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DENTAL PROBLEMS IN A PATIENT WITH THE CLASSIC TYPE OF EHLERS-DANLOS SYNDROME – A CASE REPORT*

PROBLEMY STOMATOLOGICZNE U PACJENTA Z TYPEM KLASYCZNYM ZESPOŁU EHLERSA-DANLOSA – OPIS PRZYPADKU

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Abstract

The huge progress in diagnostic and therapeutic procedures in developmental medicine allowed not only to save lives of many children and adolescents, but also enforced the necessity of close cooperation between many specialists.

Unfortunately dental treatment is still not an integral part of taking care of disabled children and youth with chronic diseases. The situation worsens, when we come across the so-called rare diseases. Lack of access to dental services, when it comes to disabled patients, results from financial situation, healthcare system, as well as parents' ignorance of necessity of more frequent prophylactic and treatment visits. Whereas the reluctance of dentists towards the care of disabled patients is caused by difficulties with enforcing the recommendations and lack of procedures for taking care of patients with rare diseases, which was repeatedly signalled by us. Such situation is ideally pictured by yet another described case of the 17 year old patient with Ehlers-Danlos syndrome. Despite many dental visits, no vital treatment decisions have been made. In our Department, in the procedures of 1-day surgery, tooth 48, being the cause of pain, has been extracted.

Basing on all of the above, it can be deduced that preserving the continuation and consequence in spreading the knowledge of rare diseases among patients, as well as physicians and dentists, is a responsibility of everyone who even once came across this problem.

Key words: Ehlers-Danlos syndrome, treatment, rare diseases

Streszczenie

Ogromny postęp w procedurach diagnostyczno-terapeutycznych wprowadzony w medycynie wieku rozwojowego umożliwił nie tylko uratowanie wielu dzieciom i młodzieży życia ale narzucił również konieczność bliskiej współpracy wielu specjalistów.

Niestety jednak, leczenie stomatologiczne w dużej mierze nadal nie jest świadczone jako integralna część opieki nad dziećmi niepełnosprawnymi lub obciążonymi chorobami przewlekłymi. Sytuacja jest jeszcze gorsza, gdy mamy do czynienia z tzw. chorobami rzadkimi. Brak dostępu pacjentów o zmniejszonej sprawności do stomatologa wynika z uwarunkowanego finansami systemu ochrony zdrowia, a także często z brakiem wiedzy rodziców oraz dzieci i młodzieży o konieczności częstego wykonywania zabiegów profilaktyczno-leczniczych. Niechęć lekarzy do opieki nad osobami niepełnosprawnymi ma swoje podstawy w trudnościach, z jakimi spotykają się w egzekwowaniu zaleceń oraz z braku procedur postępowania z pacjentami obarczonymi chorobami rzadkimi, o czym już wielokrotnie sygnalizowaliśmy. Sytuację tę odzwierciedla przedstawiony przez nas kolejny przypadek dotyczący 17-latka z zespołem Ehlersa-Danlosa. U chłopca pomimo licznych

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wizyt u stomatologa, nie podjęto żadnych istotnych decyzji leczniczych. W naszym Zakładzie, w ramach chirurgii jednego dnia usunięto ząb 48, będący przyczyną dolegliwości bólowych. Wypływa z tego wniosek ,że konsekwentne szerzenie wiedzy dotyczącej chorób rzadkich zarówno wśród pacjentów, jak i lekarzy, jest obowiązkiem każdego, kto choć raz spotkał się z tym problemem.

Słowa kluczowe: zespół Ehlersa-Danlosa, leczenie, choroby rzadkie

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In 1933 Achille Miguet in his doctorate research concerning the Ehlers-Danlos syndrome, stated that „Typical cases are rare, and such rarity can influence the insufficent knowledge of this issue" [1]. More than 80 years later, in 2015, the Ehlers-Danlos syndrome is still treated as a fairly mild, being rather an oddity, although long-standing medical considerations allowed to further the knowledge in this subject. The history of this disease dates back to the XVII century, when the Dutch surgeon Job Van Meeckeren described cases of a sailor and circus performer, whose skin was unduly stretchy. More than 200 years later, in year 1891, the dermatologist Czernogubow showed a case of a boy with thin skin, covered with numerous scars and bumps. He was the first to prove that the above mentioned symptoms indicate connective tissue abnormalities. Barely 8 years later, other dermatologist, Edward Ehlers, described a case of a law student with extreme fragility and stretchability of the skin, also with tendency for haemorrhages. Whereas in 1908, the French Henri-Alexandre Danlos intensified observations concerning the fragility and stretchability of the skin. The name Ehlers-Danlos syndrome was used for the first time by Miguet, and in 1936 Frederich Parkes suggested the name of skin and ligament Ehlers-Danlos Syndrome [2, 3].

EDS is an inherited heterogenous group of connective tissue disorders. Its incidence is from 1:5000 to 1:25 000 live births. Although it is probable that those estimates are lower than the real figures, due to the lack of correct diagnosis [4]. Initially according to the 1986 Berliner classification, 11 types of EDS have been recognized, but in 1997, during the conference in Villefranche only 6 types were left (tab. I) [5]. Yet due to the purely nosological type of present classification, the evolution of the terminology is not finished.

Most frequent type of EDS is classic subtype, in which the disease is not an uniform entity regarding the causes of occurrence and clinical manifestation. It manifests itself by unduly stretchy, thin skin, prone to injuries and hypermobility of the joints with tendency for luxations. Disturbances of posture, muscle and joint pain are also observed. In the places of prolonged pressure, hard, wax whitish bumps are reported (*molluscoid pseudotumors*). As a conseqence of collagen fibers laxity, cardiovascular disorders, such as mitral valve prolapse, and gastrointestinal tract disorders emerge. Apart from the above mentioned, such symptoms as „painful impatience", which stands for impossibility for holding one position, fatigue and drowsiness, awkwardness in walking, termoregulation disorders, painful and frequent urination, hypersensivity to light and nearsightedness can occur. From the dental point of view, most important are: periodontal disease, increased caries risk, temporomandibular disorders and decreased susceptibility to local anesthetics [6, 7].

The basis of EDS symptoms is the disturbance of collagen structure and function in connective tissue, caused by mutation of genes coding the collagen structure or regulating the post translational or post transcriptional protein processing. Most mutations of the gene responsible for EDS are caused by autosomal dominant mechanism, only in the case of kyphoscoliosis and dermatosparaxis type which are caused by autosomal recessive mechanism. The classical type EDS is caused by mutation in *COL5A1* and *COL5A2* genes, coding the collagen V chain [8].

The aim of the study was to present the dental aspect of Ehlers-Danlos syndrome, with a special aknowledgment for difficulties in treatment of patients with so called rare diseases.

CASE REPORT

The 17 y.o. patient with the classical EDS type II, reported to our clinic due to pain in the area of 48 tooth, radiating to the right temporomandibular joint and retromandibular space of the same side. The pain was sharp, permanent and 7/10 on the NRS scale. It intensified itself during the changing of position and at night.

During patient's first visit in our Department and thorough clinical examination, patient's mother handed us the medical documentation confirming the EDS.

Since childhood, the patient attracted attention by upper and lower limb joint hypermobility, but no tendency of luxations. In the age of 5 to 6 years old irregular activity and sleeping times occurred, and in high school dips of mood and learning difficulties showed. The above mentioned symptoms did not raise any suspicion regarding the disease. Joint hypermobility and son's lassitude and fatigue was treated by patient's mother as difficult growing up period.

In the end of year 2013, the patient reported to the dental office in the place of residence, for easing the

Table I. Classification of Ehlers-Danlos Syndrome.
Tabela I. Klasyfikacja zespołu Ehlersa-Danlosa.

Type *Typ*	**Previous name (Berlin-1986)** *Poprzednia nazwa (Berlin-1986r.)*	**Inheritance** *Dziedziczenie*	**Biochemical defect** *Defekt biochemiczny*	**Gene** *Gen*
Classical EDS *Klasyczny*	I, II	AD	Type V collagen *Kolagen typu V*	*COL5A1 COL5A2*
Hypermobility EDS *Z nadmierną ruchomością stawów*	III	AD	Tenascin b *Tenascyna b*	Unknown *Nieznany*
Vascular EDS *Naczyniowy*	IV	AD	Type III procollagen *Prokolagen typu III*	*COL3A1*
Kyphoscoliosis EDS *Kifoskoliotyczny*	VI	AR	Lysyl hydroxylase *Hydroksylaza lizynowa*	*PLOD1*
Arthrochalasia EDS *Z wiotkością stawów*	VIIA/VIIB	AD	Type I collagen *Kolagen typu I*	*COL1A1 COL1A2*
Dermatosparaxis EDS *Skórny*	VIIC	AR	Type I collagen N-proteinase *N-proteinaza kolagenu typu I*	*ADAMTS2*

pain of teeth and temporomandibular joints, which radiated to the whole face. After excluding the dental focal infection, the patient was referred for neurological consultation with the suspicion of trigeminal nerve neuralgia. During the waiting for the home specialist visit, the patient suffered from the seizures characteristic for epilepsy and was taken away to the hospital by paramedics. The EEG examination showed slight pathological changes in temporal sensors with the prevalence on the left side, without any convulsivity features. This single seizure incident was probably caused by the patient's alcohol overuse, who also suffers from heavy nicotinism (fig. 1). As the cause of his addictions, the patient points out the pain accompanying him during the everyday life and incomprehension of the environment, in which he was raised. During the hospitalisation, trigeminal nerve neuralgia was excluded, but due to the fact of not diagnosing the cause, carbamazepine treatment was induced, which is recomennded also in the case of epilepsy, psychological disorders and alcohol abstinence. Performed blood examination, magnetic resonance imaging of the head and echocardiography showed no pathological changes. Immunological diseases were also excluded. The patient was referred to genetic department for further diagnostics. After determining the correct kariotype, the specialist in genetics suggested a consultation in a renowed Department of Human Genetics in Poznan, where the patient went with a suspicion of Ehlers Danlos syndrome. In September of 2014 the initial diagnosis was confirmed.

In the October of 2014 the described pain cumulated, when the acute pain of tooth 48 emerged. The patient searched for help in a dental office, but after presenting the medical documentation, the dentist only prescribed an antibiotic. Such situation repeated itself in 6 consecutive dental offices. The desperate and helpless patient presented himself as a completely healthy person in the last visited office. Only then has the dentist begun to perform anesthesia using lidocaine, but due to the existing inflammation in the area of tooth 48 and resistance to lidocaine in the Ehlers Danlos syndrome, the patient declined the proposed treatment. After 3 months the patient came to our department, begging for help.

The extra oral examination showed normal body composition. The skin of the hands was thin, hyperelastic, and the hands were livid red (fig. 2). The patient was overall sluggish, with reportedly decreased mood.

Fig. 1. Yellowish fingers and nails of the left hand, caused by nicotinism.

Ryc. 1. Zażółcenie palców i paznokci lewej dłoni spowodowane nikotynizmem.

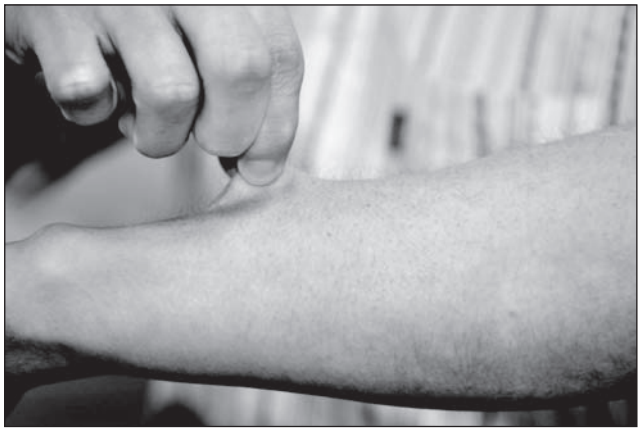

Fig. 2. Greyish-red hands and arms of the patient, with unduly stretchy skin.

Ryc. 2. Dłonie i ręce pacjenta były sinoczerwone, a skóra nadmiernie elastyczna.

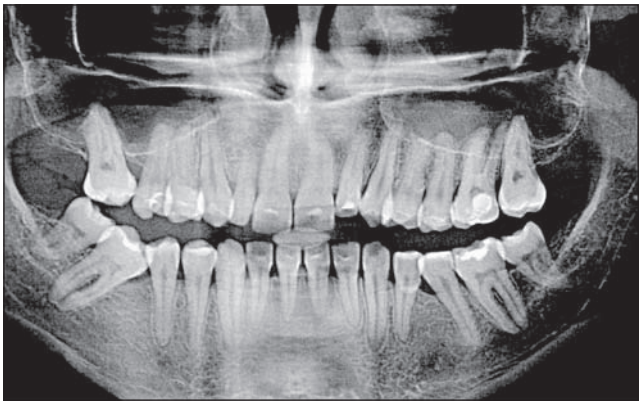

Fig. 4. Loss of maxillary and mandibular bone and tooth 48 caries, visible on the OPG.

Ryc. 4. Na zdjęciu pantomograficznym widoczne ubytki kości szczęki i żuchwy oraz próchnica zęba 48.

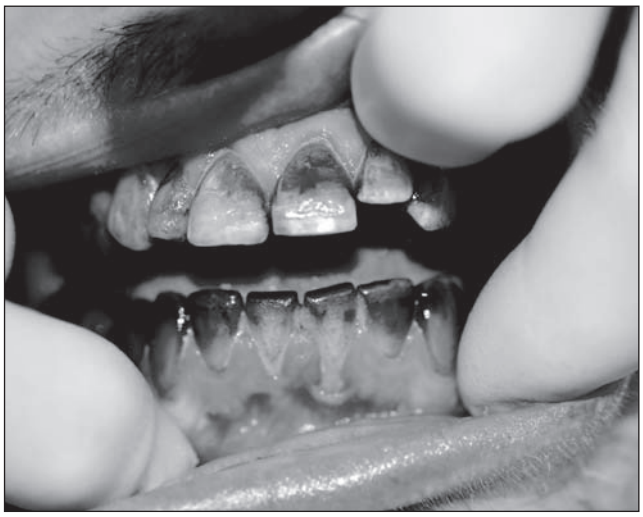

Fig. 3. Poor oral hygiene with general gingivitis.

Ryc. 3. Naganna higiena jamy ustnej z uogólnionym zapaleniem przyzębia.

tests analysis, the anesthesiologist tested the stability of respiratory muscles, the range of mandible discuasion and presented the patient with the essence of brief general anesthesia. After acquiring the written consent from the patient and his legal guardian, the surgery has been scheduled.

In general anesthesia, using propofol, the tooth 48 was surgically removed. The wound has been sutured, and the intra and post operative course has been uneventful (fig. 5, 6, 7).

After the surgery the patient has been transferred to the recovery room, where his condition has been monitored by specialists in oral surgery, anesthesiology and a nurse.

Special attention has been paid to the slow and step by step recovery of the patient, because every injury in a patient with EDS can end with haemorhage, skin injuries and joint dislocation. Furthermore, eventual respiratory problems, balance disorders, diplopia, pain

The intraoral examination showed lack of hygiene and overall periodontal inflammation with local loss of collagenous enthesis (fig. 3). During palpation, the pain of alveolar part of maxilla and mandible was observed and tooth 48 was acutely positive to horizontal and vertical percussion.

The pantomographic x ray showed visible horizontal bone loss in maxilla and mandible, caused by generalised inflammation of the oral cavity and profound caries in the tooth 48 (fig. 4).

The patient's mother and the patient were presented with diagnosis and surgical treatment plan, which included the removal of tooth 48 in the procedures of 1-day surgery.

During the surgical consultation, a specialist in anesthesiology was present. After filling out the anesthesiological questionnaire, apart from the laboratory

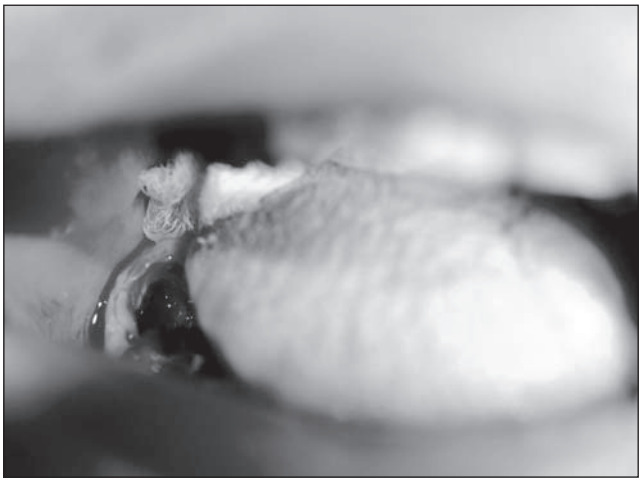

Fig. 5. Tooth 48 extracted under general anaesthesia.

Ryc. 5. W znieczuleniu ogólnym usunięto ząb 48.

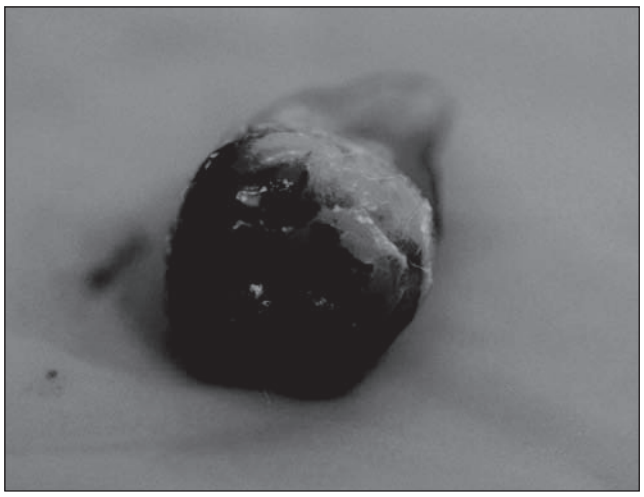

Fig. 6. Extracted 48 tooth.
Ryc. 6. Usunięty ząb 48.

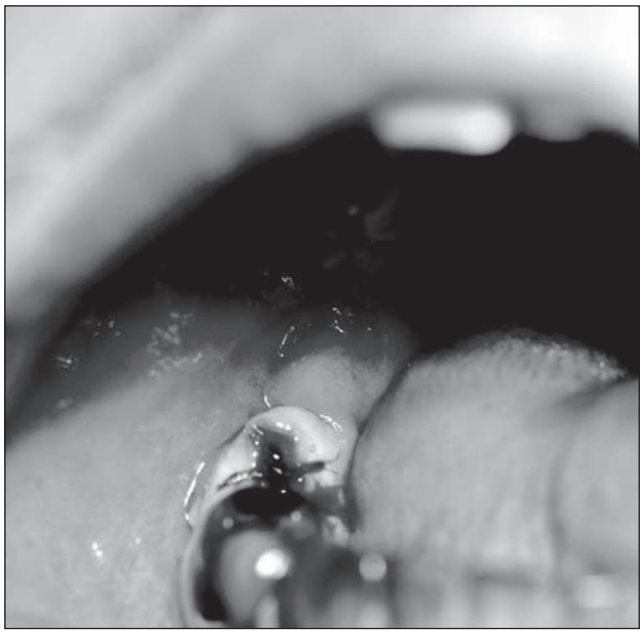

Fig. 7. Wound sutured surgically.
Ryc. 7. Rana zaopatrzona szwami chirurgicznymi.

and dizzines, nausea and vomiting has been taken into consideration. After 3 hours, the patient has been discharged under the care of his mother.

The follow-up examination in first day after the surgery showed no oedema of the operated area. The rinsing of post operative wound has been performed with the use of 0,02% chlorhexidine solution and further follow-up visitis have been scheduled. In the 7th day after the surgery, the wound has been healed. The patient was instructed to engage the hygenic treatment of the oral cavity.

At the moment the patient is slowly learning about the course of his disease and under control of physicians and physiotherapists is fighting with burdensome pains of joints, muscles and whole body.

DISCUSSION

Patients with the Ehlers-Danlos syndrome often come across various social problems, which are caused by lack of knowledge regarding this disease. That, in turn, affects the correct diagnosis. The fact of diagnosing the patient with a rare disease can not, however, justify the failure in medical management. It is hard to visualise a situation where, because of the rare disease status, the patient does not receive help for acute tooth pain. Unfortunatly the described case is not a single one. In our publications, again and again [9, 10, 11] we underline that one of physicians' duties is to broaden their knowledge to meet the standards set by medical advances.

There are no medical contraindications for dental treatment of a Ehlers-Danlos type II patient. In case of dental pain, there is an outline with standard procedures for a healthy patient, which include administering articaine as a local anesthetic and ensuring the protection of temporomandibular joints. In case of any doubts, after providing help, the patient can be referred to a dental department, which conducts treatment in general anesthesia as part of one day surgery. During plan therapy special attention must be paid through prophylactic and hygenic treatment of the oral cavity [12].

Pain is one of the basic symptoms of EDS and it often accompanies the patients through all their life. It can casuse chronic stress and lead to frustration and depression, which is confirmed by our case. The intensity of pain is variable and among other things, depends on the type of syndrome. Prokop and alias' [13] thesis is that it can be secondary, caused by frequent luxations in temporomandibular joint, or occur as a cause of soft tissue and nerve injuries. The key role is played by psychogenic mechanism.

According to the research of General Clinical Research Centre of the University of Conecticut Health Centre in Farmington, dating the 1995, in 70% of 51 examined patients with EDS, pain involved also inferior extremities, ankles, hands, feet, spine and hips, and the whole body was considered achy. In all cases, the dominant feature is the retentivity of pain, which stands for the constancy, although the cause has been removed [14]. Pain treatment in EDS is primarily its prediction and using rehabilitation elements in everyday life. Pharmaceuticals are inherent and should be used in cases of chronic pain [15].

The hypermobility of joints is one of the characteristic symptoms of EDS, specially those spectacular forms, in which the patients can touch the ground with their whole hands, with straight legs, suck the big toe or touch the inner part of the forearm with the thumb of the same hand. These symptoms do not occur always and can change or even subside with age [16].

Zweers and alia [17] point out that also the stretchibility of the skin is very eye-catching. This symptom, although usually dicreet, can cause major body injuries. Thin, delicate and prone to injuries skin is often a location of haemorrhages, and its injuries heal

very slowly. The EDS syndrome is often only considered as problems with motor organ, while its main basis is the vast disorder of the connective tissue.

Collagen is a structural protein of the outercell connective matrix. From Greek, the word collagen is translated as glue-giving (colla-glue, genno-give birth), which explains its role in ascertaining the correct physical, mechanical and elastic durability of the tissues [18]. It is accounted for 70% of the whole body mass, which means that in a 70 kg person, 14 kg are proteins, in which above 4 kg is collagen.

It helps to realise the fact that the disorder in its creation can cause many pathological changes, which is confirmed by our case. The treated patient has type II classic EDS syndrome, which, as it is underlined by Mitchell and alia [19], is very hard to diagnose in molecular stage. In 1979 Vogel et al [20] discovered that the biggest changes are in collagen fibres of the skin, which consists mainly of type I collagen. This theory has been discredited in 1991 by Sokolov et al [21]. Their research, performed in a woman with type I EDS, showed the translocation of gene COL5A1 on the 9th chromosome, which coded the type V collagen. The detailed sequencing of the og the COL5A1 and COL5A2 genes, performer by Torielo and al [22] and also the research of Burrows [23], Nichols [24] and Wenstrup [25] in 1996, caused the identification of mutations in those genes in patients with EDS type I and II. These investigations have been confirmed by Symeons et alia [2] in year 2012.

CONCLUSION

The Ehlers Danlos syndrome is still an unfamiliar disease. It is necessary to bring this knowledge closer to all the physicians, which could allow to eliminate the diagnostic and therapeutic mistakes, which in turn cause the suffering of the patients.

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