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Cervical artery dissections and type A aortic dissection in a family with a novel missense COL3A1 mutation of vascular type Ehlers–Danlos syndrome

Georgios Makrygiannis [a, b, *], Bart Loeys [c], Jean-Olivier Defraigne [a, b], Natzi Sakalihasan [a, b]

[a] Department of Cardiovascular Surgery, University Hospital of Liège, Liège, Belgium
[b] Department of Surgery, Surgical Research Center (CREDEC), GIGA Cardiovascular Sciences, University of Liège, Liège, Belgium
[c] Center for Medical Genetics, Faculty of Medicine and Health Sciences, University of Antwerp and Antwerp University Hospital, Antwerp, Belgium

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ABSTRACT

Cervical artery dissection (CeAD) is a rare condition. One of the causes is the vascular type of Ehlers–Danlos syndrome (vEDS). A novel missense mutation in *COL3A1* was found in a young patient with CeAD as the single manifestation of vEDS. This is a heterozygous c.953G > A mutation in exon 14, disrupting the normal Gly-X-Y repeats of type III procollagen, by converting glycine to aspartic acid.

1. Introduction

Cervical artery dissection (CeAD) includes carotid and vertebral artery dissection, and represents an important cause of ischemic stroke in young adults (Debette, 2014). CeAD is a relatively rare and complex disorder with genetic (multifactorial, monogenic disorder) and environmental (cervical trauma, recent infection, hypertension, migraine) predisposing risk factors. The annual incidence is estimated around 2.6 to 3 cases per 100,000 people. Morphologically, CeAD is manifested as a mural hematoma, double lumen, aneurysmal dilatation, tapering stenosis, intimal flap, or occlusion of the affected artery. Despite a rare cause of CeAD, monogenic connective tissue diseases (CTD) must always be taken into consideration due to their severe complications. The most frequent detected among them are the vascular type of Ehlers–Danlos syndrome (vEDS), fibromuscular dysplasia, Marfan syndrome, and osteogenesis imperfecta.

vEDS is a rare autosomal dominant disease with an incidence of 0.2–1 case per 100,000 people and median survival of 48 years. The diagnosis is confirmed by the detection of abnormal type III procollagen or of a mutation in the *COL3A1* gene, and is based on the presence of at least two out of four major diagnostic criteria (Beighton et al., 1998) (thin translucent skin with visible veins, extensive-easy bruising, characteristic facial appearance, arterial, intestinal or uterine fragility or rupture). Of note, CeAD has been odserved in 2% of patients with genetically described vEDS (North et al., 1995, Pepin et al., 2000), and vEDS was found in less than 2% among large CeAD series (Debette and Markus, 2009). Although vEDS appears to be genetically homogeneous, there is remarkable allelic heterogeneity, which results in varied natural history with gender and type of mutation of a *COL3A1* (Pepin et al., 2014). Here we describe a case of a young woman with CeAd as the single manifestation of genetically verified vEDS.

2. Case presentation and diagnosis

A 21-year-old woman admitted to the emergency department for severe neck pain of the left side radiating to head and shoulders,

* Corresponding author. Department of Cardiovascular Surgery, Surgical Research Center (CREDEC), University Hospital of Liège, CHU, Avenue de l'Hôpital 1, B23/+5, 4000 Liège, Belgium.
E-mail address: gmakrygiannis@ulg.ac.be (G. Makrygiannis).

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vomiting, followed by paresis and paresthesia of the superior members and chest during less than one hour. From her past medical history she presented hypothyroidism, obesity, syndrome of micro-polycystic ovaries and she was current smoker of 4–5 cigarettes/day.

Magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) revealed dissection of the upper part of the internal carotid artery before its entry at the base of cranium and dissection of the vertical part of the left vertebral artery (Fig. 1). Treatment consisted of low molecular weight heparin during hospitalization substituted by warfarin for 6 months, and replaced by acetylsalicylic acid. The patient did not present further neurologic complications. Despite that no recent trauma was mentioned and from the clinical examination the patient did not show any sign of CTD, a CTD was suspected. A mutation analysis was performed by sequencing of all coding exons, inclusive intron/exon boundaries of the current thoracic aortic aneurysm and dissection panel (TAAD). The current TAAD panel consists of the following genes: *ACTA2*, *COL3A1*, *EFEMP2*/*FBLN4*, *FBN1*, *FLNA*, *MYH11*, *MYLK*, *NOTCH1*, *PRKG1*–exon3, *SKI*, *SLC2A10*, *SMAD3*, *TGFB2*, *TGFBR1* and *TGFBR2*. Sequence analysis of the *COL3A1* showed the presence of a heterozygous c.953G > A (p.Gly318Asp) mutation in exon 14 that has not been reported before, disrupting the normal Gly-X-Y repeats of type III procollagen. This mutation is not present in the *COL3A1* mutation database (http://www.le.ac.uk/genetics/collagen/). However since this mutation affected a glycine residue of the collagen helix, there is no doubt about its causality. Anecdotally, the same period, the patient's 60 year-old maternal aunt (II:1) presented with a type A aortic dissection and in the sequence analysis the same mutation was identified. Further genetic testing that was conducted to the family revealed the same mutation in the patient's mother (II:2), whereas the remaining members of the family were found negative (II:4, III:2, III:3, III:4) (Fig. 2). An angiographic investigation performed at the level of cervical arteries and thoracoabdominal aorta did not reveal any pathology, nor typical signs of vEDS were found in the 59 year-old mother. I:2 suffered from spontaneous intestinal rupture which was treated by colectomy and after many years she died from sudden death. A written informed consent and authorization to use the blood samples and images for research were obtained from the patients or their relatives.

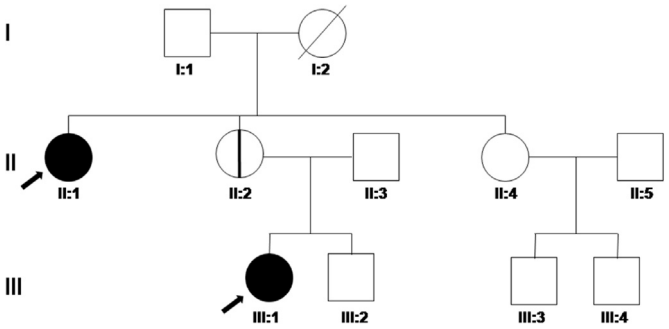

Fig. 2. Pedigree; In grey member of the family heterozygous of the c.953G > A (p.Gly318Asp) mutation in the exon 14 of *COL3A1* gene, II:1; Type A aortic dissection, III:1; Cervical artery dissections, II:2; heterozygous asymptomatic mutation carrier, I:1; very old person to whom we did not perform genetic analysis.

3. Discussion

Here we present a young patient with CeAD to whom a mutation analysis was performed by sequencing of all codings exons, inclusive intron/exon boundaries using a next generation sequencing gene panel for the current TAAD panel. The sequence analysis showed a heterozygous G to A transition at cDNA position 953 in exon 14 of the *COL3A1* gene, which converts glycine to aspartic acid at amino acid position 318 disrupting the normal Gly-X-Y repeats of type III procollagen. This is a novel finding that has never been reported before in vEDS. In general, approximately 50% of affected individuals inherit the *COL3A1* mutation from an affected parent, whilst the rest 50% of affected individuals carry a *de novo* disease-causing mutation.

CeAD is not common in vEDS, counting less than 2% of the cases according to large published series (Debette, 2014). Among all vascular complications of vEDS about one quarter involves head and neck vessels, including carotid-cavernous fistula, CeAD, intracranial aneurysms and arterial rupture (Pepin et al., 2000). The presentation of vEDS is extremely variable, and in this case the patient presented only one of the four major diagnostic criteria (Beighton et al., 1998). Although recently some phenotype–genotype correlations have been suggested (Frank et al., 2015,

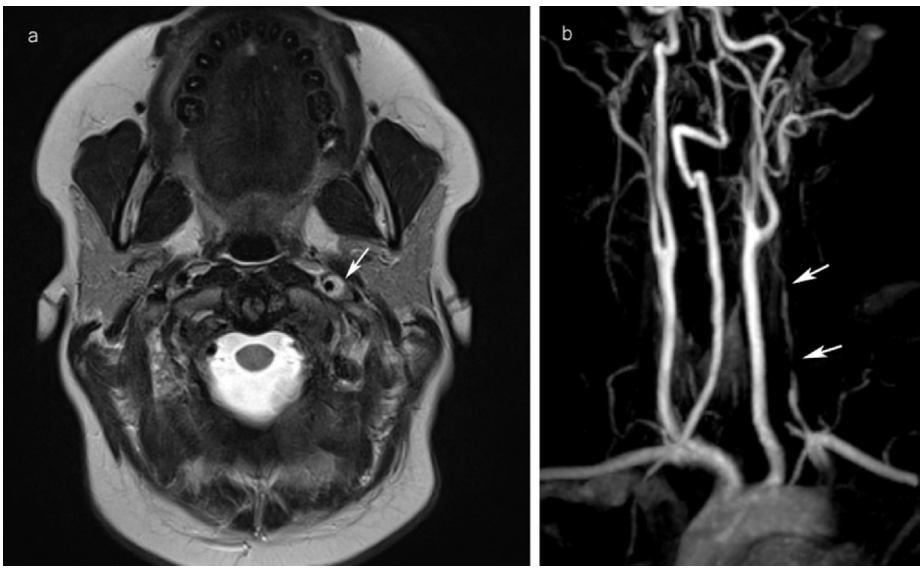

Fig. 1. a; MRI of the head, axial T2-weighted Turbo Spin Echo sequence shows the presence of the dissection of the left internal carotid artery (arrows), b; MRA of the neck, coronal view, shows the dissection of the vertical part of the left vertebral artery (arrows).

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Pepin et al., 2014), there is variability between different affected members within the same family (Kuivaniemi et al., 1997). Reducing penetrance of vEDS has been observed in families with haploinsufficiency mutations, but it is rather uncommon in families with missense mutations (http://www.ncbi.nlm.nih.gov/books/NBK1494/). These atypical forms of vEDS should increase awareness of this rare autosomal dominant disease and indicates that the same mutation in different relatives in the same family can be related with variable phenotypic expression. Currently, treatment is symptomatic and celiprolol has been proposed for the prevention of vascular complications of the vEDS (Ong et al., 2010). The study of different animal models could be useful to elucidate the pathogenesis of the disease and to identify therapeutic targets. This paradigm of a young patient showing atypical presentation should sensibilize physicians for early suspicion and detection of this syndrome. Caution should be exercised as vEDS patients are at increased risk of vessel rupture after endovascular interventions, at high bleeding risk under treatment with anticoagulants, and molecular genetic testing and clinical evaluation should be offered to at-risk patients.

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