A case of coexistence of Marfan and Ehlers-Danlos syndromes in a 15-year-old boy

Przypadek współistnienia zespołu Marfana i zespołu Ehlersa-Danlosa u 15-letniego chłopca

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Summary

Marfan syndrome (MS) and Ehlers-Danlos syndrome (EDS) are examples of two rare genetic diseases characterized by disturbances in the structure of collagen.

The paper presents a case of the disease in a 15-year-old boy with classical signs of MS with coexistence of EDS. Clinical symtomps, including abnormal movement habits, might have suggested a systemic inflammatory disease of the connective tissue.

Introduction

Ehlers-Danlos syndrome (or according to some authors, syndromes) is a group of diseases caused by defects in collagen and metabolic disorders within the connective tissue. The changes affect mainly the joints, skin, and blood vessels [1].

The first description of the disease dates from the late seventeenth century, when the Dutch surgeon Job van Meekeren described the case of a patient with extremely flabby skin, which was subjected to enormous stretch and then slowly returned to its natural position. Several similar cases have been reported subsequently, but the greatest achievements in the diagnosis of the disease were made by Edward Ehlers and Hendri-Alexandre Danlos, who in 1901 independently described the disease syndrome which today is called the Ehlers-Danlos syndrome (EDS). The current name of the disease was proposed in 1936 by Frederic Parkes-Weber [2–5].

The EDS is a genetically determined connective tissue disease with a diverse clinical picture. EDS involves

Streszczenie

Zespół Marfana (ZM) oraz zespół Ehlersa-Danlosa (ZED) to przykłady dwóch rzadkich uwarunkowanych genetycznie chorób, charakteryzujących się zaburzeniami w budowie kolagenu. W pracy przedstawiono przypadek 15-letniego chłopca z klasycznymi objawami klinicznymi współistnienia ZM oraz ZED. Występujące objawy, a przede wszystkim nieprawidłowe nawyki ruchowe, mogły sugerować zapalną układową chorobę tkanki łącznej.

abnormal collagen synthesis and disturbances in its structure. All types of EDS constitute a group of disorders mediated by mutations of single genes with the types of inheritance corresponding to all three possibilities of Mendelian inheritance. Heterogeneity of EDS could be the result of mutations in various genes as there are at least 10 genetically different EDS. Because damage to the structure of collagen are present in all of them, some clinical features can be found in all types of disorders [6].

Disorders found in most of the forms of EDS concern tissues rich in collagen, i.e. skin, ligaments and joints. Since abnormal collagen fibers lose their tensile strength, the skin becomes excessively flexible, extremely fragile and susceptible to various injuries accompanied by hypermobility of the the joints. Small wounds may lead to considerable damage, and not rarely a surgical intervention when required is impeded by the lack of proper elasticity of the skin. The disorder of the connective tissue structure can lead to internal complications such as cracks of the intestine and large vessels (EDS

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type IV), fragility around the eyeball with cracking of the cornea and detachment of the retina (EDS type VI), diaphragm hernia (EDS type I) and many others [6].

Epidemiology. The prevalence of the syndrome varies depending on the clinical form. The most common is a classical form (1: 20 000 births), while the vascular form, which constitutes the greatest threat to people is much less common (1: 100 000 births) [7–13].

Clinical picture. There are now six forms of EDS and some forms are still unclassified. The most common symptom is excessive mobility of joints.

Classical form. It is characterized by excessive joint mobility, with a tendency to bruising and damage of the skin after minor injuries. Frequent subluxations of the hip joints are observed in newborns and habitual dislocations are observed later in life. Scoliosis, recurrent effusions in the joints, flat feet and other effects of increased joint mobility are present. Hemorrhages in articular cavities may also be found.

Types of vascular form of EDS. This is the most severe type of EDS. Vascular abnormalities, present in this disorder may cause cracking and delamination of the artery walls and spontaneous formation of vascular fistulas. Thinned vessels, mostly abdominal aorta, arteries extending from the arch of the aorta and arteries in the lower limbs are not dilated and spontaneously break, sometimes leading to false aneurysms and fistulas. The heart muscle may also break. True aneurysms are rare. The clinical picture of the disease includes dermatological problems (atrophic scars in injury), skin discoloration and ecchymosis and hypermobility of the joints. Symptoms of mitral valve prolapse may occur. A severe complication that might be observed is spontaneous intestinal perforation. Pregnancy in women with type EDS IV poses concerns due to the risk of rupture of the uterus. Aortic dissection, rupture of the heart and any large vessels, as well as intestinal perforation with hemorrhage into the abdominal cavity are frequent causes of patients' death.

For a diagnosis of vascular type of EDS, apply criteria of Villefranche, presented in Table I.

Form of kyphoscoliosis. In addition to the tendency of severe kyphoscoliosis one can also observe significantly increased joint flexibility and extensibility of the skin. There are also frequent changes in the eyeball, myopia, peel off of the retina and cataracts. Not rarely a rupture of the eyeball occurs.

Laxity of joints form. The main symptoms are laxity and congenital subluxation of the joints, excessive skin stretch of varying severity, often short stature, and blue coloration of sclerae. In the course of pregnancy, premature rupture of the amniotic sac may occur.

Form of joint hypermobility. Symptoms of predominate. Changes of the skin are poorly expressed.

Reduced elasticity of the skin form. In this form, loss of skin elasticity dominates, there is also a tendency to occurrence of bruising, frequent formation of a hernia, and premature rupture of membranes.

Diagnosis is established on the basis of clinical signs corresponding to the individual characteristics of EDS. Family history is important. Criteria of increased joint mobility confirmed by the Beighton criteria are useful. EDS should be differentiated from Marfan syndrome (MS), osteogenesis imperfecta, flabby skin (*cutis laxa*), neurological disorders, and muscular diseases [7, 8, 10, 11].

Treatment is mainly all symptomatic. Steps are taken to prevent injuries and if an injury occurs it is recommended to wear prolonged bandages. If the patient's condition requires it, saving operations are performed. Surgery is used especially in cases of rupture of the walls of blood vessels or intestine but the high risk of fragility of tissues has to be kept in mind. It is essential to provide parents of children with EDS and adults with proper education on the risk associated with the disease and the possibility of prevention. In forms of EDS where joint mobility dominates, exercises that can strengthen the muscle play an important role. In case of subluxations, appropriate orthopedic surgery is performed. Pharmaco-

Major criteria	Minor criteria
1. The weakening or rupture of the walls of the arteries, gastrointestinal tract or uterus	1. A positive family history, sudden death of a close relative
2. A thin, transparent skin	2. Akrogeria
3. Excessive bruising	3. Excessive mobility of small joints
4. Characteristic facial appearance	4. Discontinuation of tendon or muscle
	5. Clubfoot (talipes equinovarus)
	6. Varicose veins expand at a young age
	7. Spontaneous pneumothorax or hemothorax

 Table I. Diagnostic criteria of Villefranche Nosology [12]

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logical therapy is possible in the form of kyphoscoliosis, where vitamin C might be helpful [1, 7, 9, 14]. If the distortion exhibits a large dynamic progression and causes deep deformation, surgical treatment is recommended. This particularly applies to children during the first months of life [15]. In cases of serious complications in the cardiovascular system one undertakes cardiac surgery involving the exchange of the heart valves [16, 17].

The prognosis depends on the form of EDS. The most severe outcomes are associated with vascular forms. One of the later consequences of excessive joint movement is the increased incidence of degenerative changes in joints [7].

Case report

We present a case of a 15-year-old boy admitted for treatment to the Clinic of Rheumatology of Developmental Age Institute of Rheumatology due to suspected arthritis. The family history disclosed that the father of the child suffers from Marfan syndrome, the mother suffers from EDS and both grandmothers have aortic aneurysms. For several years the boy had been suffering from intensifying pains and transient swelling of the interphalangeal joints of both hands, with periodic cracking of the skin over these joints. Shoulder joint pain, and transient pain and swelling of the knee and right hip joints were also present. The patient has habitual twisting of ankle joints. The echocardiographic examination revealed a small mitral regurgitation.

In 2012 in the Genetic Clinic of University Hospital No. 1 in Bydgoszcz, on the basis of characteristic clinical features, a syndrome of connective tissue disorder with elastopathy combining the features of MS and EDS was diagnosed in the patient. The boy was in the process of genetic testing. Since October 2013 the severity of pain in knee joints prompted introduction of treatment with narcotic analgesics in the Pain Treatment Clinic.

The boy was admitted to our clinic in a good general condition, but suffering from pain in the whole body. Numerous abnormal findings in the physical examination were repeated: difficult and abnormal gait (motor clumsiness), pallor of skin with numerous stretch marks, a significant deficiency of weight with the austenitic structure of the body, a large chest deformity (called "chicken" chest), scoliosis, deepened kyphosis in Th/L spine, bowing of the elbows, knees and feet, flat feet, medial setting of knee caps, generalized laxity of the muscles and joints and fatigue (the boy barely maintained a standing position), long, slender fingers, pain on passive movements and excessive warmth of the knee and interphalangeal joints with the expansion of their strokes and painful shoulder joints. Myopia, and significant osteoporosis were disclosed.

Laboratory tests revealed no features of inflammation. Deficiency of vitamin D3, and the presence of antigen HLA- B27 were found. The boy poorly tolerated cryotherapy and isometric exercises. The clinical laboratory features showed arthritis without inflammation in the course of coexisting of features of MS (meet the criteria of Ghent) [18] and EDS, both with features of classical form and the form of excessive mobility and the kyphoscoliosis (meeting the Brighton criteria with the presence of 9/.9 points on a Beighton's scale) [19].

The case of the presented patient confirms the observations of many authors regarding the possibility of arthritis in the course of EDS.

In our patient, coexisting MS also gradually has increasing responsibility for these pathological changes. At present, the patient requires constant multidisciplinary care, especially a properly conducted rehabilitation enhancing muscle strength. Importantly, the patient's education is also necessary in order to eliminate risks associated with the disease.

Genetic factors from the mother, father and two grandmothers caused in our patient a very severe course of the disease. Only the titles of descriptions of single cases of coexistence of clinical overlapping symptoms of both diseases were found in the available literature. The comparison of their course with the course of the disease of our patient is still impossible [20–24].

The authors declare no conflict of interests.

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