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EHLERS-DANLOS SYNDROME TYPE IV In Association with a (c.970G>A) Mutation in the COL3A1 Gene

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SUMMARY

The Ehlers-Danlos syndrome type IV (EDS-IV) is a hereditary, autosomal dominant disease that causes a defect in the procollagen III synthesis, which results in a structural modification in this protein. An awareness of the disease is of vital importance for the optimal outcome, since the affected individuals have a high risk of vascular, intestinal and uterine rupture. It's a disease with great clinical variability and the diagnosis is confirmed by detection of a mutation in the gene encoding collagen type III.

The authors present a case report of a patient who appeared at the emergency ward with acute abdomen and hypovolemic shock after spontaneous aortic rupture. The diagnosis was confirmed after genetic study that identified a mutation in the (c.970G>A) in the COL3A1 gene, only reported once in the literature in a family with internal carotid dissections in some of its members. It's the first time that this mutation is reported in association with the EDS-IV. The authors also make a brief review of the clinical, genetic and molecular characteristics of this syndrome.

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RESUMO

SÍNDROME DE EHLER-DANLOS TIPO IV
Em Associação com a Mutação (c.970G>A) no Gene COL3A1

O Síndrome de Ehlers-Danlos tipo IV (SED-IV) é uma doença hereditária, autossómica dominante que resulta da síntese alterada do procolagénio III. Os indivíduos afectados apresentam risco de lesão (ruptura) vascular, intestinal e uterina. Trata-se de uma doença com grande variabilidade clínica, sendo o diagnóstico confirmado por detecção da mutação no gene que codifica o colagénio tipo III.

Os autores apresentam um caso clínico de uma doente que recorreu ao SU com quadro clínico compatível com ventre agudo e choque hipovolémico na sequência de ruptura espontânea da aorta abdominal. O diagnóstico de SED-IV foi confirmado após estudo genético que identificou uma mutação no (c.970G> A) no gene COL3A1. Esta mutação aparece descrita apenas uma vez na literatura numa família em alguns dos seus membros apresentam dissecção da carótida interna. É a primeira vez que esta mutação é descrita em associação com o SED-IV. Os autores também fazem uma breve revisão das características clínicas, genéticas e moleculares do SED-IV.

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INTRODUCTION

The Ehlers-Danlos syndrome (EDS) includes a variety of phenotypically and genetically heterogeneous hereditary diseases[1,2] characterized by defects of the molecules that are the structural support of the connective tissue (collagen), therefore affecting the skin, vessels, bones, joints and other tissues.

The first descriptions of this syndrome as a systemic disease caused by a defect in the connective tissue, occurred in 1882 by Tschernogobow[3]. Approximately twenty years later, the Danish dermatologist Edvard Ehlers[4] and the French physician Alexander Henri-Danlos[5] publish, independently, their observations of this syndrome. They both combined relevant features of this syndrome and accurately delineated the phenotype of this group of disorders. In 1936 Ronchese describes, for the first time, the *classic* triad of skin and vascular fragility, skin hyperextensibility and joint hypermobility[6] that characterize most of the cases.

The prevalence of this group of hereditary disorders of the connective tissue is estimated to be between 1/10.000 and 1/25.000 and there seems to be no ethnic predisposition[2]. The latest revised nosology (table1) developed during a conference at Villefranche in 1997 allowed a classification in six clinical types based on the main symptoms, genes involved and inheritance pattern[7].

The EDS type IV (vascular form, also known as ecchymotic) is a rare, malignant form. Estimates vary widely, but this condition may account for 5-10% of the EDS[2]. It differs from the other types because it is associated with a higher risk of arterial rupture or aneurysm, gastro-intestinal perforation and uterine rupture which can lead to sudden death[8,11]. Therefore, early recognition of the clinical signs and symptoms of the EDS-IV is extremely important, because the time of diagnosis influences the patient's prognosis.

The EDS-IV is an inherited disorder transmitted in an autosomal dominant manner. The rate of new mutations is high, with sporadic cases occurring in about 50% of the patients[20]. The gene involved in EDS-IV is the COL3A1,

Table 1- Molecular classification of the different types of Ehlers-Danlos syndromes.

Classification of Villefranche (1997)	Former classification Berlin (1988)	OMIM #	Inheritance pattern	Biochemical defect (gene involved)
Classic	I II	130000 130010	AD	COL5A1 COL5A2
Hypermobility	IIII	606408 130020	AD	UKN
Vascular	IV	130050	AD	COL3A1
Kyphoscoliosis	VI	225400	AR	PLOD1 Deficiency of Lysil hydroxilase
Arthrochalasia	VIIA, VIIB	130060	AD	COL1A1, CoL1A2
Dermatosporaxis	VIIC	225410	AR	ADAMTS2
Others: Periodontitis Progeroid	VIII*	 130080 130070	 AD AD	 UKN UKN

*The existence and classification of type VIII is under debate (35), since other forms of this type have been described[36,37].
AD- Autosomal Dominant; AR- Autosomal Recessive; XL- X-linked; UKN- unknown (adapted from Germain D[2]).

Table 2- Diagnostic criteria for Ehlers-Danlos syndrome (EDS) type IV

Villefranche diagnostic criteria for Ehlers-Danlos syndrome type IV*	
***Major* criteria**	Arterial rupture Intestinal rupture Uterine rupture during pregnancy Family history of the vascular type of EDS
***Minor* criteria**	Thin, translucent skin (especially noticeable on the chest/abdomen) Easy bruising (spontaneous or with minimal trauma) Characteristic facial appearance (thin lips and philtrum, small chin, thin nose, large eyes) Acrogeria (an aged appearance to the extremities, particularly the hands) Hypermobility of small joints Tendon/muscle rupture Early-onset varicose veins Arteriovenous carotid-cavernous sinus fistula Pneumothorax/pneumohemothorax Chronic joint subluxations/dislocations Congenital dislocation of the hips Talipes equinovarus (clubfoot) Gingival recession

*The combination of any two of the *major* diagnostic criteria should have a high specificity, but warrant further laboratory investigation to confirm the diagnosis. The presence of one or more criteria supports the clinical diagnosis, but is not sufficient to make the diagnosis. (adapted from Beighton et al[7])

whose locus is located on the long arm of chromosome 2 (2q24.3 - q31), which encodes procollagen type III. Mutations in the gene alleles produce quantitative or qualitative defects on collagen type III, which can lead to arterial dissections and lacerations characteristic of this syndrome[9-11,13].

Clinical manifestations

Many of the classic features of EDS are absent in EDS-IV. The *major* clinical manifestations of EDS-IV are spontaneous arterial rupture, spontaneous intestinal perforation or rupture (most frequently at the level of sigmoid colon) and spontaneous uterine rupture, i.e.: organs rich in collagen type III (table 2).

The other common clinical manifestations are easy bruising, purpuric lesions and delayed healing[8], despite normal coagulation tests. In children this can lead to allegations of child abuse[14]. This propensity to bleed is related to capilar fragility and not to platelet deficiency or defect. Patients have thin, translucent skin, with visible subcutaneous veins on the thorax, shoulders and abdomen[14-17]. The skin on the extremities has the appearance of prematurely aged, with skin wrinkles (acrogeria). Patients are usually of short stature, low weight and characteristic facial features (pinched nose, thin lips, prominent staring eyes with periorbital pigmentation and fine telangiectasae of the eyelids, high cheekbones and sunken cheeks (because of a decrease in adipose tissue)[18]. In some cases facial dysmorphism is absent and this can be misleading[14].

The joint hypermobility that is a typical feature of the other types of EDS (I, II and III) is uncommon in type IV and is limited to small joints of the hands and feet[18].

The vascular involvement occurs in systemic arteries and may manifest as rupture, dissection or aneurysm, carotid-cavernous fistula and intracranial aneurysms (which progress into intracranial hemorrhage in 4% of the cases)[14,20-22]. The leading cause of death is arterial rupture (primarily abdominal and thoracic) which is unpredictable and accounts for 70% of deaths. Any anatomical locations can be involved and there is a tendency (50% of cases) towards large-medium calibre arteries (proximal branches of the aortic arch, the descending thoracic aorta and abdominal aorta and its distal branches)[2,9,10,23]. The fragility of the arterial wall also makes surgical repair difficult[2,24,25].The average age for the first arterial or gastrointestinal complication is 23 years old[20]. Pregnancy increases the likelihood of uterine rupture or vascular injury, particularly during the last trimester, with maternal mortality reaching 12%[2,20]. There is a higher incidence of premature rupture of membranes and congenital birth defects in newborns (clubfoot and congenital hip dysplasia). A quarter of individuals affected with EDS-IV undergo a medical problem before the age of 20 and 80% by the age of 40 years. The median survival of these individuals is 48 years[20].

DIAGNOSIS

The diagnosis of EDS-IV is based on clinical criteria (Table 2) and is easier to suspect of such disorder when the patient presents characteristic features, such as acrogeria, typical arterial or digestive complication or a positive family history[2].

Therefore family history and sudden deaths should be investigated among relatives. However, because of the clinical variability, to confirm the diagnosis of EDS-IV is necessary to demonstrate a quantitative or qualitative deficit in the amount of collagen type III and/or the identification of a COL3A1 gene mutation by molecular genetic testing.

The lack of collagen type III may be assessed by direct biochemical analysis of cultured dermal fibroblasts, which requires skin biopsy. The protein electrophoresis can demonstrate the quantitative or qualitative deficit of collagen III. These biochemical studies enables the identification of more than 95% of individuals with structural alterations in the protein synthesized[20].

Alternatively, molecular analysis of the DNA sequence is able to determine the presence of COL3A1 gene mutation. The sensitivity is low, about 60%, but because of its high specificity is considered the *gold standard* for diagnosis[26]. More than 100 mutations of the COL3A1 gene have been reported and two thirds of them result in the substitution of glycine residues in the [Gly-X-Y] triplets of the helical domain of the gene[20].The remaining mutations affect the splice sites in the COL3A1 with a predilection for the 5'(donor) splice-site in an intron[1,27,28]. The clinical complications in this syndrome don't seem to have any relationship with the specific mutation on the COL3A1 gene[20].

The use of noninvasive imaging, such as Doppler sonography, computed tomography (CT) and magnetic resonance imaging (MRI) angiography is recommended for annual or biennial[2] follow-up screening of aneurysms or arterial dissections in patients with EDS-IV. The performance of invasive exams (i.e. angiography) carries a significant risk of vascular complications, such as hematomas at the puncture site and tears of the arterial wall and is, therefore, contraindicated. The benefit/risk ratio of any invasive diagnostic procedure should be carefully assessed and left only for the cases strictly necessary (i.e. arterial embolization)[11,22,24].

TREATMENT

In view of the fact that there is no specific treatment available for the EDS-IV, medical intervention is based on symptoms control, prophylactic measures (to minimize the risk of trauma) and genetic counseling.

When a family is confronted with a positive genetic test

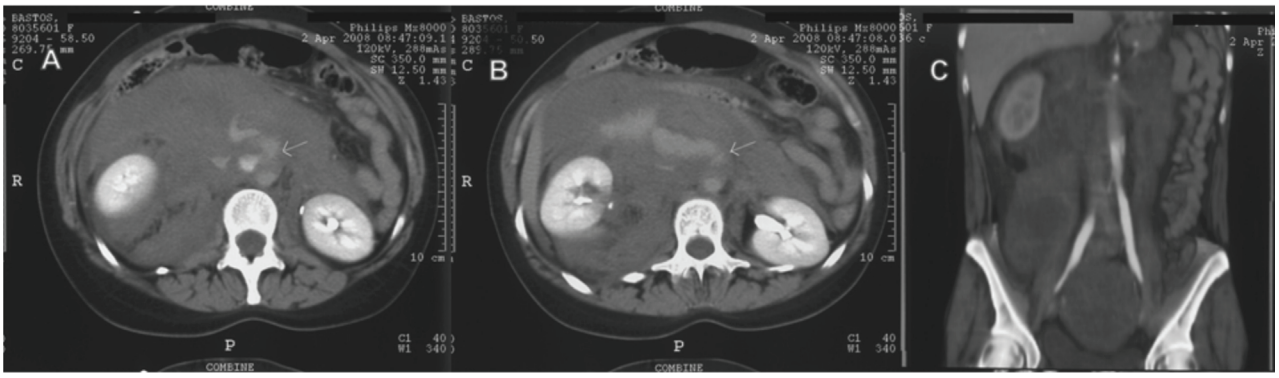

Fig. 1 - Abdominal computed tomography scan (before surgical intervention). A and B (axial views): spontaneous rupture of the abdominal aorta with active bleeding (big arrow). C (coronal view) revealing the normal caliber of the aorta.

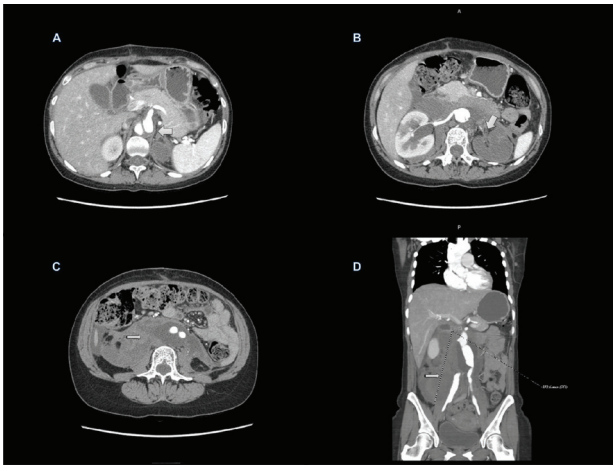

Fig. 2- Contrast enhanced abdominal computed tomography scan (two days after the surgery). A, B and C (axial views): A) Dissection of the abdominal aorta (big arrow). B) Thrombosis of the left renal artery (big arrow). C and D (coronal view): Large retroperitoneal hematoma (small arrow).

for EDS-IV, genetic counseling is an obligatory part of the medical management, not only because of the dominant pattern of transmission, but also because of the malignant features of this disorder[2,20]. Arterial, digestive and uterine complications require hospitalization, observation in an intensive care unit and sometimes surgery[14]. Arteriograms and endoscopies are contraindicated for the reasons mentioned previously. Surgical treatment is very demanding and there is a tendency to vascular tear because of tissue brittleness to pressure, delayed healing and recurrent propensity for the complications already mentioned. Most authors argue that surgical repair should be performed with arterial grafts and anastomoses avoided[2,21]. Prolonged post-operative follow-up is required and surveillance with non-invasive imaging techniques repeated. To optimize the likelihood of surgical success, surgeons should be informed of the diagnosis before beginning surgery. Therefore, patients are advised to bring a medical letter or a card indicating the nature of their disease, the vascular or visceral complications that they are at risk, their blood group and contact details of their medical doctor[2,14]. Intense physical activity is not recommended[14]. The benefits of anticoagulants or other medical treatment that interfere with platelet function should be weighed against its risks. There are ongoing clinical trials in Europe evaluating the benefits of long-term beta blockers treatment in the prevention of vascular complications of EDS-IV[2,29].

CASE REPORT

A 35-year-old Portuguese woman was admitted at the emergency department (ED), of a local Hospital (10 days after a Caesarean section) with acute abdominal pain. It was her first pregnancy. She had no other past medical history and was a non-smoker. On admission she complained of a sudden severe and sharp epigastric pain radiating to the back. Initially, on physical examination she was alert and well oriented in space and time, but afterwards she started developing clinical signs of acute abdomen with hypovolemic shock and abdominal tenderness. She had a pale thin skin (subcutaneous vessels were visible), inadequate perfusion of the extremities and temperature (37,1ºC). She had a weak and rapid pulse rate of 120 beats per minute (regular rhythm) and a blood pressure 70/30 mmHg.

Spontaneous arterial rupture was suspected and an urgent abdominal enhanced CT scan was performed revealing abdominal aorta rupture (figure 1).

She was immediately transferred to a tertiary Hospital and taken to the operating room where she underwent laparotomy. Intra-operatively a large retroperitoneal hematoma was found approximately 4 cm below the origin of the renal arteries that resulted from aortic (which showed normal caliber) dissection (figure 2).

After hemodynamic stability, the aorta was clamped proximal and distal to the tear and replaced by a cylindrical

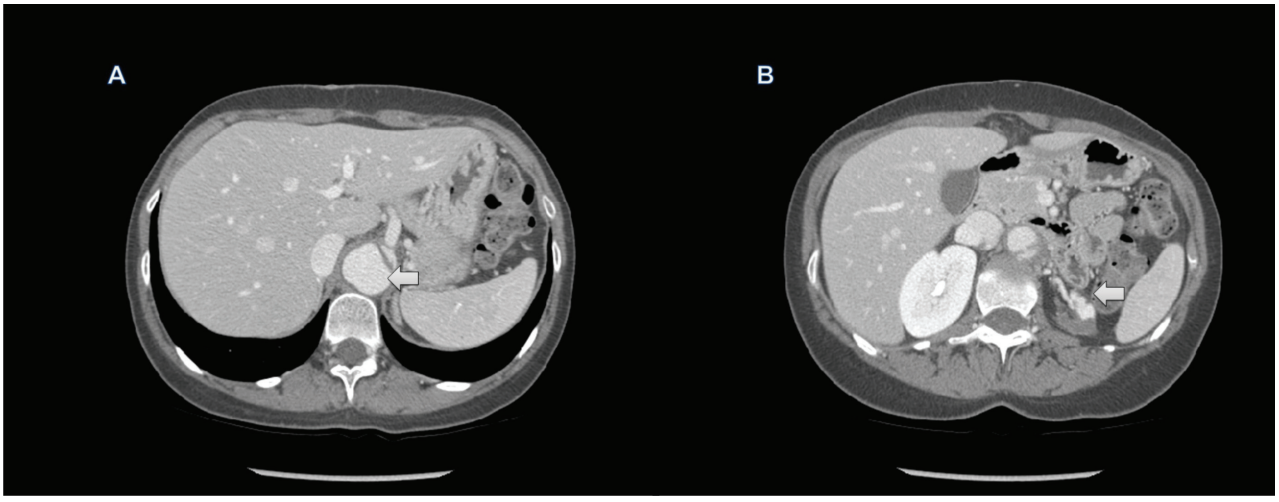

Fig. 3 - Contrast enhanced abdominal computed tomography scan (six months after the surgery, axial views): A) the dissected aorta (big arrow), B) atrophy of the left kidney (big arrow) and resolution of the retroperitoneal hematoma.

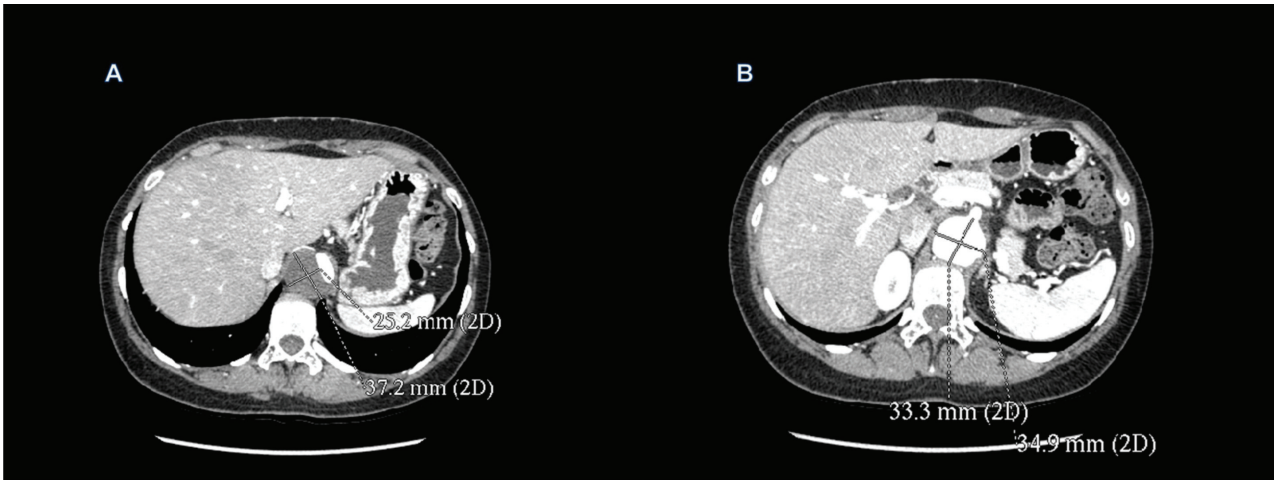

Fig. 4 - Two-year follow-up contrast enhanced abdominal computed tomography (axial views): A) dilatation and mural thrombosis of the false lumen of the dissected abdominal aorta with aneurismal dilatation of the false lumen. B) Distal communication between the true and false lumen.

Dacron prosthesis. The aortic wall was not able to stand the tension and repeatedly tore. Several unsuccessful attempts of anastomosis were made. Finally, there was a need to lengthen the cylinder with another bifurcated Dacron graft with distal anastomoses to the common iliac arteries and shear forces were avoided while performing these last sutures. After the surgical intervention, a CT scan was done, which revealed an aortic dissection (with communication between both lumens) that caused complete lack of the left kidney perfusion and a large retroperitoneal hematoma. The patient developed hypertension as a consequence of the left kidney loss. Afterwards, the patient's family history was explored. Her father had died of sudden death when he was 39 years old and which etiology was not investigated, and her sister had died of an abdominal aorta rupture at the age of 30. Based on the clinical presentation the initial diagnostic hypotheses were: Ehlers-Danlos syndrome (EDS), Cystic medial degeneration and Marfan syndrome

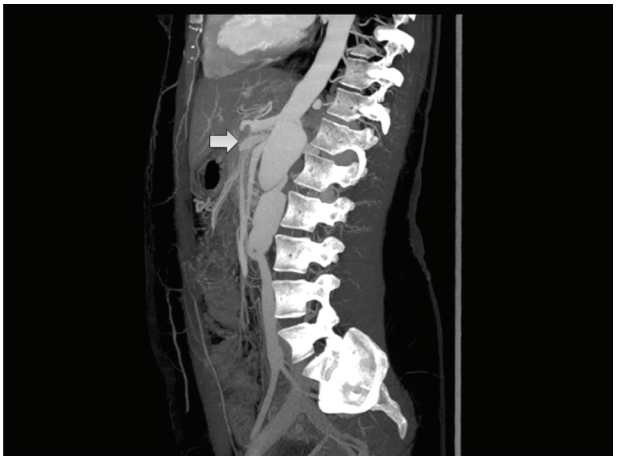

Fig. 5- Computed tomography (sagittal reconstructed image) showing the aneurysmal dilatation in the dissected aorta upstream from the mural thrombosis of the false lumen.

because of the high frequency of aneurysms that occur in these diseases. This last one less likely, because of the patient biotype. The histology of cylindrical segments of the aorta showed changes consistent with EDS. To confirm the diagnosis of EDS a genetic/molecular analysis of the COL3A1 was done, that detected the mutation c.970G>A (p.Gly157Ser) in heterozygosity in the COL3A1 gene, which resulted in a substitution of an amino acid (glycine) for another (serine). This mutation is reported (only once in the literature) in a family with internal carotid artery dissection (30). We know today that roughly two thirds of the mutations in this gene are reported as a substitution of amino acid glycine in the (Gly-X-Y) triplets of the helicoidal region of COL3A1 gene. We performed the same genetic study of COL3A1 gene in the daughter which identified the presence of the same mutation inherited in an autosomal dominant pattern.

In the last two years, biannual chest and abdominal CT scan have been performed in the patient, that have shown stability of the abdominal aortic dissection, complete resolution of the retroperitoneal hematoma and atrophy of the left kidney (figure 3). A spontaneous thrombosis of the false lumen of the dissected aorta has been developed with aneurysmal dilatation formation upstream to the level of the intramural thrombosis (figures 4 and 5), but till now with no indication for surgical intervention.

DISCUSSION

The EDS is a heterogeneous group of hereditable diseases that affect the synthesis of collagen and present clinical and genetic heterogeneity. The EDS-IV is a rare variant of the EDS and is considered a disorder with poor prognosis, often associated with vascular catastrophes, perforated viscera, uterine rupture and pneumothorax, which may remain undiagnosed until the time of autopsy[17,19,30]. Arterial aneurysms, its rupture and dissections are common in this group of disorders. The case described is a good example that early recognition of the syndrome is of vital importance to improve the prognosis of these patients, who often present themselves with life-threatening situations.

The patient presented some of the physical signs suggestive of this disorder such as thin lips, thin and translucent skin and aortic rupture. The hiperextensibility joint is rare in EDS-IV and often absent, as in this case.

The arterial rupture is the leading cause of death in this syndrome and is associated with and increased morbidity and mortality risk[2,20,21]. Although surgical approach in these situations is difficult and the operative mortality is very high due to the tendency of the vessels to tear at minimum handling, mortality from hemorrhage without surgical intervention is also greater. The vascular fragility in this patient was not only demonstrated by the initial clinical presentation of spontaneous aortic rupture, but also during the reconstructive surgery that was complicated by the difficulty to anastomose and repair of the lacerated vessels, that repeatedly tore. In these cases there is also a process of coagulation compromised, related to platelet aggregation and interaction with the endothelium of blood vessels. This process is hampered by the absence of collagen type III at the level of the endothelium[31]. The authors Pepin et al. conducted a review of 220 patients and 199 family members affected by the disease and 131 deaths were registered, of whom 103 had arterial rupture and 78 vascular rupture related to thoracic-abdominal vasculature[20]. The same study identified 135 patients with mutations in COL3A1 gene, however it was not found any correlation between the location and nature of the mutation and the type and frequency of major vascular complications[20], unlike initial descriptions of the disease[32].

In this case vascular complication led to the left kidney loss and the patient developed hypertension detected postoperatively. The patient began taking beta-blocker and an angiotensin II antagonist, not only for blood pressure control but also for vascular protection, since an uncontrolled hypertension can result in rupture of the dissected aorta. After two years, the follow-up CT scan reveals a thrombosis of the false lumen of the dissected aorta and aneurismal dilatation, but without indication for surgical intervention. Surgical management in these cases is hazardous and often unrewarding, left only for the cases of life threatening situations with appropriate modification of surgical techniques, particularly in emergency situations.

This patient had an uneventful pregnancy and delivery by caesarean section, which also took place without complications. In the same study by Pepin *et al.* from 183 pregnancies reported was possible the delivery of 167 live births, but 12 women died in the peri-partum or two weeks after birth[20]. Pregnancy increases the risk of complications, with a mortality rate of 12%[20]. Pregnant women with EDS-IV identified should be followed in reference centers, as they are high-risk pregnancies. Until now no study has shown that elective Caesarean section reduces mortality during child delivery.

The patient had a family history of sudden death in both father and sister (this last one with a vascular catastrophe documented) which supports the diagnosis of EDS type IV familial with an autosomal dominant transmission pattern.

The diagnosis of EDS-IV would probably have been easier if the patient had presented typical skin features, such as acrogeria and if initially her family history of sudden deaths had been valorized. The molecular study of COL3A1 gene revealed the mutation c.970G>A (p.Gly157Ser) only once reported in a German family with internal carotid dissections[30]. This type of mutation (glycine substitutions in triple helical region of COL3A1) characterizes the EDS-IV as it was stated by the same

author who describes this family with carotid dissections. However, because the same family didn't present the clinical signs of the EDS-IV, the author only suggested that could be a mild form of an unrecognized EDS. In our case the clinical features typical of EDS-IV are present and the identification of the mutation in COL3A1 gene confirmed the diagnosis. We also explore any possible relationship between our patient's family and the family with carotid dissections, but the patient denied any emigration of a relative to another country. However, it's intriguing the finding of such a mutation in two different families, since this type of mutations is particular to a given family[2]. It's the first time this mutation is reported in association with Ehlers-Danlos type IV, since it isn't still referred in the OMIM (Online Mendelian Inheritance in Man) pages of the genes associated to EDS-IV.

When trying to find a reason for the existence of the same mutation in two different families we found in the literature other reports of COL3A1 gene mutation whose phenotypic expression were not representative of normal malignant nature of EDS-IV. In some cases symptoms are produced because the normal COL3A1 protein may be reduced to half (*haploinsufficiency)* as was reported in recent study of various types of gene mutations COL3A1[33].

Recently Borck *et al.* reported the case of a 42-year-old woman with spontaneous rupture of common iliac artery, but whose genetic study of the COL3A1 gene didn't detect any mutation. The patient presented cutaneous lesions typical of EDS type I and molecular analyzed of the COL5A1 gene was made, which identified a new heterozygous nonsense mutation (c.3184C> T (p.R1062X)[34].

All these findings support the heterogeneity of genotypes and phenotypes of the EDS and that overlap between phenotypes may also occur in the different types of EDS.

The identification of families carrying the mutation allows a better surveillance of this disease, because sometimes the skin and vascular symptoms are mild or even absent until adulthood. It also allows a more timely prenatal diagnosis for the COL3A1 gene mutation carriers. Patients affected have a 50% risk of transmitting the disease to each of their children and in our case the identification of a mutation in the COL3A1 gene allowed the detection of the same mutation in the daughter and family screening of the other relatives. A high index of suspicion should always be taken into account in the clinical situations that present themselves as vascular catastrophes. Examples are pregnant women with a family history of vascular events that require a strong surveillance because those are considered high-risk pregnancies.

The vascular complications of EDS-IV always require hospitalization and multi-disciplinary approach by surgeons, internists, imaging, obstetricians and geneticists. It already exists in some countries, emergency networks connected to Hospitals that allow a timely evaluation for medical and surgical intervention of patients with this syndrome. Careful decisions related to the use of diagnostic and therapeutic interventions are necessary to prevent iatrogenic complications that obscure the already reserved prognosis.

CONCLUSION

and learning points:

- - EDS type IV is a rare inherited disorder caused by a defect in the synthesis and metabolism of the collagen.
- - Early recognition of this disorder is of vital importance to improve the prognosis of these patients, who often present themselves with life-threatening situations, such as arterial rupture and hollow organs perforations.
- - Clinical findings support the diagnosis, but molecular and biochemical laboratory analysis are required to confirm it.
- - Approximately two thirds of the COL3A1 gene mutations are caused by substitutions of the glycine residues in the triplets of the helical domain of the gene.
- - Each mutation is particular to a given family.
- - The mutation c.970G>A (p.Gly157Ser) in the COL3A1 gene is a new mutation associated to the EDS-IV.
- - Genetic counseling and a multidisciplinary patient approach is a requirement in medical follow-up.
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REFERENCES

1. WATANABE A, Shimada T. The Vascular Type of Ehlers-Danlos Syndrome. J Nippon Med Sch 2008; 75 (5)
2. GERMAIN D. Ehler-Danlos syndrome type IV. Orphanet Journal of Rare Diseases, 2007; 2: 32
3. TSCHERNOGOBOW A. Cutis laxa. Mhft Prakt Dermatol 1892; 14-76
4. EHLERS E. Cutis laxa, Neigung zu Haemorrhagien in der Haut, lackerrung mehrerer Artikulationen. Derm Zschr 1901; 8: 173-174
5. DANLOS PM. Un cas de cutis lasa avec tumours par contusion chronique des coudes et des genoux (xanthome juvenile pseudodiabetique de MM. Halopeau et Mace de Lepinay). Bull Soc Franc Derm Syph 1908; 19: 70-72
6. RONCHESE F. Dermatorrhexis with dermatochalasis and arthrochalasis (the so called Ehlers-Danlos syndrome). Am J Dis Child 1936; 51: 1403-1414
7. BEIGHTON P, Paepe A, Steimann B, Tsipouras P, Wenstrup R. Ehlers-Danlos syndrome: revised nosology, Villefranche, 1997. Ehlers-Danlos National Foundation (USA) and Ehlers-Danlos Support Group (UK). Am J of Med Genet 1998; 77:31-37
8. PREVITERA A, Milkhu C, Datta V, Sayegh M, Cohen R, Windsor A.

Spontaneous Rupture of the Spleen in Type IV Ehlers-Danlos Syndrome: Report of a case. Surg Today 2009; 39: 52-54
9. MAGALHÃES E, Fernandes S, Zanardi V, Medeiros C, Midori R, Sachetti Z. Ehlers-Danlos Syndrome Type IV and Multiple Aortic Aneurysms - A case report. Angiology, 2001; 52 (3): 223-228
10. KERWIN W, Pepin M, Mitsumori L, Yarnykh V, Schwarze U, Byers P. MRI of great vessel morphology and function in Ehlers-Danlos syndrome type IV. Int J Cardiovasc Imaging 2008; 24: 519-528
11. NORTH KN, Whitman DA, Pepin MG, Byers PH. Cerebrovascular complications in Ehlers-Danlos syndrome type IV. Ann Neurol 1995; 38(6): 960-964
12. KOH J, Kim J, Hong S, Choe Y, Soo Do Y, Byun H, Lee W, Kim D. Skin Manifestations, multiple aneurysms and carotid-cavernous fistula in Ehlers-Danlos syndrome type IV. International Journal of Cardiology, 1996; 54: 283-286
13. HAUSSER I, Anton Lamprecht I. Differential ultrastructural aberrations if collagen fibrils in Ehlers-Danlos syndrome types I-IV as means of diagnostic classification. Hum Genet 1994; 3:394-407
14. GERMAIN D, Guzman Y. Vascular Ehlers-Danlos syndrome. Annals de génétique, 2004 (47): 1-9
15. DALGLEISH R. The human Collagen Mutation Database. Nucleic Acids Research 1998; 26 (1): 253-255
16. OKITA H, Ikeda Y, Mitsuhashi Y, Namikawa H, Kitamura Y, Hamasaki Y et al. A novel point mutation at donor splice-site in intron 42 of type III collagen gene resulting in inclusion of 30 nucleotides into the mature mRNA in a case of vascular type of Ehlers-Danlos syndrome Ach Dermatol Res 2010; 302: 395-399
17. DE PAEPE A, Malfait F. Bleeding and bruising in patients with Ehlers-Danlos syndrome and other collagen vascular disorders. J Haematol, 2004 127: 491-500
18. GERMAIN DP. Clinical and genetic features of vascular Ehlers-Danlos syndrome, Ann Vasc Surg 2002; 16: 391-397
19. BREARLEY S, Fowler J, Hammer JP. Two vascular complications of the Ehler-Danlos syndrome. Eur J Vasc Surg 1993; 7: 210-213
20. PEPIN M, Schwarze U, Superti-Furga A, Byers P. Clinical and Genetic Features of Ehlers-Danlos Syndrome type IV, the vascular type. NEJM 2000; 342 (10):673-680
21. ODERICH G, Panneton J, Bower T, Lindor N, Cherry K, Noel A, Sullivan T, Gloviczki P. The spectrum, management and clinical outcome of Ehlers-Danlos syndrome type IV: a 30 year experience. Journal of Vascular Surgery, 2005; 42(1):98-106
22. ZILOCCHI M, Macedo T, Oderich G, Vrtiska T, Biondetti P, Stanson A. Vascular Ehlers-Danlos Syndrome: Imaging findings. AJR 2007; 189: 712-719
23. ROSSI P, Scher L, Friedman S, Hall M, Boxer R, Bialer M. Subclavian artery pseudoaneurysm in the type IV Ehlers-Danlos Syndrome. Journal of Vascular Surgery 1998; 27(3): 549-551
24. MATTAR SG, Kumar AG, Lumsedn AB. Vascular complications in Ehlers-Danlos syndrome. Am Surg 1994; 60: 827-831
25. FREEMAN RK, Swegle J, Sise MJ. The surgical complications of Ehlers-Danlos syndrome. Am Surg 1996; 62: 869-873
26. Pyeritz R, Ehlers-Danlos Syndrome. Editorial. NEJM 2000; 730-732
27. YANG J, Lee S, Kim J, Kim H, Jang S. Genetic Analysis of three korean Patients with Clinical Features of Ehlers-Danlos syndrome type IV. J Korean Med Sci 2007; 22:668-705
28. SCHWARZE U, Goldstein JA, Byers PH: Splicing defects in the COL3A1 gene: marked preference for 5'(donor) spice-site mutations in patients with exon-skipping mutations in Ehlers-Danlos syndrome type IV. Am J Hum Genet 1997; 61: 1276-1286
29. BOUTOUYRIE P, Germain DP, Fiessinger JN, Laloux B, Perdu J, Laurent S: Increased carotid wall stress in vascular Ehlers-Danlos syndrome. Circulation 2004, 109: 1530-1535
30. MARTIN J, Hausser I, Lyrer P, Busse O, Schwarz R, Schneider R et al. Familiar Cervical artery Dissections: Clinical, Morphologic and Genetic Studies. Stroke 2006; 37: 2924-2929
31. ADAMI P, Manzoni P, Rohmer P. Anévrysmes évolutifs au cours d'un syndrome d'Ehlers-Danlos de type IV, Ann Radiol (Paris), 1993; 36:129-133
32. DE PAEPE A. The Ehlers-Danlos syndrome: a heritable collagen disorder as cause of bleeding. Thromb Haesmot 1996; 75: 379-386
33. SCHWARZE U, Schievink WI, Petty E, Jaff MR, Babovic-Vuksanovic D, Cherry KJ *et als*. Haploinsufficiency for one COL3A1 of type III procollagen results in a phenotype similar to the vascular form of Ehlers-Danlos Syndrome, Ehlers-Danlos Syndrome Type IV. Am J Hum Genet 2001; 69(5): 989-1001
34. BORCK Guntram, Breighton P, Wilheim C, Kohlhase J, Kubisch C. Arterial rupture in classic Ehlers-Danlos Syndrome with COL5A1 Mutation. Am J of Med Genet 2010; Part A 152A: 2090-2093
35. MATAIX J, Banuls J, Munoz C *et al.* Periodontal Ehlers-Danlos syndrome associated with type III and I collagen deficiencies. Br J Dermatol. Apr 2008; 158(4): 825-830.
36. JUUL-KRISTENSEN B, Rogind H, Jensen DV *et al*. Inter-examiner reproducibility of tests and criteria for generalized joint hypermobility and benign joint hypermobility syndrome. Rheumatology (Oxford). Dec 2007; 46(12): 1835-1841.
37. GOTTE M, Spillmann D, Yip GW *et al*. Changes in heparan sulfate are associated with delayed wound repair, altered cell migration, adhesion and contractility in the galactosyltransferase I (beta4GalT-7) deficient form of Ehlers-Danlos syndrome. Hum Mol Genet. Apr 1 2008; 17(7): 996-1009