Review Article

Elastopathies and Other Genetic Syndromes Predisposing to Aortic Pathology

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ABSTRACT

Aortic diseases and their complications are related to high mortality. Genetic disorders of the elastic components of the aorta (elasthopaties) cause earlier manifestation and worse prognosis of the aortic pathology among the affected subjects. Early diagnosis of such genetic disorders can lead to better control and preventive medical and surgical treatment in order to prevent complications and improve prognosis. We describe the main genetic disorders leading to elastic components dysfunction, namely: Marfan syndrome, bicuspid aortic valve, Ehlers-Danlos syndrome, Loyes-Dietz syndrome, polycystic kidney disease, Turner's syndrome, osteogenesis imperfecta.

INTRODUCTION

Diseases of the aorta represent a specific group of diseases often associated with urgent clinical condition and high lethality. This fact applies especially for developed countries, where both morbidity and mortality caused by aortic pathology increase. The most common complications of aortic wall pathology are the formation of an aneurysm, dissection, rupture, and aortic occlusion. The incidence of these increases in the elderly, and is the result of changes in aortic anatomy due to aging. However, there are many comorbidities leading to a more frequent and earlier manifestation of complex aortic pathology, like trauma, risk factors for early and aggressive atherosclerotic arterial damage (smoking, arterial hypertension, dyslipidaemia, male gender, age, diabetes mellitus), but also some inherited anatomical conditions like bicuspid aortic valve and aortic coarctation. A number of genetic mutations are directly related to the early and malignant expression of aortic diseases: Marfan syndrome, bicuspid aortic valve, Ehlers-Danlos, Loyes-Dietz, polycystic kidney disease, Turner's syndrome, osteogenesis imperfecta, and others.

The purpose of this paper is to describe these genetic diseases associated with a higher incidence of aortic pathology and complications. They can be classified under the common term of “elastopathies”, which reveals a common pathophysiological and pathoanatomic finding showing a defect in the elastic properties of the aortic wall. In many cases, the clinical manifestation of all described elastopathies (especially in their advanced form) is limited to only several severe and life-threatening vascular complications - aneurysm formation, rupture, dissection, embolism, occlusion of a large vessel.

Proper aortic microstructure, especially elastin and collagen fibres integrity, plays a major role in the subsequent function of the aorta and arteries in the body (Figure

1a). This specific composition of the aortic wall is crucial for accepting large stroke volume, keeping blood pressure even during diastole, reducing turbulence and after all generation of almost constant blood flow in the capillaries, where diffusion happens constantly, although pulsatile work of the heart. The disturbed aortic wall architectonic plays a key role in the development of all aortic diseases [1]. Genetic disorders can lead to elongation, tortuosity and size enlargement of all the segments of the aorta. This is the reason why it is so important for the clinician to have good knowledge about the normal sizes of all aortic segments (Figure1b).

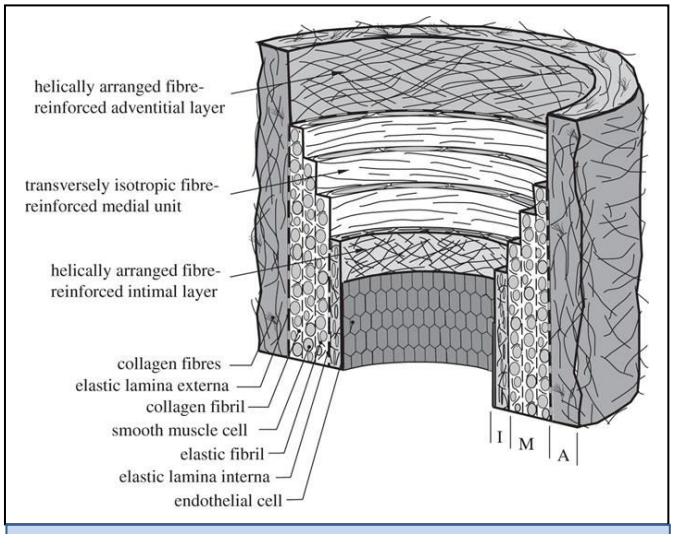

Figure 1a: Microstructure and composition of the aortic layers subject of pathologic changes in elastopathies.

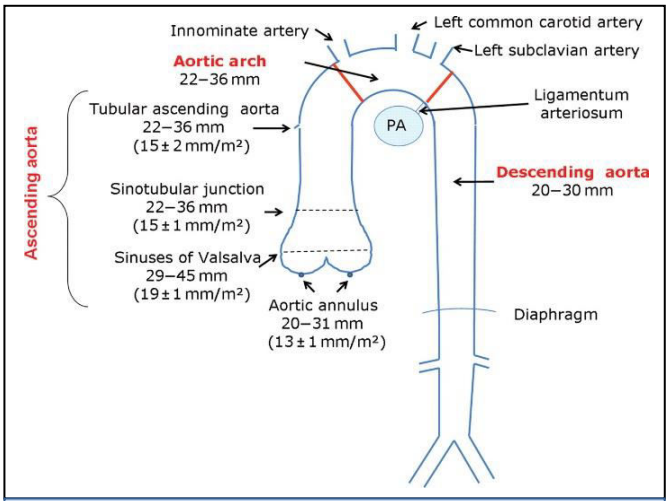

Figure1b: Segments and segmental sizes of the normal aorta.

By Diseases of the aorta. In: Feigenbaum H, Armstrong WF, Ryan T, eds. Feigenbaum's Echocardiography. 6th edn. (1)

Depending on the location of the pathologic process, the symptomatology can be largely variable. As it was suggested by the large and comprehensive IRAD registry, the most probable common pathway in genetically dependent aortic pathology is the early (before the age of 40) cystic medial degeneration (medial necrosis) [2]. Below we describe several genetic disorders and some mutations predisposing to earlier and more complex aortic pathology and especially to aortic dissection.

MARFAN SYNDROME

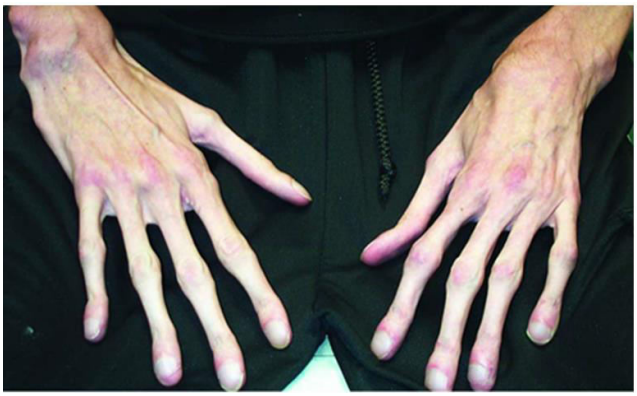

Figure 2a: Long fingers, arachnodactyly ("spider fingers") in a patient with Marfan syndrome. Arachnodactyly is a condition of abnormally long and slender fingers and toes.

The Marfan syndrome is an autosomal dominant disease with a frequency of about 1:5000individuals. It is associated with a variety of symptoms, in some cases pathognomonic for the disease detection. The onset and progression of symptoms is observed from early childhood to adulthood. The phenotypic manifestation of the disease affects a number of systems in the human body: the locomotor apparatus (longer bones, arachnodactyly Figure 2a), chest deformities (Figure 2b), the eyes (dislocation of the lens), respiratory system (lung emphysema, spontaneous pneumothorax) and frequent recurrent hernias. Disturbances of the cardiovascular system occur primarily with aortic dilation at level of Valsalva sinus, aortic dissection, or rupture. The aortic pathology and its complications are the leading cause of death in patients with Marfan syndrome [3]. In some patients, the disease is additionally manifested by mitral valve prolapse leading to significant mitral regurgitation, supraventricular arrhythmias, systolic or diastolic left ventricular dysfunction.

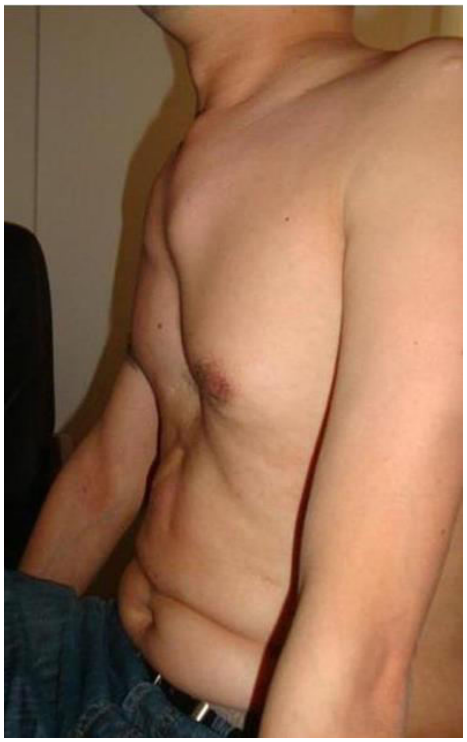

Figure 2b: Pectus carinatumin a Marfan positive subject. Anterior chest wall deformity which main characteristics are: abnormal and excessive growth of the sternum and costal rib cartilages in the anterior chest wall.

In 1991, the structural defect in the gene coding the synthesis of fibrin-1 FBN1 (a structural component of myofibrils) was described as a cause of Marfan syndrome. To date, several hundred mutations in the gene have been described, directly related to the development of the disease. Interesting, in families carrying the same mutation, there is an exceptional variability in the phenotypic manifestation of the disease– both in localization and severity [4]. This fact is the reason for searching for additional genes, called "modifiers", which play a significant role for the possible manifestation and progression of the aortic pathology in Marfan syndrome [5].

Making the diagnosis until recently was based on Ghent criteria. These criteria were revised in 2010 by an expert panel, and following these new revised criteria (cited below) particular attention is paid to family history, genetic tests and cardiovascular manifestations (not only as the most common, but also the most significant, leading to the most severe disturbance and clinical prognosis worsening condition [6].

REVISED GHENT CRITERIA

In the presence of family history

- Ectopia lentis AND Family History of Marfan syndrome (as defined above) = Marfan syndrome - The presence of Ectopia lentis and a family history of Marfan syndrome (as defined in 1-4 above) is sufficient for a diagnosis of Marfan syndrome.
- A systemic score ≥ 7 points AND Family History of Marfan syndrome (as defined above) = Marfan syndrome - A systemic score of greater than or equal to 7 points and a family history of Marfan syndrome (as defined in 1-4 above) is sufficient for a diagnosis of Marfan syndrome. However, features suggestive of Shprintzen Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers Danlos syndrome must be excluded and appropriate alternative genetic testing (TGFBR1/2, SMAD3, TGFB2, TGFB3 collagen biochemistry, COL3A1, and other relevant genetic testing when indicated and available upon the discovery of other genes) should be performed.
- Aortic Root Dilatation Z score ≥ 2 above 20 yrs. old, ≥ 3 below 20 yrs. old) + Family History of Marfan syndrome (as defined above) = Marfan syndrome - The presence of aortic root dilatation (Z ≥ 2 above 20 yrs. old, ≥ 3 below 20 yrs. old) and a family history of Marfan syndrome (as defined in 1-4 above) is sufficient for a diagnosis of Marfan syndrome. However, features suggestive of Shprintzen Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers Danlos syndrome must be excluded and appropriate alternative genetic testing (TGFBR1/2, SMAD3, TGFB2, TGFB3, collagen biochemistry, COL3A1, and other relevant genetic testing when indicated and available upon the discovery of other genes) should be performed.

In the absence of family history

- Aortic Root Dilatation Z score ≥ 2 (Z-scores are a means of expressing the deviation of a given anatomic or physical measurement from a size- or age-specific population mean) AND Ectopia Lentis = Marfan syndrome. The presence of aortic root dilatation (Z-score ≥ 2 when standardized to age and body size) or dissection and Ectopia lentis allows the unequivocal diagnosis of Marfan syndrome, regardless of the presence or absence of systemic features except in case these

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are indicative of Shprintzen Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers Danlos syndrome.

- Aortic Root Dilatation Z score ≥ 2 AND FBN1 = Marfan syndrome. The presence of aortic root dilatation (Z ≥ 2) or dissection and the identification of a bona fide FBN1 mutation are sufficient to establish the diagnosis, even when Ectopia lentis is absent.
- Aortic Root Dilatation Z score ≥ 2 AND Systemic Score ≥ 7pts = Marfan syndrome - Where aortic root dilatation (Z ≥ 2) or dissection is present, but Ectopia lentis is absent and the FBN1 status is either unknown or negative, a Marfan syndrome diagnosis is confirmed by the presence of sufficient systemic findings (≥ 7 points, according to a scoring system) confirms the diagnosis. However, features suggestive of Shprintzen Goldberg syndrome, Loeys-Dietz syndrome, or vascular Ehlers Danlos syndrome must be excluded and appropriate alternative genetic testing (TGFBR1/2, SMAD3, TGFB2, TGFB3, collagen biochemistry, COL3A1, and other relevant genetic testing when indicated and available upon the discovery of other genes) should be performed.
- Ectopia lentis AND a FBN1 mutation associated with Aortic Root Dilatation = Marfan syndrome - In the presence of Ectopia lentis, but absence of aortic root dilatation/dissection, the identification of an FBN1 mutation previously associated with aortic disease is required before making the diagnosis of Marfan syndrome.

The pathophysiology of the disease is poorly known. It is clear that structural deficiency of fibrillin-1 leads to weakening of microfibrils. The latter gives a satisfactory explanation of the vascular pathology and lens dislocation but cannot explain the pathological growth of skeletal bones and thickening of the heart valves. Experimental studies of mice with Marfan syndrome have shown greater activation of cytokine-Transforming Growth Factor Beta (TGFβ). In Fbn1- deficient experimental models, significant TGFβ dysregulation and appearance of a phenotype with Marfan syndrome (including aortic aneurysm and dissection) were observed [5].

In practice, no etiological treatment has yet been developed for Marfan syndrome. Since the prognosis is lead by the aortic pathology presence or absence special attention is given to aortic diameters, close monitoring and treatment to prevent the excessive aortic growth. In the scientific medical literature, there are several drug agents showing hope of slowing the process of aortic diameter increase [7,8]. Patients are treated with beta-blockers and dilatation of the aortic root is monitored by echocardiography. Indication for surgical treatment is dilatation of the aorta root over 45 mm or an increase of more than 10 mm over 1 year. Several publications in recent years cite Losartan (angiotensin-receptor blocker) as a drug that affects cytokine-transforming growth factor beta and slows the progression of dilatation of the aortic root [8]. Medication combining Losartan and Atenolol is currently indicated to be most effective in reducing disease progression.

BICUSPID AORTIC VALVE (BAV)

The second genetically dependent leading cause for early degeneration of the aortic media and hence predisposing factor for early aortic dissection and aneurysm formation is the inherited bicuspid aortic valve. It is already well known that those with a congenital bicuspid aortic valve have a significantly increased risk for aortic dilatation, aneurysm, and dissection. Systemic cardiac ultrasound in young people with BAV showed enlargement of the ascending aorta independently of the functional status of the valve itself (stenosis and/or regurgitation). In the IRAD registry, the incidence of bicuspid aortic valve among people with diagnosed aortic dissection in the age bellow 40 was 3 times higher (9%) compared to the population above 40 years of age (3%) [2]. The explanation of that finding is that in subjects with BAV early medial degeneration process is evident. This degeneration is otherwise characteristic for elderly and hypertensive subjects. The dilatation process and aortic wall vulnerability can involve both ascending and descending aorta. The systematic histologic examination of a large series of surgical aortic valve replacement was shown that75% of BAV positive patients had cystic medial degeneration, compared with a rate of only 14% in those with tricuspid aortic valves [9]. The most probable mechanism in BAV (like in the majority of elastopathies) for cystic medial degeneration is the loss of elastic microcomponents of the media (especially the inadequate production of fibrillin-1 during embryogenesis that is both predisposing factor for bicuspid aortic valve and a weakened aortic wall [10]. Large variability of genes responsible for BAV was described, such as mutations in ACTA2, FBN1, and TGFBR2 genes. Depending on whether BAV

is part of the phenotypic expression of one of the frequent aortic genetic syndromes (Marfan, Ehlers- Danlos, Loyes-Dietz, Turner) or is found in subjects not fulfilling the criteria for neither of them the BAV is characterized as syndromic or non-syndromic (sporadic).

EHLERS-DANLOS SYNDROME

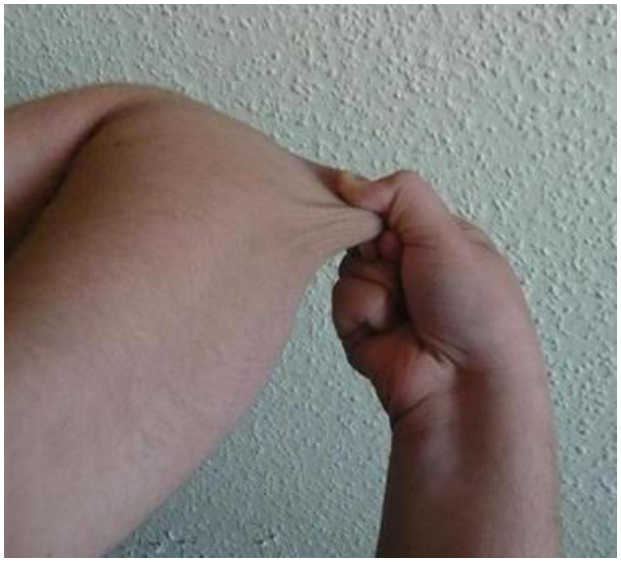

Figure 3a: Hyper-extensibility of the skin in a patient with proven Ehlers-Danlos syndrome.

Figure 3b: Example of extreme articular hypermobility in a patient with Ehlers-Danlos syndrome.

The disease affects about 1:5000 people. It is characterized by hypermobility of the joints, hyper-extensibility of the skin (Figure 3a) and spontaneous skin wounds, in some cases osteoarthritis. A syndrome of articular hypermobility (Figure 3b) was described by Hippocrates, but as a separate diagnostic entity was first described by the Danish physician Edvard Ehlers and the French physician Henri-Alexandre Danlos [11]. Genetic mutations lead to phenotypic manifestation of the disease, but all of them affect genes encoding the collagen synthesis or collagen-reactive proteins directly, mainly at the post synthetic processing level. Most of the mutations are transmitted by autosomal dominant mechanism, fewer are autosomal-recessive, but “de novo” mutations were described as well.

The phenotypic manifestations of the disease are multiple and include: hypermobility of the joints, tendency to joint dislocations, subluxation and luxation, thoracic outlet syndrome, swelling deformation of the toes, spinal deformities, arthralgia, myalgia, easy skin, livedo reticularis, dilatation or rupture of arteries, heart valve prolapse, Reynaud’s phenomenon, varicose veins, hiatal hernia and many others. All phenotypic manifestations are directly related to the functional deficiency of collagen and its inability to fully fulfil its essential function, namely to confer "strength" to the connective tissue anywhere in the body. On the basis of the leading phenotypic expression, several clinical forms of Ehlers-Danlos have been described. Such are: classical, hypermobile, vascular, kyphoscoliolithic, arthrochalasia and dermatopraxis. Each of these types is associated with a mutation in certain genes.

The vascular form of Ehlers-Danlos is associated with impaired collagen type III synthesis (a mutation in the COL3A1 gene located on the second chromosome and responsible for the collagen III precursor synthesis). Its incidence is between 1:200000 and 1:50000. In practice, the vascular form is associated with poor prognosis. In addition to the tendency to dilation and rupture of the vessels, patients are often characterized by thin, ragged and transparent skin, making visible multiple venous vessels on the chest, and elsewhere in the body. The tendency for easy ecchymoses formation in different parts of the body is a typical characteristic. Aortic rupture can develop both: as a complication of aneurysm formation and spontaneously without previous aortic size increase. Significant complications of the disease are seen in 80% of patients before the age of 40, with an average life expectancy of about 50 years. Pregnancy in affected women is associated with a 5.3% risk of arterial rupture, including uterine artery rupture. The diagnosis is currently based on

Beighton's criteria [12]. Patients covering 1 large or 2 or more small criteria should be examined thoroughly for the disease presence.

Large diagnostic criteria

- Aneurysm, dissection or rupture of the artery
- Intestinal rupture
- Uterine artery rupture during pregnancy
- Family burden for vascular form of the disease

Small diagnostic criteria

- Thin, transparent skin (particularly visible in the thorax)
- Characteristic facial pathologic findings (thin red part of the lips, micrognathia (small chin), narrow nose, protruding eyes)
- Acrogeria (limbs' appearance characteristic for older calendar age)
- Arteriovenous fistula at supraaortic level (most often carotid – cavernous fistula)
- Hypermobility of small joints
- Rupture of muscle and/or tendon
- Early-onset varicose veins
- Pneumothorax/hemopneumothorax
- Easy bruising (spontaneously or with minor trauma)
- Chronic subluxations and joint dislocations
- Congenital femoral dislocation
- Equinovarus
- Gingival recession

Predilective localization for arterial aneurysm formation and rupture are: the thoracic and abdominal segments of the body (66%), the head and neck (17%) and the limbs (17%). The clinical manifestation depends on the localization of the affected arterial vessel, but in all individuals with proven Ehlers-Danlos and sudden pain, vascular complication must be suspected. Urgent diagnostic effort should be applied because common complications are spontaneous coronary artery dissection and rupture and spontaneous rupture of valvular chords with extremely poor prognosis. Gastrointestinal complications: In addition to arterial rupture, gastrointestinal perforation occurs in 15% of individuals with a mutation in COL3A1, most on sigmoid level. The condition is lethal in about 3%. A frequent complication in Ehlers-Danlos positive patients is the rupture of arterial vessel during non-cardiovascular surgical intervention.

LOEYS-DIETZ SYNDROME

In 2005, Loeys and Dietz described an autosomal dominant disease characterized by multi-systemic involvement [13]. Loeys-Dietz's syndrome is classically described as a triad of: hypertelorism, double uvula and/or a cleft of the palate, and tortuosity of the arteries with aneurysm and/or dissection formation. Additional manifestations such as craniosynostosis (premature adhesion on bone stitches of the skull), Chiari malformation (characterized by cerebral structural defects), and persistent ductus arteriosus are common for the disease. Two types of phenotypic manifestation are described. Loeys-Dietz type 1 is associated primarily with cranial malformations (craniosynostosis, cleft of the palate and hypertelorism), whereas type 2 is predominantly associated with skin manifestations of the disease (velvety and translucent skin, vulnerable skin, atrophic scars). In subjects with Loeys-Dietz syndrome features, characteristic forthe Marfan syndrome can be found, such as: aortic aneurysm, arachnodactyly, deformity of the chest; however, in Loyes-Dietz positive subjects we do not find prolongation of skeletal bones and dislocation of the lens. It should be noted that the progression of vascular manifestations of the disease is significantly faster compared to Marfan syndrome positive subjects. The development and progression of aortic aneurysms is significantly faster, dissection and rupture are observed with smaller aorta sizes and all of this is directly related to earlier mortality with an average life span of about 26 years. The latter suggests an earlier clinical observation and more aggressive therapeutic intervention in patients with proven Loeys-Dietz. Clinical diagnostic criteria for the disease have not yet been developed strictly and diagnosis requires confirmation with molecular-genetic tests.

Loeys-Dietz syndrome is due to mutations in the genes encoding two growth factor beta: (TGFBR1 and TGFBR2 receptors). It is virtually impossible to distinguish the mutation in one or the other receptor based on phenotypic expression. The genetic variability described in Marfan syndrome within one and same mutation, leading to clinical manifestation variability of disease in sick families, here is even more pronounced. All mutations described in both receptors lead to loss of their function. Paradoxically, TGFβ signalling activity is pathologically high in

cell cultures of fibroblasts (taken from the aortic wall) of patients with proven Loeys-Dietz [14].

ANEURYSM-OSTEOARTHRITIS SYNDROME OR LOEYS-DIETZ TYPE 1C SYNDROME

This is a genetic disorder recently described by Van de Laar et al. [15] which is characterized by manifestations characteristic of Loeys-Dietz syndrome: aneurysm, dissection, and arthritis, in the presence of the above-mentioned facial malformations, arachno-asthma, scoliosis and Loeys-Dietz skin changes described in type 2. However, patients with this disease more often developearly age osteoarthritis. The gene mutation responsible for the disease is also described in the gene encoding SMAD3, a protein directly responsible for the TGFβ signalling system. Patients carrying this mutation also have marked hyperreactivity in the signalling system.

ARTERIAL TORTUOSITY SYNDROME

Arterial tortuosity syndrome is an autosomal recessive disorder characterized by tortuosity, elongation, stenosis and more frequent formation of aneurysms in the large arteries. Patients most often die at an early age. The manifestations of the disease overlap significantly with Loeys-Dietz syndrome and include: arachnodactyly, hypertelorism, palatine clefts and double uvula, hypermobile joints, micro and retrognathia. The genetic basis of this disorder is associated with a variety of mutations in the SLC2A10 gene encoding the GLUT10 protein belonging to the family of glucose transporters. Without a clear biochemical relationship between this protein and TGFβ, patients with Arterial tortuosity syndrome again have pathologically high activity on this signalling system [16].

CUTIS LAXA SYNDROME

In fact, Cutis Laxa syndrome is a heterogeneous group of several nosology units united by a common phenotypic expression: loose, drooping, inelastic skin, along with a number of systemic and vascular manifestations [17]. Both autosomal dominant and autosomal recessive forms of the disease are described, with the latter generally having a worse prognosis. Autosomal dominant forms are commonly associated with gastrointestinal diverticula, hernias and genital prolapse, presence of stenosis of the pulmonary artery, bronchiectasis or emphysema. The described genetic defect in an autosomal dominant group of diseases affects the synthesis of elastin or is due to tandem duplication in the gene encoding fibulin-5. As a rule, mutations in the gene coding for the synthesis of Elastin (ELN) leading to increased function lead to the autosomal dominant forms of Cutis Laxa syndrome, loss of function mutations lead to isolated supravalvular aortic stenosis, and mutations associated with gene deletion cause Williams-Beuren syndrome. Autoimmune-recessive Cutis Laxa type 1 is a life-threatening disease characterized by vascular abnormalities, pulmonary emphysema, diverticulitis of the urinary and gastrointestinal tract as well as characteristic skin changes. The prognosis is poor and depends mainly on the progression of cardiovascular events. The latter are more common in the mutation of the gene responsible for the synthesis of fibulin-4 [18]. In all forms of the disease, there is proven dysregulation in the TGFβ signalling system.

CONGENITAL SUPRAVALVULARAORTIC STENOSIS

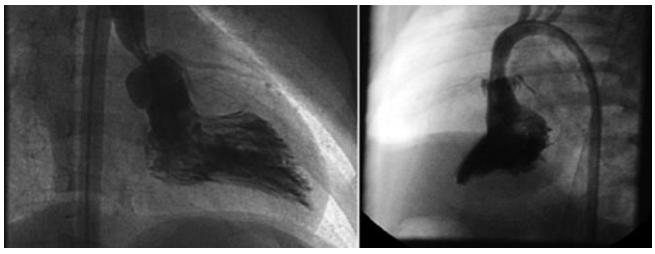

Figure 4a and 4b: Conventional contrast angiography of patient with congenital supravalvular aortic stenosis evident in LAO 40° projection (4a) and RAO 90° (4b).

Congenital supravalvular aortic stenosisis a disease of large (especially elastic) arteries with extremely high clinical variability. The most common localization of the disease is in the proximal part of the ascending aorta (Figure 4), followed by the large-calibre clusters of the pulmonary artery. The histological finding is characterized by disorganized, unevenly distributed and thickened elastin fibrils, hypertrophy and smooth muscle cell hyperplasia, intimal fibrosis and pathogenic deposition of collagen in the media [18,19]. There are two main theories explaining the mechanisms by which the elastin haploinsufficiency leads to the abnormal pathological findings. According to one of them, quantitative elastin deficiency makes elastic fibres more sensitive to haemodynamic stress. According to the second, the correct synthesis of the elastic fibres is impossible if there is a disproportion between the elastin and

the other components. In models of experimental mice with exclusion of the elastin gene from protein synthesis, a generalized arterio-occlusive disease associated with pathological proliferation and disorganization of smooth muscle cells in the media is rapidly developed. At the same time, a number of cell culture experimental models demonstrated independence between described pathoanatomic changes and haemodynamic stress [19]. The last two statements give reason to believe that elastin, in addition to a structural role, has an extremely important regulatory function during aortic development. The clinical finding in patients with congenital supravalvular aortic stenosis is usually characterized by systemic hypertension, an exceptionally high incidence of cerebrovascular accidents, myocardial infarction and obstructive cardiomyopathy. Congenital supravalvular aortic stenosis may occur within Williams syndrome along with other morphological manifestations (broad forehead, short nose, full cheeks, intellectual deficit, CNS abnormalities, periods of hypercalcemia). The latter is due to deletion in the long arm of the 7th chromosome, where besides elastin there are more than 25 described genes.

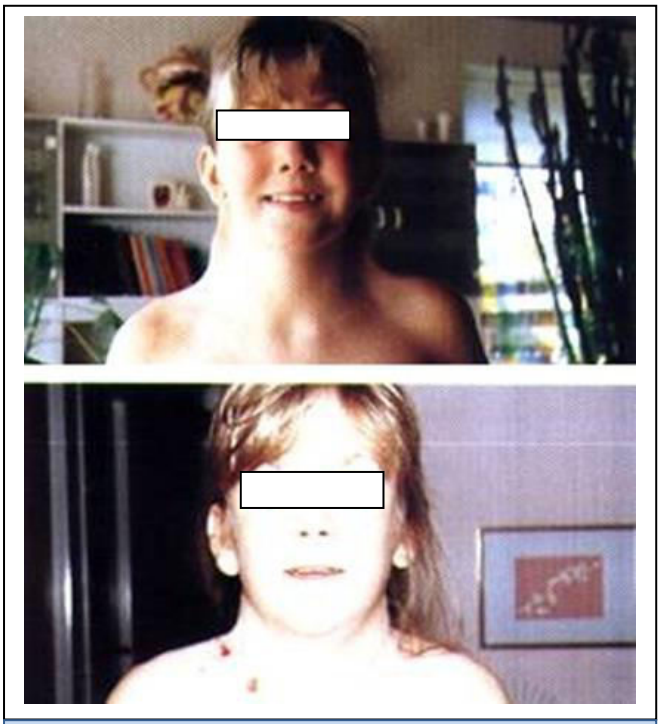

Figure 5a and 5b: An example of a girl with typical phenotypic appearance for May-Turner syndrome: distant nipples, a low line of neck hair, low ears, "thorax quadratum".

TURNER'S SYNDROME

Turner's syndrome is a rare disease (1:2000-1:5000 new-borns, with a proven higher prenatal frequency, which in many cases does not tolerate development of foetus). The disease develops in women with genomic haplo-genesis genotype 45, X0 (rarely 46, Xxp), and its phenotypic manifestations include primary amenorrhea, short stature, "thorax quadratum" and a number of cardiovascular diseases. Other phenotypic manifestations include: characteristic lymphedema on the dorsal surface of the hands and feeds, distant nipples, a low line of neck hair, low ears, short nails and the 4th metacarpal bone, horseshoe kidneys, impaired hearing, etc. Similar to number of other syndromic diseases, in Turner's syndrome the limiting factor in life expectancy is often cardiovascular pathology. This is evidenced by the fact that the latter is observed in 75% of foetuses and only 25-45% of new-born girls [20].

The cardiovascular phenotype in Turner syndrome is associated with dilated aorta, with thickened aortic walls leading to pathological propagation of the pulse wave. Pathology was most widely studied in a large French cohort study of 2012 involving 336 patients with Turner syndrome aortic dilation (indexed by BMI) in 91 (39%) of the patients studied in the cited cohort study. [21] The same proves the statistical significance between the pathological karyotype and the dilated aorta and gives rise to more frequent echocardiographic monitoring of the affected individuals. In patients with Turner's syndrome, as a dilated aorta with a maximum diameter greater than 2.0 cm / m 2, with a ≥ 2.5 cm / m2 there is a significantly increased risk of aortic dissection [22]. According to the guidelines for the diagnosis and treatment of aortic disorders [23] all patients with Turner's syndrome have to be subject to routine heart and aortic imaging (search for bicuspid aortic valve, aortic dilatation) once per every 5 -10 years if there is no known pathology and once per year when there is a proven one. According to the same guidelines, aortic dissection is significantly more common in sick individuals than in the general population. The latter is examined epidemiologically only in a clinical study that reported a dramatic difference 78:100 000 compared to only 1:100 000 of the total population of Danish women in between the ages of 30 and 40 [23]. In the same study, the mean age of dissection was 35 years for patients affected by the

syndrome, with no other risk factor observed in 25% of the cases. The histological finding of aortic dissection in a patient with Turner syndrome corresponds to cystic necrosis of the media, the pathogenesis of which is poorly studied and possibly different from that of Marfan syndrome.

We published the case of a young woman affected by Turner syndrome, presenting with huge dissecting aortic aneurysm treated with stent-graft implantation [24]. This was one of the first very young patients (19y old at the time of treatment) treated by endovascular method, who has had an uneventful follow-up for more than 10 years thus far.

OSTEOGENESIS IMPERFECTA

"Osteogenesis imperfecta" represents a heterogeneous group of diseases primarily affecting bones and characterized by blue sclera, loose joints, deafness, and dental problems. Almost all patients with the disease have been shown to have a defect leading to the synthesis of collagen type I, and in over 90% of cases, the defect affects the genes COL1A1 or COL1A2.Seven types of the disease are described; each can be related to cardiovascular impairment. Most frequent among them are aortic valve defect, dilation of the ascending aorta or mitral valve defect. There are several published (mostly retrospective) studies of patients with osteogenesis imperfecta, proving that the latter are a more frequent subject of cardiac surgery due to high-grade valve pathology and/or dilated ascending aorta [25]. Therefore, periodic cardiovascular screening of all patients with the disease is recommended.

AUTOSOMAL-DOMINANT POLYCYSTIC KIDNEY DISEASE (ADPKD)

Autosomal dominant polycystic kidney disease is caused by mutations in the PKD1 and PKD2 gene. It is the most common monogenic disease in men. About 90% of all cases of Polycystic Kidney Disease (PKD) are inherited in an autosomal dominant fashion. Characteristic of the disease, from where its name comes, is the development and progression of multiple kidney cysts, leading to loss of nephron and kidney failure. Symptoms usually develop between the 3rdand 4th decade, sometimes earlier. The specific symptoms are back pain and headache. Sometimes they are combined with liver and pancreatic cysts, urinary tract infections, abnormal heart valves, high blood pressure. Patients with ADPKD also have vascular abnormalities; intracranial aneurysms can be found in roughly 10% of asymptomatic patients and in up to one fourth of those with a family history of intracranial aneurysms or subarachnoid haemorrhage. Dissections and aneurysms of almost every large artery—including the aorta, coronary arteries, cervico-cephalic arteries, and vertebral arteries have been reported in patients with ADPKD. This large variability of vascular anomalies in ADPKD has led to the assumption that polycystins (whose synthesis is coded by PKD1 and PKD2 genes) are very important for the vascular integrity [26].

NONSYNDROMIC GENETIC MUTATIONS ASSOCIATED WITH AORTIC ANEURYSM OR DISSECTION

There are also many nonsyndromic mutations that have been shown to be directly linked to aortic aneurysm or dissection [27]. Thus, for example, mutations in the FBN1 and TGFBR1 / 2 genes cause aneurysm and/or dissection at the level of thoracic aorta, phenotypically resembling Marfan or Ehlers-Danlos syndromes. Mutations in the ACTA2 gene are described in 14% of patients with thoracic aortic aneurysm, whereas MYH11 (smooth muscle heavy-myosin coding) mutations are associated with both the development of aneurysm and persistent ductus arteriosus. Mutations in the ACTA2 gene lead to a greater incidence of bicuspid aortic valve, iris floccules, cerebrovascular pathology, Moya-Moya, and coronary abnormalities.

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