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Vascular Ehlers-Danlos syndrome in two Polish patients: identification of two novel COL3A1 gene mutations

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Introduction

The Ehlers-Danlos syndrome (EDS) is a genetically and clinically heterogeneous disorder involving hypermobility of the joints, hyperextensibility of the skin and tissue fragility [1]. According to the 2017 International Classification [2], EDS is divided into 13 types. Vascular EDS (vEDS) is the most severe form inherited in an autosomal dominant pattern and characterized by increased risk of sudden death due to the rupture of large arteries,
gastrointestinal perforation or uterine rupture during pregnancy (criteria – Table S1). Additional symptoms defining this syndrome are thin translucent skin with prominent subcutaneous vessels, easy bruising, small joint hypermobility, early-onset varicose veins and tendon/muscle rupture [1]. Minimal criteria suggestive of vEDS, i.e. a family history of the disorder, arterial rupture or dissection in individuals less than 40 years of age, unexplained sigmoid colon rupture, or spontaneous pneumothorax in the presence of other features consistent with vEDS should all lead to diagnostic work-up to verify if the clinical diagnosis could be confirmed by genetic testing. Molecular testing for vEDS should also be considered in the presence of a combination of the other “minor” clinical features listed above [2]. vEDS is usually caused by mutations in the collagen type III alpha I chain (COL3A1) gene, mostly heterozygous missense mutations, typically glycine substitutions in the Gly-X-Y repeat, or splice-site variants affecting the triple helical sequence leading to altered type III collagen synthesis and assembly [2,3]. As a consequence of a molecular defect in the COL3A1 gene, resistance to mechanical stress of the arteries, bowel and uterus is decreased [4]. Women with vEDS have an increased risk of obstetric complications including uterine rupture and dissection of major arteries and veins [5].

To our knowledge, we report the first two Polish patients with vEDS, in whom new causal mutations have been detected.

Case 1
A 33-year-old female (height, 158 cm; weight, 48 kg) was referred to the John Paul II Hospital for genetic work-up. At the age of 2 years, she underwent Achilles tenotomy due to clubfoot and at the age of 29, she underwent stent implantation for the spontaneous right common iliac artery (RCIA) aneurysm and dissection. At the age of 32, she experienced spontaneous sigmoid colon perforation and underwent colostomy with partial colectomy. The patient was pregnant twice and gave birth by uneventful vaginal delivery. Currently, computed tomography (CT) angiography showed that the ascending and descending aorta were not dilated, the maximum diameter of the abdominal aorta on the level of the bifurcation was 20 mm, along with dilation of RCIA to 16 mm and the left common iliac artery to 17 mm. There were no abnormalities in other vessels. Transthoracic echocardiography (TTE) yielded normal findings.

On physical examination joint hypermobility (Beighton score 6/9) and increased skin elasticity were observed. The skin was thin, shiny protruding with signs of bruising and atrophic scars.
The patient’s father (at the age of 39) and brother (at the age of 18) experienced a fatal thoracic aorta dissection. The paternal grandmother of the patient was successfully operated for the ascending aortic aneurysm at the age of 66. Two sisters, 1 brother and her two children remain asymptomatic. The relatives were not genetically tested.

**Case 2**

A 26-year-old female (height, 167 cm; weight, 62 kg) complained of hypermobility of small joints and easy bruising. At the age of 13, she broke her right ankle, at the age of 19, she twisted the knee joint and a year later she underwent a reconstruction of anterior cruciate ligament of the right knee. Recurrent ligament rupture occurred at the age of 21 and the re-operation took place the year after. For 6 years, she has had recurrent luxation in the arm joint and the right wrist. She showed no cardiac symptoms and her TEE showed solely mild tricuspid insufficiency. She has never been pregnant.

On examination, joint hypermobility was noted (Beighton score 7/9) and a thin, translucent skin with prominent subcutaneous vessels (Fig.1).

The patient’s father died of an aortic dissection at the age of 45. He also suffered from joint hypermobility. Her grandfather died of an aortic aneurysm rupture. The relatives were not genetically tested.

**Genetic testing**

After obtaining written informed consents, the molecular analysis was performed on genomic DNA by PCR amplification of all coding exons and the flanking intron regions. The amplicons were analyzed by Illumina’s Sequencing By Synthesis (SBS) technology (MiSeq Personal Sequencer, Illumina). The following gene panel containing FBN1, TGFBR1, TGFBR2, TGFBR2, SMAD2, SMAD3, ACTA2, COL3A1, MYH11, TGFBR3 and SKI was selected based on the clinical signs and a positive family history. The presence of the variants was confirmed by Sanger sequencing. The sensitivity of SBS sequencing is >99.9%.

We identified two novel COL3A1 mutations, c.1348-2A>G and c.1455+1G>T in case 1 and 2, respectively. Both mutations disrupt the normal splice sites, thereby interfering with normal splicing. In our patient (case 1) a history of colon perforation and the iliac artery aneurysm and dissection can be considered as typical. In contrast to older patients with aneurysms [6], at younger age genetic syndromes associated with aortic aneurysmal disease are relatively common [7]. In vEDS, spontaneous arterial rupture is most prevalent in the 3rd-4th decade
and often involves thoracic or abdominal vessels, the descending and abdominal aorta [5,8]. There is no specific treatment for vEDS, however, the early diagnosis can help monitor disease progression. The patients should be offered genetic counselling. The risk of an affected parent passing on the mutation to their child can be as high as 50% [5]. In our second case the recurrent ligament rupture was observed. Mutations in the COL3A1 gene have been reported to lead to such kind of complications [9,10]. In those cases, lifestyle changes can be advised to minimize the risk of injuries in the future and regular control visits and clinical surveillance is extremely important. Typical joint and skin manifestations should draw attention of a consulting cardiologist to vEDS. Regarding reproductive history, the first patient gave birth to two children, however, according to the 2018 ESC guidelines, pregnancy in women with vEDS is not recommended (class IIIC) due to high risk of serious vascular complications [11]. Murray et al. [12] reported that life-threatening complications occurred in 14.5% of deliveries in women with vEDS, including arterial dissection/rupture (9.2%), uterine rupture (2.6%), surgical complications (2.6%) and finally, the pregnancy-related death rate of 5.3%. It is unclear whether elective cesarean section decreases mortality among such women [5].

Our report clearly indicates that molecular analysis should be conducted in young patients with unexplained bowel or arterial rupture and also in those cases with a family history of similar events. The two familial cases we present here also nicely illustrate the clinical variability of the disorder with means that carriers of the same mutation may present variable clinical presentations [13]. Importantly, genetically confirmed vEDS may influence pregnancy and reproductive counseling. Pregnant women with vEDS should be considered at high risk of complications and they need to be referred to specialized centers. Our report also draws attention to the importance of searching for genetic causes of rare diseases in Poland including thrombophilia [14, 15]. Molecular genetic analysis is essential tool in this type of diagnostics.

References:

Fig. 1. Case 2. Joint hypermobility in the fingers (A) and thumb (B), elbow bending (C), translucent skin with visible scarf and subcutaneous vessels on the lower back (D).