

Internal carotid artery dissection in a patient with Ehlers-Danlos syndrome type IV: diagnosis and management

Dissecção da artéria carótida interna em paciente com síndrome de Ehlers-Danlos tipo IV: diagnóstico e manejo

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Abstract

Ehlers-Danlos syndrome (EDS) type IV, also known as vascular EDS, is an inherited connective tissue disorder with an estimated prevalence of 1/100,000 to 1/250,000. In EDS type IV, vascular complications may affect all anatomical areas, with a preference for large- and medium-sized arteries. Dissections of the vertebral and carotid arteries in their extra- and intra-cranial segments are typical. The authors report the case of a patient with EDS type IV for whom the diagnosis was established based on clinical signs and who developed internal carotid artery dissection at the age of 44 years. In the absence of a specific treatment for EDS type IV, medical interventions should focus on symptomatic relief, prophylactic measures, and genetic counseling. Invasive imaging techniques are contraindicated, and a conservative approach to vascular complications is usually recommended.

Keywords: carotid artery; internal; dissection; Ehlers-Danlos syndrome; diagnosis; disease management.

Resumo

A síndrome de Ehlers-Danlos (EDS) tipo IV, também conhecida como EDS tipo vascular, é uma doença genética do tecido conjuntivo com prevalência estimada entre 1/100.000 e 1/250.000. Na EDS tipo IV, as complicações vasculares podem afetar todas as áreas anatômicas, com comprometimento preferencial de artérias de médio e grande diâmetros. Dissecções das artérias vertebrais e carótidas em seus segmentos intra e extracranianos são típicas. Os autores relatam o caso de uma paciente com EDS tipo IV na qual o diagnóstico sintomático foi realizado com base nos achados clínicos e que desenvolveu dissecção da artéria carótida interna aos 44 anos. Na ausência de um tratamento específico para EDS tipo IV, a intervenção médica deve ser voltada para o tratamento sintomático, para medidas profiláticas e para o aconselhamento genético. Técnicas de imagem invasivas são contraindicadas e, geralmente, recomenda-se uma abordagem conservadora ao cuidar das complicações vasculares.

Palavras-chave: dissecção da artéria carótida interna; síndrome de Ehlers-Danlos; diagnóstico; manejo da doença.

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INTRODUCTION

Internal carotid artery (ICA) dissection is a condition that results from the infiltration of blood into the vessel wall. It may affect the subintimal and medial layers and lead to artery stenosis or occlusion, or the sub-adventitial layer, which leads to aneurysm formation.¹ Dissections, which usually affect the superior cervical segment of the extracranial ICA and the supraclinoid segment of its intracranial portion, are often caused by trauma¹. Other possible causes include fibromuscular dysplasia, fibroelastic changes of the intima, cystic fibrosis of the media and connective tissue diseases, such as the Ehlers-Danlos syndrome¹.

The Ehlers-Danlos syndrome (EDS) comprises a heterogeneous set of at least 11 syndromes with specific clinical and genetic characteristics resulting from defects in the synthesis or the structure of several types of collagen². The vascular form of the disease is called EDS type IV, which is an inherited dominant autosomal disorder caused by mutations in gene *COL3A1*, located in 2q32.2, which encodes the pro- α 1 chain (III) of the fibrillar collagen type III³⁻⁵. The estimated prevalence of EDS type IV is about 1:100,000 to 1:250,000 in the general population, and there is no ethnic or sex predilections^{3,4}.

Clinically, EDS type IV is characterized by important vascular involvement and a mean life expectancy of 48 years⁴. Vascular complications may affect all anatomic areas, with a preference for large- and medium-sized arteries, and dissections of vertebral and carotid arteries in intra- and extracranial segments are typical events.

EDS type IV is very rare and physicians are not familiar with it. Therefore, the diagnosis is usually made after a catastrophic vascular complication or during autopsy⁴. This report describes a case of EDS type IV in a patient whose most obvious clinical sign was hemiplegia due to spontaneous dissection of the internal carotid artery. The authors also discuss the diagnosis and management of this syndrome in this specific case.

CASE REPORT

A white, married, 44 years old, woman with no history of pregnancy was seen in the emergency department presenting with dysarthria, hemiplegia and hemiparesia of sudden onset in the upper and lower right extremities. Based on symptoms and imaging studies, a diagnosis of ischemic stroke (IS) was made, and she was treated conservatively in an intensive care unit for one week. After that time,

she was discharged and started clinical follow-up with a vascular surgeon, who suspected a connective tissue congenital disease and referred the patient to a geneticist, who established the clinical diagnosis of EDS type IV.

Her family history was relevant, as her brother had a brain aneurysm diagnosed at 17 years, a maternal aunt had an ischemic stroke at 40-45 years, and her maternal grandmother died suddenly due to cardiac arrest at the age of 36 years. Her medical history included umbilical hernia surgery at 21 years of age, resection of uterine leiomyomata at 35 years of age, and operation of varicose veins in the lower limbs at 37 years.

Physical examination revealed a slender profile, thin facial features with deep-set eyes, thin lips, delicate and translucent skin, paucity of subcutaneous tissue, discrete signs of ageing (acrogeria) (Figure 1), loose ligaments in the hands, elbows and knees, negative Steinberg thumb sign and positive Walker-Murdoch wrist sign. Anthropometric data showed that her height was 176.5 cm (90th-97th percentile), arm span, 173.5 cm (arm span/height: 0.98), weight, 63 kg (50-75 p) and cranial circumference, 54.5 cm (50th-75 the percentile).

Color Doppler ultrasound showed a thin band a two-phase turbulent flow in left ICA, with hypochoic material in its lumen filling more than 60% of the diameter of the segment evaluated (Figure 2).

She underwent magnetic resonance angiography (MRA) to examine cervical vessels, and results revealed stenosis of about 80% to 90% of the proximal segment of the left ICA, about 2.5 cm above its emergence (Figure 3).

The investigation continued by using other imaging methods and, because the patient was allergic to iodinated contrast, angiography with carbon dioxide was chosen. The scan showed an image compatible



Figure 1. Patient in reported case. Thin facial features, thin lips, thin skin and paucity of subcutaneous tissue.

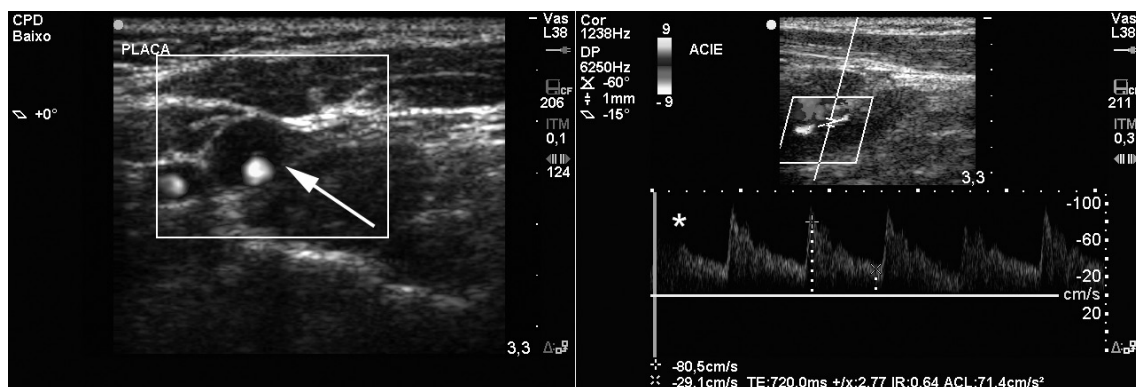


Figure 2. Doppler ultrasound scan of carotid artery shows hyperchoic material in left ICA lumen (arrow) and narrow area of two-phase, turbulent flow (*).

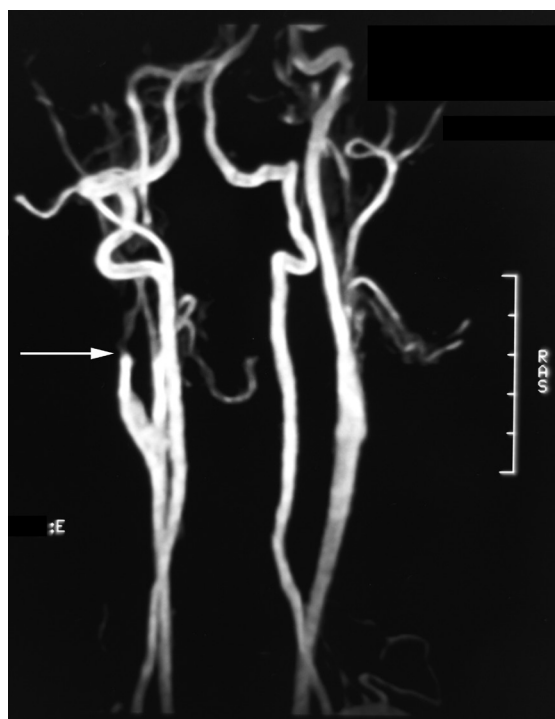


Figure 3. MRA of cervical vessels shows narrowing of left ICA segment (arrow).

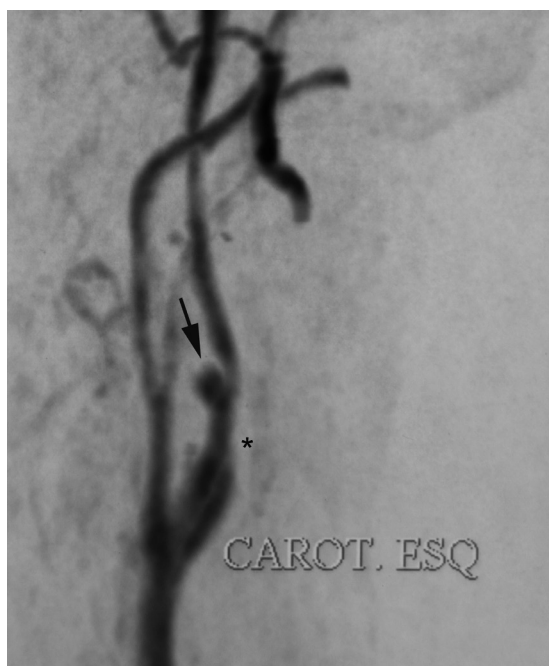


Figure 4. Carbon dioxide angiogram shown narrowing of left ICA segment starting in bulbous region (*) and pseudoaneurysm (arrow).

with an intimal flap in the bulbous portion of the left ICA and narrowing up to about the beginning of the petrous segment, findings associated with acute dissection of the left ICA. In addition, there was a saccular dilatation measuring 0.5 cm of diameter at about 1.5 cm from the carotid bifurcation, which was suggestive of a pseudoaneurysm (Figure 4).

She has been followed up by a vascular surgeon in the outpatient service, and has been taking antiplatelet agents (clopidogrel, 75 mg/day). At every 6 months, she undergoes ultrasound

scanning because of her bicuspid aortic valve; abdominal ultrasound to evaluate the abdominal aorta; and ultrasound scanning of the carotid arteries. She also undergoes treatment with a speech therapist and a physiotherapist due to the sequelae of the ischemic stroke. She was seen by a geneticist, underwent non-directive genetic counseling, and received information about prophylactic measures, risks associated with pregnancy and the clinical and inherited characteristics of EDS type IV.

DISCUSSION

The clinical diagnosis of EDS type IV is usually made according to the criteria defined in 1997 during the Villefranche Conference⁶⁻⁹, shown in Table 1. The presence of two or more major diagnostic criteria suggests the diagnosis, and biochemical or molecular genetic tests should be performed for confirmation.² Biochemical tests evaluate collagen type III by means of electrophoresis of proteins in fibroblasts cultured in material collected for skin biopsy⁹. Molecular tests evaluate DNA directly, and include the complete sequencing of the *COL3A1* gene (reference criterion for laboratory investigation because it detects 95% of the mutations that cause the disease⁴) and the analysis of deletions and insertions more frequently associated with the disease using different techniques, such as *polymerase chain reaction* (PCR) and *multiplex ligation-dependent probe amplification* (MLPA)¹⁰.

In clinical practice, it is very difficult to perform genetic tests to confirm EDS type IV. Currently, biochemical and molecular tests to identify EDS type IV are performed by only 18 laboratories registered in GeneTests, an American site sponsored by the *National Center for Biotechnology Information (NCBI)*, an association of international laboratories that conduct genetic tests approved by the *Food and Drug Administration (FDA)*¹⁰. In Brazil, despite the National Comprehensive Health Care Policy for Clinical Genetics of the Brazilian Unified Health System, most patients with genetic diseases do not have access to medical geneticists or the necessary genetic testing¹¹. The patient in this case report had a clinical diagnosis because she met three major

criteria (thin and translucent skin, characteristic facial features and fragility of arterial walls) and at least three minor criteria (joint hypermobility, early onset of varicose veins and family history of sudden death), but she has not had access to specific genetic tests to this date. An American study analyzed a series of 31 cases of EDS type IV and found that 24 patients (77.3%) underwent biochemical tests, 11 (35.5%) had molecular tests and 7 (22.7%) had a clinical diagnosis¹².

The diagnosis of EDS type IV may be suggested by any ischemic stroke in a young individual^{13,14}, as the syndrome is usually suspected only after vascular complications^{7,9}. Intracranial hemorrhages affect 4% of the patients with EDS type IV, and half of these cases are caused by the rupture of previously detected intracranial aneurysms¹⁵. In a series of 31 patients with EDS type IV, 25% had complications that affected the carotid arteries, and 2 patients had dissections¹². ICA dissections are clinically characterized by a triad of headache (frontal, orbital or peri-orbital), neck pain and partial ipsilateral Horner syndrome (ptosis and myosis). However, carotid dissection is unilateral in most cases, and the patient rarely presents with the classical triad¹. About 50% to 95% of the patients with ICA dissection are estimated to have a subsequent stroke. A Brazilian study with 48 patients conducted from 1997 to 2003 found that the mean time interval from symptom onset to ischemic focal deficit was four to five days¹⁶.

In cases of ICA dissection, the diagnosis of EDS type IV is important for the vascular diagnosis and should define treatment. Defects in collagen type III synthesis make patients highly susceptible to artery or vein ruptures that are difficult to repair surgically^{9,12}. Therefore, invasive imaging studies^{3,17}, such as intra-arterial digital subtraction angiography, the reference standard in the investigation of ICA dissection^{1,18}, are contraindicated. Several non-invasive vascular imaging techniques may be helpful in establishing a diagnosis: extracranial and transcranial Doppler ultrasound and color-coded duplex ultrasound; computed tomography (CT); magnetic resonance (MR); and magnetic resonance angiography (MRA). Ultrasound studies have a joint sensitivity of 95%, but are limited for the visualization of distal ICA dissections. MRI and MRA provide better visualization of morphology and blood flow in the carotid arteries, but also have disadvantages, such as a tendency to overestimate the degree of stenosis, the production of artifacts due to swallowing or patient movements, and a lower capacity to detect acute hematomas^{1,16,18}. When

Table 1. Diagnostic criteria of EDS type IV (adapted from BEIGHTON et al., 1998)²

Major diagnostic criteria
Thin and translucent skin
Arterial, intestinal or uterine fragility or rupture
Extensive bruising
Characteristic facial appearance, including thin and delicate nose, deeply-set eyes, thin lips and hollow cheeks with paucity of adipose tissue
Minor diagnostic criteria
Acrogeria
Hypermobility of small joints
Muscle and/or tendon rupture
Early-onset varicose veins
Talipes equinovarus (clubfoot)
Arteriovenous, carotid-cavernous sinus fistula
Pneumothorax/pneumohemothorax
Gingival retraction
Positive family history, sudden death of (a) close relative(s)

combined, non-invasive vascular imaging studies are the best option for patients with EDS type IV^{3,12,17}.

In the case reported here, Doppler ultrasound, MRA and carbon dioxide angiography confirmed ICA dissection, and the patient did not have to undergo surgery. Studies in the literature suggest that the risk of weakening arterial walls during surgery is high because of the fragility of vessels in patients with EDS type IV. Standard vascular sutures usually lead to tearing, and the best choices for these patients are arterial ligatures, as long as they do not compromise the blood supply to the organ, or a carotid bypass. Other precautions include the delicate and atraumatic handling of the artery and the use of soft, coated clamps or occlusion balloons instead of standard clamps^{1,3,9,12}. However, no conclusive data about the use of stents are available¹².

In general, patients that had spontaneous ICA dissection should receive prolonged anticoagulation treatment with heparin and warfarin for 3 to 6 months to prevent artery-to-artery embolism, and the treatment should be discontinued when there is full arterial recanalization^{1,16}. In a small percentage of cases, recanalization is not achieved after six months, and surgical revascularization may be used¹. In patients with EDS type IV, treatment should be conservative whenever possible, and surgery should be limited to unavoidable, life-threatening situations^{3,12,17}. Minimally symptomatic aneurysms should not be operated on electively unless there are signs of rapid expansion and imminent rupture¹². Patients with aneurysms treated conservatively should be examined at intervals of 3 to 6 months using non-invasive vascular imaging techniques¹². When there is no aneurysm, the usefulness of routine vascular screening is controversial³, but some authors recommend a yearly follow-up visit for a careful physical examination, echocardiogram, carotid and abdominal ultrasound, as well as chest and abdominal CT and MRI in case there are incidental findings^{3,12}.

Several studies have compared anticoagulants and antiplatelet agents for cases of cervical artery dissections, and both medications seem to have similar results¹⁹. Additionally, a recent multicenter study with patients with EDS type IV showed that the use of celiprolol, a $\beta(1)$ -adrenoceptor antagonist with a $\beta(2)$ -adrenoceptor agonist action, reduces the incidence of dissection or arterial ruptures threefold²⁰. Although celiprolol was approved for use in Brazil in 1996,²¹ it is not easily found in the market in this country²², and it is usually imported, which complicates its use by patients.

Specifically, the clinical management of patients with EDS type IV should include the adoption of general prophylactic measures: the elimination of intense physical activity, violent sports or diving; the awareness of the vascular risks of pregnancy (maternal death is about 12%); and, ideally, the use of contraception³. As EDS type IV is an autosomal dominant trait, patients should receive genetic counseling and be aware that the risk of recurrence for their offspring is 50%³⁻⁵.

CONCLUSION

Vascular surgeons should keep in mind the possibility of EDS type IV and its severe vascular complications. Patients with this disease require special care before, during and after operation.

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