Review of neurological aspects in a 3-month-old boy with Ehlers-Danlos syndrome (EDS) – case report

Spektrum objawów neurologicznych u 3-miesięcznego chłopca z zespołem Ehlersa i Danlosa (EDS) – opis przypadku

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ABSTRACT

Ehlers-Danlos syndrome (EDS) is a heterogeneous group of heritable connective tissue disorders. The actual classification recognizes 13 subtypes of the syndrome. The classic type is the most common and in 90% of cases is caused by mutations in the *COL5A1* and *COL5A2* genes responsible for the synthesis of type V collagen. In other cases mutations in the *COL1A1* gene encoding type I collagen are responsible for this disease. Classic EDS is characterized by skin hyperextensibility, poor wound healing and joint hypermobility. The clinical manifestation is dominated by symptoms from the musculoskeletal system, cardiovascular system, gastrointestinal tract and nervous system. Patients with Ehlers-Danlos syndrome also have a higher prevalence of obstructive sleep apnoea syndrome. The article presents the case of a 3-month-old boy with a classic type of the syndrome with tonic-clonic seizures, apnoea, fever of unknown cause, delayed psychomotor development with hypotonia, gastroesophageal reflux, fragility of blood vessels and easy bruising.

Keywords: hypotonia, epilepsy, apnoea, delayed motor development, tissue fragility, *COL5A1 gene*

STRESZCZENIE

Zespół Ehlersa i Danlosa to grupa chorób uwarunkowanych genetycznie, w których dochodzi do syntezy nieprawidłowych form kolagenu. Wyróżniamy 13 postaci klinicznych zespołu, z których postać klasyczna należy do najczęstszych i w 90% spowodowana jest mutacjami w genach *COL5A1* i *COL5A2* odpowiedzialnych za syntezę prokolagenu typu V. W pozostałych przypadkach odpowiedzialną za wystąpienie tej choroby jest mutacja w genie *COL1A1* kodującym prokolagen typu I. Postać klasyczną zespołu Ehlersa i Danlosa charakteryzuje nadmierna ruchomość stawów i rozciągliwość skóry oraz słabe gojenie się ran.

W obrazie klinicznym dominują objawy ze strony układu mięśniowo-szkieletowego, sercowo-naczyniowego, przewodu pokarmowego oraz układu nerwowego. U pacjentów z zespołem Ehlersa i Danlosa stwierdzono również zwiększoną częstość występowania zespołu obturacyjnego bezdechu.

Artykuł prezentuje przypadek 3-miesięcznego chłopca z klasyczną postać zespołu, u którego obserwowano napady toniczno-kloniczne, bezdechy ze spadkami saturacji, gorączki o nieustalonej etiologii, opóźnienie rozwoju ruchowego z uogólnioną wiotkością, refluks żołądkowo-przełykowy, kruchość naczyń krwionośnych i skłonność do siniaczeń.

Słowa kluczowe: uogólniona wiotkość, padaczka, bezdechy, opóźnienie rozwoju ruchowego, kruchość tkanek, gen COL5A1

CASE REPORT

A 3-month-old boy was transferred in October 2017 from the ICU (intensive care unit) to the Department of Paediatrics and Developmental Age Neurology due to the suspicion of epilepsy with generalized seizures and apnoea. The boy was a second child delivered by natural forces at 40 hbd. His birth weight was 3550g, Apgar score - 8/6/8/8 (less points for muscle tone and respiration) and head circumference - 35 cm. After the delivery breathing disorders (apnoea) and intrauterine infection were diagnosed. The boy was hospitalized in the Neonatal Pathology Department where apnoea with cyanosis, reduced saturation and undifferentiated fever were observed. Meningitis was diagnosed based on the examination of the cerebrospinal fluid (pleocytosis 100/3 ul, protein 91.0 mg/dL). After 3 weeks of antibiotic therapy the parameters of the cerebrospinal fluid were normalized. In the cranial ultrasound examination IVH (intraventricular haemorrhage) stage II was found, whereas abdominal ultrasound showed no abnormalities. The cardiological examination revealed atrial septal aneurysm and patent foramen ovale. During diagnosis carried out due to significant hypotonia the Prader-Willi syndrome was excluded (methylation test gave normal result). Then, during a short stay at home, parents observed incidents of increased muscle tone with rotation of the eyeballs upwards, several episodes

of thrashing, limb extension and screaming. The boy was admitted to the Paediatric Department where epilepsy with generalized seizures was diagnosed. Treatment with phenobarbital and levetiracetam was implemented. There was another episode of apnoea with cyanosis after discharge. The boy was admitted to the ICU Department where a urinary tract infection was diagnosed. Targeted antibiotic therapy was introduced and the antiepileptic treatment was continued.

On admission to the Department of Paediatrics and Developmental Age Neurology at the age of 3 months the boy's condition was stable. The neurological examination revealed head circumference 37 cm (<3 centile), right-sided plagiocephaly, anterior fontanelle- 3x3 cm, anisocoria (L> P), hypotonia and muscle weakness and present deep tendon reflexes.

The physical examination showed pale skin, lack of the left testicle in the scrotum, the liver 2 cm below the right costal arch. After admission to the Department, periodic, short-term (lasting up to several minutes) episodes of apnoea with cyanosis and a reduction in saturation to 0% were observed. The EEG recording was abnormal, with spike-wave complexes in the temporal regions, mainly on the left side. Magnetic resonance imaging of the brain showed the normal range for the age. The psychological examination revealed delayed motor development. The boy's hands did not clutch the rattle. He did not control his head both during traction and sitting on his mother's lap. He raised his head unsteadily in prone position.

During his stay at the Department the diagnosis was extended to possible causes of apnoea. A 24-hour pH-metry was performed showing pathological gastroesophageal reflux of high severity. Anti-reflux treatment was applied in accordance with the recommendations of the consulting gastroenterologist. Then, 24- hour electrocardiography (Holter-ECG) which was performed twice, excluded cardiac arrhythmias. Imaging (x-ray, computed tomography and ultrasound) of the thorax and abdomen showed no pathologies that could cause apnoea.

Periodic fevers, which were observed during the stay at the Department did not lead to an elevation in inflammatory factors. A test for primary immunodeficiency diseases was performed. The levels of immunoglobulins, C3 complement component and lymphocyte typing in flow cytometry were normal. A consultant haematologist excluded proliferative blood diseases.

Due to periodic fevers a lumbar puncture was performed. In the cerebrospinal fluid, which was slightly exsanguinated, pleocytosis 17/1ul and increased protein concentration (70.0 mg/dl) were found. To relieve fever of unknown cause the antiviral therapy (acyclovir) and 3 gammaglobulin infusions were applied. There were no changes in the cerebrospinal fluid. Diagnosis of metabolic and genetic diseases was also extended. The results of the organic acids profile in the urine, transferrin isoforms, long-chain fatty acids, amino acids profile in the plasma and cerebrospinal fluid did not indicate any inborn errors of metabolism. Molecular testing for SMA did not show mutations in the *SMN1* gene. Analysis of the mitochondrial genome also did not show mutations within the analysed regions (region mtDNA m.6861_16525). Whole-exome sequencing (WES) was performed to diagnose the observed neurological symptoms. During the stay at the Department anti-epileptic treatment was modified by increasing levetiracetam doses and adding valproate and clobazam. Tonic-clonic seizures correlating with changes in the bioelectric brain activity were recorded in the video-EEG (electroencephalography). Clonazepam and topiramate were added to the treatment which caused the regression of generalised seizures but not apnoea. A consultant anaesthesiologist suggested installing a tracheostomy tube but the child's mother did not consent.

Finally the patient was diagnosed, according to clinical presentation, with epilepsy with generalized seizures, apnoea with decreased saturation, undifferentiated fevers, delayed motor development with hypotonia, gastroesophageal reflux, atrial septal aneurysm and patent foramen ovale. In addition, the child had fragile blood vessels and was susceptible to bruising.

At the age of 7 months the boy had obstruction of the small intestine with segmental ileitis and perforation during a gastrointestinal infection.

After discharge from the Department the exome sequencing (WES) results were received which revealed the pathogenic mutation in the *COL5A1* gene responsible for the classic type of Ehlers-Danlos syndrome (NM_000093.3:c.3023C>T NP_000084.3:p.Thr1008Met Chr9:137694750C>T).

DISCUSSION

Ehlers-Danlos syndrome is a heterogeneous group of heritable connective tissue disorders with clinical symptoms from the musculoskeletal system, skin, blood vessels and internal organs [1,2]. The frequency of Ehlers-Danlos syndrome is estimated at 1;5000 to 1;25000 live births [3]. The disease, in its classic type, is characterized by joint hypermobility, skin hyperextensibility and tissue fragility. However, there is clinical and phenotypic heterogeneity of this syndrome due to the genetic background [1].

We distinguish the following clinical types of Ehlers-Danlos syndrome: [1]

Among listed types the most common are the classical and hypermobile ones [3]. The classic type in 90% of cases is caused by mutations in the *COL5A1* and *COL5A2* genes, which are responsible for the synthesis of type V collagen. In other patients mutations in the gene *COL1A1* encoding type I collagen are responsible for this disease. The type of inheritance is autosomal dominant, but 50% of cases are caused by *de novo* mutation [1,2]. Type V collagen builds fibrils in the connective tissue and its reduced amount is the main cause of symptoms in the classic type of Ehlers-Danlos syndrome [2]. Type I collagen is in the skin, tendons, ligaments, bones and teeth, blood vessels and scars [1,2]. Based on the analysis of clinical cases, major and minor criteria were developed to facilitate the diagnosis and/or decision-making about genetic testing (fulfilment of one of the major or tree minor criteria).

Tab. I. Clinical Classification of Ehlers-Danlos Syndrome, Inheritance Pattern, and Genetic Basis
Tab. I. *Klasyfikacja zespołu EDS, podłoże genetyczne i zasady dziedziczenia*

	Clinical EDS subtype	Abbreviation	IP	Genetic basis	Protein
1	Classic EDS	cEDS	AD	Major: COL5A1, COL5A1	Type V collagen
				Rare: COL1A1	Type I collagen
				c.934C>T, p.(Arg312Cys)	
2	Classic-like EDS	clEDS	AR	TNXB	Tenascin XB
3	Cardiac-valvular	cvEDS	AR	COL1A2 (biallelic mutations that lead to COL1A2	Type I collagen
				NMD and absence of pro a2(I) collagen chains)	
4	Vascular EDS	vEDS	AD	Major: COL3A1	Type III collagen
				Rare: COL1A1	Type I collagen
				c.934C>T, p.(Arg312Cys)	
				c.1720C>T, p.(Arg574Cys)	
				c.3227C>T, p.(Arg1093Cys)	
5	Hypermobile EDS	hEDS	AD	Unknown	Unknown
6	Arthrochalasia EDS	aEDS	AD	COL1A1, COL1A2	Type I collagen
7	Dermatosparaxis EDS	dEDS	AR	ADAMTS2	ADAMTS-2
8	Kyphoscoliotic EDS	kEDS	AR	PLOD1	LH1
				FKBP14	FKBP22
9	Brittle Cornea syndrome	BCS	AR	ZNF469	ZNF469
				PRDM5	PRDM5
10	Spondylodysplastic EDS	spEDS	AR	B4GALT7	b4GalT7
				B3GALT6	b3GalT6
				SLC39A13	ZIP13
11	Musculocontractural EDS	mcEDS	AR	CHST14	D4ST1
				DSE	DSE
12	Myopathic EDS	mEDS	AD or AR	COL12A1	Type XII collagen
13	Periodontal EDS	pEDS	AD	C1R	C1r
				C1S	C1s

IP, inheritance pattern; AD, autosomal dominant; AR, autosomal recessive, NMD, nonsense-mediated m RNA decay.

Major criteria:

1. Significant skin hyperextensibility and atrophic scarring
2. Generalized joint hypermobility

Minor criteria:

1. Easy bruising
2. Soft, doughy skin
3. Skin fragility (or traumatic splitting)
4. Molluscoid pseudotumours
5. Subcutaneous spheroids
6. Hernia (or history thereof)
7. Epicanthal folds.
8. Complications of joint hypermobility (e.g. sprains, dislocations, subluxations, pain, pes planus).
9. Family history of a first-degree relative who meets clinical criteria. [1,2]

EDS clinical features:

The clinical manifestation is dominated by symptoms from organs containing large amounts of connective tissue. The most common musculoskeletal symptom is joint hypermobility leading to complications such as sprains, dislocations, instability of the mandibular joint, flat feet, dyspraxia and osteopenia. In addition, there is hipotonia and muscle weakness, which often cause delayed motor development. The skin of patients with EDS is hyperextensible and soft with severe atrophic scarring and easy bruising. Main cardiovascular symptoms contain mitral valve prolapse, aortic root dilatation and, in a few cases, aneurysms and arterial dissection. Gastrointestinal symptoms include dysphagia, dyspepsia, gastroesophageal reflux, hiatal hernia, non-specific abdominal pain, problems with defecation and rectocele [2,3]. Patients with EDS have also a higher

prevalence of obstructive apnoea syndrome, which is associated with craniofacial malformations, instability of the mandibular joints and a tendency of soft palate to collapse during sleep [4,5].

Neurological aspects of Ehlers-Danlos syndrome:

There are many neurological symptoms associated with the synthesis of abnormal forms of collagen building ligaments, blood vessels, nerve and muscle sheaths, although the nervous system is not a primary target underlying molecular defects [6,7]. One of the most common symptoms is chronic musculoskeletal pain, which is connected with joint hypermobility leading to pathological sprains, dislocations and subluxations [6,7]. There is progressive muscle weakness as well as hypotonia which result from the abnormality of collagen in muscle sheaths. This often leads to delayed motor development in early childhood and an abnormal gait pattern, clumsiness and problems with motor coordination at a later age. Another neurological symptom is peripheral neuropathy, related to the dislocations of ligaments building joints and their pathological stretching and pressure on peripheral nerves, as well as abnormalities in the construction of collagen (I, III and V) constituting the tissue surrounding nerves. Neuropathy affects both neural plexus lesions (brachial and lumbosacral) as well as individual nerves (e.g. ulnar) [6].

Cerebrovascular diseases mainly concern vascular EDS caused by the mutation in the *COL3A1* gene and include intracranial aneurysms, subarachnoid haemorrhage and spontaneous dissection of the carotid and aortic arteries [6]. Patients with classic EDS occasionally have aneurysms whereas other cerebrovascular abnormalities are rare. Vascular EDS is a potential cause of stroke in young people [6].

In the available literature there are descriptions of single cases of association between EDS and brain and spinal structural anomalies. They include, in particular, periventricular heterotopia, polymycrogyria, agenesis of the corpus callosum, dilation of the ventricular system, meningomyelocele and Tarlov cysts [6,7].

A potential complication of all types of Ehlers-Danlos syndrome is the instability of atlantoaxial and atlantooccipital joints, which may cause head and neck pain, dizziness, fainting, nausea, dysphagia, and even lead to quadriparesis. [7]

Another neurological aspect is epilepsy described both in patients with and without brain defects, such as periventricular heterotopia or polymycrogyria [7, 8]. The pathomechanism linking epilepsy to a hereditary defect of connective tissue remains poorly studied. However, there is an attempt to explain it by the fact that collagen plays an important role in the growth, migration, metabolism and differentiation of neurons [7, 8]. Among described cases, epilepsy with generalized tonic-clonic, focal and secondary generalized seizures, most often starting in early childhood, was observed [8, 9].

A. Verrotti et al. [10] published an analysis of 42 cases of patients with Ehlers-Danlos syndrome and epilepsy, most of which, apart from three cases, were classic. Patients were subdivided into two groups: A - without brain abnormalities (26 cases) and B - with brain lesions (often with periventricular heterotopia - 16 cases). In both groups the majority of cases had epilepsy with focal seizures - 28 patients and the remaining 14 with generalized ones. The EEG record was abnormal with sharp waves, spike-wave complexes in the temporal, temporo-parietal (group A) and fronto-temporal (group B) regions. The majority of patients (23) responded well to treatment with one antiepileptic drug. In group B a significantly higher percent of patients required treatment with several drugs, suggesting a correlation of brain structural defects with a higher frequency of drug resistance in this group of patients [8,10].

SUMMARY

Ehlers-Danlos syndrome is characterized by a variety of clinical symptoms and complications within the musculoskeletal system, skin, blood vessels and internal organs. Neurological aspects are as follows: chronic musculoskeletal pain, headaches, progressive muscle weakness and hypotonia, delayed motor development, peripheral neuropathy. In addition, EDS may be linked to cerebrovascular diseases, structural brain and spinal defects and epilepsy. In the presented clinical case neurological symptoms such as epilepsy with generalized seizures, hypotonia, delayed motor development, as well as other symptoms like apnoea and recurrent fevers contributed to the search for their cause among rare genetic syndromes to make a proper diagnosis. In addition, the described case provides more information about the possible clinical manifestation of this disease. We would like to point out that EDS should be taken into account as the cause of not only joint and skin anomaly, but also early onset of neurological symptoms, including apnoea.

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