# REVIEWS

Adv Clin Exp Med 2010, **19**, 4, 537–542
ISSN 1230-025X


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# Ehlers-Danlos Syndrome

## Zespół Ehlersa-Danlosa

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### Abstract

Ehlers-Danlos syndrome (EDS) is a group of genetically determined vascular purpura. The pathological changes mainly involve joints, skin and the vascular wall. The incidence of the EDS is 1 per 20 000–100 000 births. The defects involve the structure of collagen as well as other enzymes associated with it. Today there are the following types of EDS: classical, hypermobility, vascular, kyphoscoliotic, arthrochalasia and dermatosparaxis. The individual types of EDS are accompanied by complications of heart muscle, respiratory system, gastrointestinal tract, eyes, teeth, periodontal tissues and obstetric problems. The current paper presents issues relating to epidemiology, pathogenesis, clinical manifestations and treatment of various forms of Ehlers-Danlos syndrome (**Adv Clin Exp Med 2010, 19, 4, 537–542**).

**Key words:** Ehlers-Danlos syndrome, classification, symptoms.

### Streszczenie

Zespół Ehlersa-Danlosa (ZED) to grupa genetycznie uwarunkowanych skaz naczyniowych. Zmiany dotyczą głównie stawów, skóry i ścian naczyń krwionośnych. Częstość występowania zespołu wynosi 1/20 000–100 000 urodzeń. Defekty dotyczą budowy kolagenu oraz związanych z nim enzymów. Obecnie rozróżnia się następujące postacie zespołu: klasyczną, z nadmierną ruchomością stawów, naczyniową, kyfoskoliotyczną, z wiotkością stawów oraz skórną. Poszczególnym postaciom ZED towarzyszą powikłania ze strony mięśnia sercowego, układu oddechowego, przewodu pokarmowego, oczu, zębów, tkanek okołozębowych oraz problemy położnicze. W pracy przedstawiono problemy dotyczące epidemiologii, patogenezy, objawów klinicznych oraz leczenia poszczególnych postaci zespołu Ehlersa-Danlosa (**Adv Clin Exp Med 2010, 19, 4, 537–542**).

**Słowa kluczowe:** zespół Ehlersa-Danlosa, klasyfikacja, objawy.

The EDS is one of the hereditary vascular purpura. The incidence of the EDS is 1 per 20 000–100 000. The classical type is most common and the vascular type is one of the rarest type of EDS [1]. Excessive joint mobility was already described by Hippocrates who noticed it at horse riders from the Scythian tribe and describe it in the work "Airs, waters and places" [2]. The first description of the syndrome was created by Russian dermatologist – Tschernogobow in 1892 [3]. The name of the syndrome comes from the name of a Danish dermatologist Edward Ehlers who described it in 1901 and a French dermatologist Henri-Alexandre Danlos who described it in1908 [4, 5]. The symptoms of EDS were noticeable in famous Italian violinist Niccolo Paganini [6].

The first classifications of EDS were produced in late sixties 20$^{th}$ century. In 1986 the terminology of types of EDS was formalized. Originally 11 types of EDS have been distinguished. The new, simplified classification of EDS was proposed in 1997, in Villefranche-sur-Mer in France. Currently the EDS is divided into six types: (1) classical, (2) hypermobility, (3) vascular, (4) kyphoscoliotic,

* The work was partially funded from Medical University of Lodz resources in the years 2006–2009 as a research project No. N406 050 31/1860.

(5) arthrochalasia, (6) dermatosparaxis. The first three types of EDS are the most common [7]. Types not included in the currently used classification occur sporadically and were reclassified or removed from classification (Table 1).

The hereditary pattern of EDS is autosomal dominant, autosomal recessive or depending on the X chromosome.

The symptom of EDS is connective tissue anomaly that consists of disturbance of synthesis of perivascular collagen and enzymes connected with it: lysyl hydrolase that is necessary to create cross-bonding of hydroxylysine in collagen, N-proteinase type I procollagen which split ends telopeptides of collagen after they are separated in the extracellular space. The defects in collagen structure mainly affect its type V which is vessels, cornea, placenta and cartilage, type III which is the component of blood vessels, skin, intestinal wall and uterus and type I which is the component of bones, skin, tendon, ligament, sclera and cornea tissues, blood vessels, and hollow organs. The deficiency of lysyl hydrolase, that is necessary to create cross-bonding of hydroxylysine in collagen, was indicated in kyphoscoliosis type [8, 9].

The excessive movement of joints is evaluated according to Beighton scale (Table 2). The scale has two versions. In the first version of the scale, there is an additional criterion for evaluating the dorsiflexion of foot. According to Beighton criteria, one can recognize the hypermobility of the joints when there are at least 3 to 6 possible symptoms [10].

For all the type of the Ehlers-Danlos syndrome, changes in the skin and joints are characteristic. The various types differ in intensity of cutaneous-articular symptoms. In the classical type the hypermobility of joints occurs already in newborns, and the symptoms involve mainly the peripheral joints such as shoulder, knee, and a temporomandibular joint and spine. Children often have flat feet and scoliosis [10]. In the hypermobility type – they dominate, and skin symptoms are less pronounced. In the kyphoscoliotic type there is excessive, generalized loosening of joints, scoliosis at birth, increasing with age, which may lead to respiratory and circulatory failure. The significant muscular hypotonia (called "floppy infant") is also characteristic. However, in the vascular type excessive joint mobility affects only the joints of the fingers. Children with arthrochalasia type often have congenital bilateral hip subluxation, there are also articular-musclar aches. In the classical type recurrent effusions in the ponds, floods to the articular cavities can be also observed [7, 11, 10]. Skin lesions include excessively stretch, thin, gauzy and atrophic skin. It easily comes to injuries and bruises. The healing of the wounds is disturbed. It comes to significant scarring. The wide scars

**Table 1.** Characteristics of each type of Ehlers-Danlos syndrome

**Tabela 1.** Charakterystyka typów zespołu Ehlersa-Danlosa

| Type (Typ) | Previous naming (Poprzednia nazwa) | Pattern of inheritance (Wzór dziedziczenia) | Abnormal protein (Nieprawidłowe białko) | Abnormal gene (Nieprawidłowy gen) |
|---|---|---|---|---|
| Classical (Klasyczny) | type I/II | AD | collagen-type V and I | COL5A1, COL5A2 |
| Hypermobility (Z nadmierną ruchomością stawów) | type III | AD | tenascin-X – in some | unknown |
| Vascular (Naczyniowy) | type IV | AD | mainly collagen- type III | COL3A1 |
| Kyphoscoliotic (Kifoskoliotyczny) | type VI | AR | lysyl hydroxylase deficiency | PLOD |
| Arthrochalasia (Z wiotkością stawów) | type VII A/B | AD | collagen-type I | COL1A1, COL1A2 |
| Dematosparaxis (Skórny) | type VIIC | AR | N-proteinase of type I procollagen | ADAMTS2 |

AD – autosomal dominant.
AD – autosomalne dominujące.

AR – autosomal recessive.
AR – autosomalne recesywne.

X – depending on chromosome X.
X – w zależności od chromosomu X.

**Table 2.** Scale by Beighton (version I)
**Tabela 2.** Skala Beightona (wersja 1)

| | |
|---|---|
| 1 | Hyperextension of the knee pond beyond 10° |
| 2 | Hyperextension of the elbow pond beyond 10° |
| 3 | Passive apposition of the thumbs to the flexor aspect of the forearm |
| 4 | Passive dorsiflexion of the fingers beyond 90° |
| 5 | Forward flexion of the trunk with knees fully extended so that the palms of the hand rest flat on the floor |
| 6 | Dorsiflexion of the foot > 20 ° in relation to angle |

with thin, parchment skin, in the Anglo-Saxon literature known as "cigarette paper scars", are very characteristic. They are mainly located in areas exposed to pressure such as elbows, knees, chin. The excessive extensibility of tissues may manifest as a symptom of Gorlin (the possibility of touching tip of the nose with the end of the tongue). There may be discoloration of the skin of the forehead, chin and legs. The dermatosparaxis type, in turn, is characterized by loss of elasticity of the skin and fascia. In the vascular type, symptoms affecting the skin are relatively poorly expressed [7, 11, 10].

Defects in collagen, other connective tissue proteins and related enzymes cause problems not only in the skin and joints, but also in many other tissues and organs in which connective tissue occurs. As is apparent from the available literature, in various types of EDS there are clinical symptoms resulting from damage to other organs such as heart muscle, blood vessels, respiratory system, gastrointestinal tract, urinary bladder, skeletal system, eyes, periodontal tissue, amniotic membrane, and others.

In a classical, hypermobility, vascular and kyphoscloliotic type mitral valve prolapse flap can be observed. The expansion of the trunk of the aorta has been reported in the classical and hypermobility type [11, 10]. The symptoms associated with blood vessels are most dramatically expressed in the vascular type. It represents 5–10% of all the types of EDS [12]. Average survival of patients with this type of EDS is 50 years. Mainly large and medium-sized arteries are abnormal [12, 13]. Severe symptoms of arterial vessels and cavernosum organs are dominant in this type of EDS. These are mostly fatal hemorrhage from the aorta, iliac artery, splenic artery, liver, kidney, bleeding into the lung, the alveoli, to the chest as a result of rupture of the internal thoracic artery aneurysm and bleeding in pregnancy and childbirth due to rupture of the aorta, vena cava, uterus, intestines, liver, vagina, perineum [10, 14–18]. The syndrome of sudden infant death due to subarachnoid hemorrhage has also been described [19] as well as the presence of spontaneous carotid-cavernosal fistulas, vertebral artery and carotid artery dissections [20–25]. One of the symptoms of idiopathic carotid-cavernous fistula may be unilateral paralysis of the eyes and headache on the side of the fistula [24]. The vascular fragility occurs in the wall of the arteries but also intestines and uterus [7, 11, 10, 23, 26]. Symptoms affecting the skin and joints are here rather poorly expressed in comparison to other types of EDS. Spontaneous retroperitoneal bleeding is the most common cause of death in patients with type IV EDS [27]. There is an increased risk of aneurysm [10]. There were some cases of abdominal aortic aneurysms, intracranial arteries, renal arteries, hepatic artery [15, 20, 26, 28]. A patient developed hepatic artery aneurysms after splenectomy and an 8-month old child, giant aortic aneurysm [29, 30]. The occurrence of hemorrhage is also possible in the kyphoscoliotic type of EDS. Wenstrup et al. described patients with rupture of the vertebral artery, multiple cracks in the femoral artery and two episodes of bleeding inside the chest [31]. In the classical and vascular type varicose veins can be observed [10, 32].

Spontaneous pneumothorax, spontaneous mediastinal emphysema, formation of the blisters under the pleura have been seen in the classical and vascular type. In the vascular type the pneumothorax may be accompanied by bleeding into the pleural cavity and hemoptysis [10, 33]. In the vascular type the spontaneous rupture of the large intestine has been described and in the classical type the diverticula of the bladder was found [34, 35]. In the Ehlers-Danlos syndrome urinary incontinence and prolapse of pelvic organ in women has also been reported.

One of the skeletal-related changes observed in the kyphoscoliotic type is scoliosis that appears at an early age [31, 36, 37]. Distortion of the chest can cause respiratory and circulatory failure. Some cases of marfanoid habitus with arachnodactylia of the limbs have been also observed in this type. In the arthrochalasia type there are patients with short stature, round face and hypoplasia of the mandible [7, 10, 11, 36].

The pathological changes of the eye were observed in the kyphoscoliotic type. They included bleeding to the retina resulting in its detachment, to the vitreous humor, cracking of the cornea, rupture of the eyeball, subconjunctival lens dislocation after trauma. Such changes as a small cornea, cone of the cornea, cataracts, myopia, brown color of the sclera can also be observed [10, 36, 38–41]. The blue color of the sclera occurs in arthrochalsia and kyphoscoliotic type [10, 40]. Badauy et al.

described the case of a 23-year old patient with vascular type, who lost 12 teeth. He also developed alveolar bone loss [32].

In the classical and kyphoscoliotic type, the absence of frenulum of the lower lip and tongue has been reported [10, 25, 42]. There are also characteristic facial features of infants with a vascular type of Ehlers-Danlos syndrome, for example prominent eyes, caused by the deficiency of fat around the eyes. A small mouth, sharp nose, hollow cheeks and a narrow auricle without petals are also characteristic [43].

There are few reports on the coexistence of the Ehlers-Danlos syndrome with other hamorrhagic diathesis [44, 45–50].

Actually in all types of EDS there is a risk associated with pregnancy, including risk of uterine rupture, prematurity due to premature rupture of membranes [10, 17, 51]. In the vascular type of EDS, pregnancy-related mortality ranges from 11.5 to 25% [23]. All pregnancies should be treated as high-risk pregnancies. Cesarean section is recommended.

A case of difficult intubation in a patient with hypermobility type of EDS which probably was caused by the collapse of fibro-elastic tissues and cartilages of the trachea was described. The general anesthesia was performed for cesarean section due to prolonged second stage of labor [53]. Lind et al. studied a group of 46 pregnant women with Ehlers-Danlos syndrome. The most common complications were pelvic pain, instability of the pelvic, premature labor, postpartum hemorrhage, complicated perineal wounds [54]. It is also obvious that during the pregnancy the pathology of the spine can increase and there can be difficulty in obtaining the vascular access.

Epidural anaethesia may be technically difficult [55]. There is a risk of injury of the cervical spine during intubation due to lax ligaments of the neck and risk of pneumothorax during positive pressure ventilation [56]. Various imaging studies are used in diagnosing type IV, for example CT scanning, MRI scanning, ultrasonography. In this type of EDS, classic arterography with catheterization should be avoided as it may cause an aneurysm or vessel rupture. Ultrastructural examination of collagen fibrils is useful in diagnosis classical and arthrochalasia type [7, 52].

The differential diagnosis should include diseases of the nervous system and muscles, Aarskog-Scott syndrome, fragile X syndrome, congenital flaccidity of the skin (cutis laxa), osteogenesis imperfecta and achondroplasia [7, 52]. It is possible to apply genetic testing in case of known molecular defects.

Currently there is no causal treatment. It is suggested that vascular interventions should be systematically performed and not differed when it comes to acute complications such as rupture of the vessel. Brooke et al. described 40 patients with EDS who underwent 45 endovascular and 18 open procedures including embolization, angioplasty, arterial bypass and aortic aneurysm repair. 5-year survival free of complications was appropriately 85 and 54% [57]. In literature there are also cases of successful mitral and aortic valve replacement [58, 59].

It has been showed that desmopressin may be effective in bleeding associated with Ehlers-Danlos syndrome [60]. A case of bleeding in type IV EDS which was successfully treated with rVIIa was described [61].

High dose of vitamin C (1–4 g/day) can be used in treatment the kyphoscoliotic type of EDS [7, 52].

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Conflict of interests: None declared

Received: 1.07.2010
Revised: 28.07.2010
Accepted: 28.07.2010