3, glucosamine sulphate, metoprolol and ketoprofen 100 mg/day or interchangeably meloxicam 15 mg 1–3 times a day. This might have stemmed from the fact that the patient was not treated by one doctor.

The patient said that she tried not to abuse the medicines, but she did not want the pain to exclude her from life. The patient was studying under an individual course of education, taking doctoral courses and working at home as a psychologist. During the first visit to the Clinic of Palliative Medicine it was evaluated that the pain was effectively relieved with morphine, thus it was introduced in a controlled-release preparation 2 × 30 mg — and 5 mg as needed in an immediate-release preparation (solution). Moreover, in case of pain paracetamol was recommended (1–3 times a day), although at the request of the patient, who evaluated highly the efficiency of the paracetamol and codeine preparation in the form of effervescent pills (500 mg and 30 mg, respectively) such a treatment was accepted. A small dose of baclofen (1 × 5 mg) was given due to increased tension of paraspinal muscles. Lactulose 3 × 15 ml and a diet rich in fibre were recommended to prevent constipation. The administration of non-steroidal anti-inflammatory drugs was discontinued due to their long-term use of high doses and poor efficacy. After 2 days pain control improved, and after 2 weeks the patient reported that she could finally function in a normal manner. For approximately a year the pain was fairly well-controlled. During that time the dose of intermediate-release morphine for breakthrough pain was increased to 20 mg (average 3 times a day), and the patient still took paracetamol with codeine (up to 1 pill 3 times a day) in case of pain. The attempts of increasing the dose of controlled-release morphine did not have a good result — the patient felt excessive drowsiness and apathy, and she evaluated the control of pain as insufficient. This partly resulted from the fact that the pain intensified depending on the intensity of physical effort, time of day (greater in the afternoon), weather conditions and stress. Distinctly stronger pain was felt during menstruation. The rehabilitation and psychotherapy described above were used simultaneously with the pharmacological treatment.

In June 2009 during a 4-week hospitalisation in the Rehabilitation Department the patient observed an intensification of pain. The cause was probably increased physical activity. The patient took medicines as before. After returning home, the pain decreased.

In July 2009, after a fall where she landed on her buttocks (while walking), the pain in the lumbar part of spine, radiating mostly to the left lower limb, intensified. In a radiological test no bone fracture was observed. Ketoprofen was introduced and, due to the lack of effect, was changed for lornoxicam, and

used for a short period of time. At the same time the patient began taking more doses of immediate-release morphine (30 mg even every 4 hours), continuing the dose of controlled-release morphine as well. Attempts of decreasing or skipping a dose of morphine resulted in such an intensification of symptoms that normal functioning was impossible. An MR image of the lumber spine taken in this period (7th August 2009) showed a high degree of short arc scoliosis of the lumbar spine with rotation of the vertebral bodies and characteristics of lateral listhesis (7 mm) at the level of L2/L3. At the level of L1/L2 and L5/S1, subligamental protrusion of intervertebral discs with modelling of the thecal sac was seen. The other levels showed no characteristics of vertebral canal stenosis.

In November the patient was hospitalized in the Orthopaedics and Rehabilitation Department in Zakopane for three weeks. During the stay the pain was significantly relieved and patient's wellbeing improved, which led to a decrease of additional immediate-release morphine doses taken in case of pain (the patient took 30 mg of morphine 2–3 times a day).

At the end of January 2010 the pain intensified, the symptoms linked by the patient to examination session (stress, forced position while studying). Currently the patient takes 2 × 30 mg of controlled-release morphine and immediate-release morphine usually 20–20–50–50 mg (at night she does not take immediate-release morphine). Such a scheme allows the patient to function satisfactorily. The patient reports the pain as 2–4/10 on the NRS. In March 2010 she complained about constipation for the first time. It was discovered that the patient did not take the recommended laxatives regularly. Good control over defecation was achieved using lactulose.

Discussion

Ehlers-Danlos syndrome is a disease where pain is one of the basic symptoms, often accompanying patients for most of their lives. The degree of symptom intensity is highly changeable and partly depends on the type of syndrome. In most patients it is not treated properly, which greatly affects the psychosocial functioning of people with EDS. Despite the fact that the presence of pain is part of the disease, so far no clear rules of pain treatment in patients with EDS have been developed.

In 1995 in USA (General Clinical Research Center of the University of Connecticut Health Center in Farmington) 51 patients with EDS were evaluated using a short questionnaire; it evaluated the character of pain, its influence on psychosocial functions, and methods of treatment. The study showed that 46 of the patients had suffered from chronic pain for 6 months or longer, and only 2 adult individuals were free from chronic pain; 43 reported that the pain started in an early period of life and intensified over time.

In 70% of participants the pain affected the lower limbs, ankles, feet, hands, spine and hips. In 70% of cases the pain had a significant influence on the functions in everyday life. Only 11.8% of the participants indicated that the pain had no influence on their everyday lives. 5% of the participants used non-pharmacological means of pain treatment: TENS, relaxation, diet, or a water bed; 88% took pharmacological preparations and 51% "had taken narcotics" [3].

The mechanism of pain formation in patients with EDS is complex. It might be secondary to frequent dislocations, result from injuries of the soft tissues, nerve damage or surgery. The role of the psychogenic mechanism is also significant. Getting to know these mechanisms should allow the determination of guidelines for pain-killing treatment for these groups of patients.

At the moment we can only rest on the recommendations for chronic pain treatment in non-cancer patients. According to the analgesic ladder, pain-killers are divided into 3 groups: non-opioid analgesics (paracetamol and non-steroidal anti-inflammatory drugs — NSAIDs), weak opioids and strong opioids.

The use of NSAIDs seems to be significant, especially when the pain has an inflammatory component. It should be remembered, however, that long-term use bears a great risk of complications on the part of gastrointestinal tract, kidneys, blood-forming and circulatory system. Thus they were not introduced as a basic treatment for our patient. It is also worth noting here that the use of NSAIDs should be especially cautious in the vascular type of EDS due to an increased risk of haemorrhages. The use of paracetamol as an independent medicine was not found to be a particularly effective form of pain treatment. An attempt to introduce tramadol did not bring the expected benefits either. In addition, combination of tramadol with paroxetine (prescribed earlier for depression) may increase the risk of serotonin syndrome, thus they should not be used concomitantly. Only the use of morphine, requiring dose increases in a relatively short period of time, led to pain relief to the extent that the patient could quite satisfactorily function in everyday life.

While taking morphine, for a short period of time the patient took paracetamol with codeine in case of pain, although such intervention does not seem pharmacologically justified. What is more, paroxetine (prescribed ealier to the patient) as a CYP2D6 inhibitor, may block the biotransformation of codeine to morphine. As a result, codeine might lack significant analgesic activity. However, the attending physician agreed to try the treatment due to a definite request from the patient resulting from the efficiency of these preparations observed by her. It was found quickly that the treatment was not a success, and the dose of immediate-release morphine had to be increased (and codeine with paracetamol discontinued).

We might ask whether starting morphine was a good decision?

The problem of using opioids in chronic, non-cancerous pain is still significant, although in the recent years we have been observing the more frequent use of these medicines in this group of patients. The American Pain Society (APS) in cooperation with American Academy of Pain Medicine (AAPM) has recently published guidelines on chronic opioid treatment of adult patients with chronic non-cancerous pain. According to their guidelines [6]:

1. Before the beginning of chronic treatment with opioids, doctors should take the medical history, perform a physical examination and other appropriate tests, including risk evaluation of abuse, improper use or dependence on medicines.
2. In starting chronic opioid treatment, doctors need to obtain the patient's informed consent.
3. Doctor and patients should treat the initial opioid treatment as a therapeutic trial to determine whether chronic opioid treatment is the appropriate course of action.
4. Methadone is characterised by complicated and changeable pharmacokinetics and pharmacodynamics, thus the beginning of treatment and dose titration should be conducted by a doctor well-acquainted with the codes of practice concerning use and related risks.
5. Doctors should assess opioid-treated patients periodically, and after any change of circumstances.
6. Doctors may consider chronic opioid treatment in patients with chronic non-cancerous pain, whose history shows medicine abuse, mental disorders or serious pathological behaviour related to medicine administration - but only if there is a possibility of introducing more frequent and strict monitoring.
7. In patients showing pathological behaviour related to medicine administration, doctors should evaluate whether the opioid treatment is appropriate, the necessity to reorganise care or refer to a specialist, or the need to discontinue chronic opioid treatment.
8. If doses during chronic opioid treatment are increased numerous times, doctors should evaluate potential causes and consider once again the rate of benefits to risks.
9. Doctors should consider rotation of opioids when a patient receiving chronic opioid treatment experiences intolerable adverse effects or the clinical benefits are not satisfactory despite increased doses.
10. Doctors should decrease the dose or discontinue chronic opioid treatment in patients showing pathological behaviour related to medicine administration, abusing the medicine or taking it arbitrarily, not showing progress with regard to treatment or experiencing intolerable adverse effects.
11. Doctors should expect, diagnose and treat frequent adverse effects resulting from opioids.
12. Since chronic non-cancerous pain is often a complex biological, psychological and social problem, doctors using chronic opioid treatment should routinely include psychotherapeutic interventions, methods of restoring functioning and other supplementary methods of treatment.
13. Doctors should inform patients chronically treated with opioids about temporary or permanent impairment of cognitive functions, which may influence safety while driving or working. Patients should be advised not to drive a car or perform potentially dangerous activities when they do not feel well or will be diagnosed with symptoms of impaired fitness (in Poland people taking opioid drugs are forbidden to drive mechanical vehicles at all).
14. People chronically treated with opioids should have a doctor to assume the main responsibility for their entire medical care.
15. In patients with breakthrough pain during regular (taken at regular times) chronic opioid treatment doctors may consider breakthrough doses of immediate-release opioids, depending on initial and regular analysis of the benefits and risks rate.

According to Polish guidelines, strong opioids may be used in chronic non-cancerous pain when [5]:

— patient suffer from constant pain;
— pain lasts for more than 3 months;
— pain is very strong, more than 5 in VAS;

— pharmacological treatments to date have been unsuccessful;
— to date treatment causes adverse effects;
— combined treatment does not give good results;
— there are no other, e.g. surgical, possibilities of treatment;
— pain is ruining patient's life (loss of job, family, no possibility of movement);

All the above criteria fulfilled in the patient. They were no contraindications for opioid treatment in patients experiencing chronic pain, which include [4]:
— alcoholism;
— earlier periods of addiction to opioids or other medicines;
— mental illnesses.

A "gold standard" of non-cancer pain therapy is the determination of its cause and selecting a cause-oriented treatment. Opioids should be used when other methods of treating chronic pain have failed, and the decision to treat with strong opioids should be made after consultations with the patient and their family. The patient must be informed in detail about the nature of opioid treatment, its dosing, effect, possible adverse effects and methods of their prevention and coping with them. The fact of conducting such conversation must be at least included in the medical documentation, although the Polish Pain Society recommends also giving patients written information about opioids.

The aim of using opioids is not only pain relief, but the improvement in the patient's functioning. Thus, if pain is relieved, patients may return to such activities as rehabilitation, which is a necessary element of combined treatment.

It is also important to start treatment with strong opioids after consulting, or when ordered by Pain Clinic. A specialist in pain medicine should evaluate whether other methods of treatment have been unsuccessful and if a combined treatment has been used at all. Moreover, it is recommended to perform an evaluation of risk of opioid addiction in a given patient and use pharmacological tests or appoint a trial period for the thorough monitoring of the clinical effect of opioids and their influence on the patient's functioning.

The decision to apply regular morphine treatment was discussed with the patient by a consulting specialist in palliative medicine, considering any adverse effects that might occur during therapy. The doctor evaluated that the treatment to date (including therapy applied by a doctor from the Pain Clinic) was of insufficient effectiveness and there were indications to start opioids. He assessed that the risk of opioid addiction was low. It was established with the patient that he would be the only doctor prescribing opioids. The degree of pain intensity, life quality, condition of motor activity, both before and during the treatment were evaluated [5]. The analyses showed an improvement in life quality and a lack of significant adverse effects. The patient experienced constipation temporarily but good control of defecation was achieved with regular use of purgative preparations. The method of administering morphine, especially frequent use of immediate-release preparations may lead to some doubts. It is generally recommended to use controlled-release preparations for the treatment of chronic non-cancer pain. In the case of our EDS patient the presented method of administering morphine resulted from very significant changes in pain intensity that were dependent on circadian rhythm, movement, menstruation and stress level. The patient was observed cautiously but no behaviour indicating addiction was noted. The patient complied with the doctor's arrangement. The most convincing was improvement within both physical and cognitive activities, translating into the coping skills of a student and psychologist in a professional life. It does not, however, change the fact that our aim should be achieving good pain control by means of controlled-release preparations and avoid immediate-release preparations.

The important role of antidepressants in chronic pain treatment should also be kept in mind. They act as pain-killers — especially in neuropathic pain, have beneficial influence on mood and may improve sleep. The medicines used most often are tricyclic antidepressants (TCAs), serotonin–norepinephrine reuptake inhibitors (SNRIs) and, to a significantly smaller extent serotonin-specific reuptake inhibitors (SSRIs).

The patient was given paroxetine (an SSRI) due to depressive disorders. The medicine was continued due to good therapeutic results and no adverse effects.

In conducting pain-killing treatment in EDS we cannot ignore the most important method — rehabilitation. It has a pain-killing effect and allows patients to keep fit. The selection of exercises must be very individual, adjusted to the patient's possibilities. An important role in the treatment process is played by psychotherapy. The recommended methods include: relaxing breathing techniques, meditation and visualisation [3]. The patient has been rehabilitated since babyhood. It is thanks to this process that, to

some extent, she can function and walk on her own. Equally important is psychotherapy, which is an element of pain-killing treatment as well as a way of coping with the disease.

Summary

Ehlers-Danlos syndrome is a rare disease. The problem of pain concerns a high percentage of the patients with the syndrome. There are few publications on the disease concerning problems experienced by patients or methods of dealing with individual situations. This is true for both professional literature and self-help books for patients and their families. No guidelines for pain treatment in patients with Ehlers-Danlos syndrome have been established. Currently we can only rely on the guidelines for chronic pain treatment and codes of practice for using strong opioids in non-cancer pain.

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