Cerebrovascular Involvement in Ehlers-Danlos Syndrome

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Current Treatment Options in Cardiovascular Medicine 2004, **6:**231–236
Current Science Inc. ISSN 1092-8464

Opinion statement

Ehlers-Danlos syndrome type IV is one of the most prominent heritable disorders of connective tissues associated with neurovascular disease. It is an uncommon disorder characterized by thin translucent skin, distinctive facial features, excessive bruising, and rupture of blood vessels or viscera. The typical neurovascular complications of this syndrome are carotid cavernous fistulas, intracranial aneurysms, and cervical artery dissections. Because of the inordinate fragility of the blood vessels in patients with this syndrome, conservative treatment is always indicated. However, in select cases in which the person or family history indicates a more benign form of the disease, treatment that includes surgical or endovascular treatment of asymptomatic lesions may be indicated.

Introduction

The Ehlers-Danlos syndromes are a heterogeneous group of disorders characterized by joint hypermobility, hyperelasticity, fragility of the skin, easy bruising, and abnormal scarring. Ehlers-Danlos syndrome (EDS) was first described in 1668 by van Meek'ren [1], a surgeon in Amsterdam. Of the nine currently established types of Ehlers-Danlos syndromes, it is the type IV or vascular variant that is the most lethal and is also one of the least common, with a prevalence of approximately one in 50,000 to one in 500,000 persons. This type of EDS was first described in 1967 by Barabas [2], a vascular surgeon. Although spontaneous rupture of the bowel or gravid uterus are well-described life-threatening complications of Ehlers-Danlos syndrome type IV (EDS IV), vascular catastrophies account for the great majority of morbidity and mortality associated with this syndrome (70%) [3••]. The vascular complications of EDS IV are characterized by spontaneous rupture, dissection, or aneurysm formation of large and medium-sized arteries in all parts of the body. The average age at the time of the first vascular complication is 25 years and the average age of death is 45 to 50 years. In this article, I specifically review the cerebrovascular manifestations of EDS IV.

GENETICS

Ehlers-Danlos syndrome type IV is inherited in an autosomal-dominant fashion, but the family history is frequently noncontributory because of the high spontaneous mutation rate (approximately 50%). Mutations in the gene encoding the pro α-1 (III) chain of collagen type III (COL3A1) on chromosome 2 are the cause of EDS IV [4]. This type of collagen is the major structural component of this distensible tissue, including arteries, veins, hollow viscera, and the uterus. In addition, collagen type III may play an important role in the fibrillogenesis of collagen type I. A large number of mutations in the *COL3A1* gene have been reported in patients with EDS IV, but there is no good correlation between the type of mutation and the clinical phenotype of the syndrome [3••]. Also, "null" mutations have been reported in patients with EDS IV [5•]. In contrast to the situation with mutations in the type I collagen genes (*COL1A1* and *COL2A1*), in which null mutations result in milder phenotypes, these mutations result in similar severe phenotypes of EDS IV. Thus, it has been suggested that the major effect of the dominant mutations in the *COL3A1* gene is expressed through protein deficiency rather than through incorporation of structurally altered molecules into fibrils.

Table 1. How to recognize Ehlers-Danlos syndrome type IV

History	Examination
Easy bruisability	Face: expressive eyes, thin nose, thin lips, lobeless ears
Vascular rupture, dissection, or aneurysm	Skin: thin and fragile, ecchymoses, abnormal scarring, subcutaneous veins, easily visible
Gastrointestinal perforation	
Uterine rupture	Joints: hypermobility (often just of fingers)
Pneumothorax	

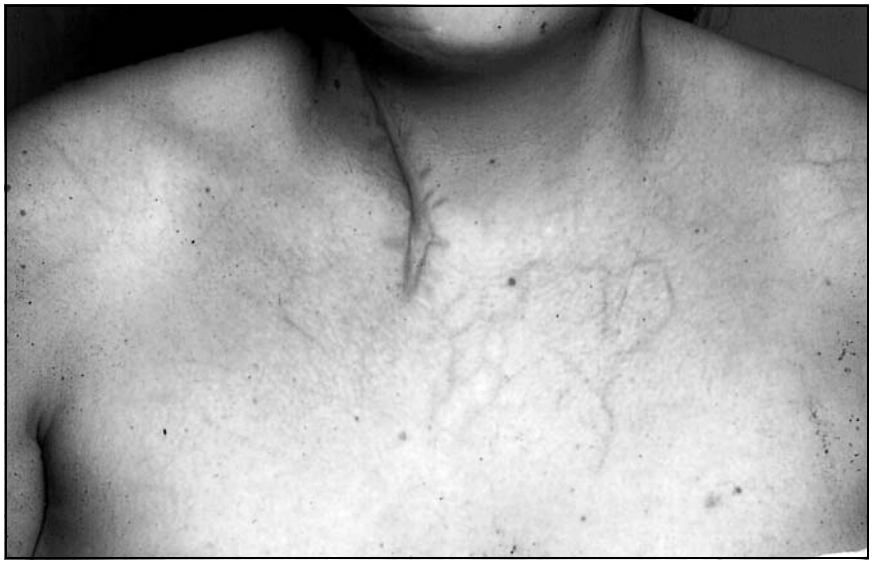

Figure 1. Anterior chest and neck of a 20-year-old woman with Ehlers-Danlos syndrome type IV and bilateral carotid cavernous fistulas. Note the translucent skin with readily visible subcutaneous venous network and keloid scar.

DIAGNOSIS

The clinical diagnosis of EDS IV is based on four cardinal findings: 1) thin translucent skin, 2) distinctive facial features, 3) excessive bruising, and 4) rupture of vessels or viscera (Table 1). In contrast to EDS type I, the skin in EDS IV is not hyperelastic, but rather it is fragile and thin or it may even be normal, and joint hypermobility is not prominent but mild and often it is limited to the small finger joints. These factors make it difficult to diagnose EDS IV before a major vascular or visceral complication occurs. However, a characteristic facial appearance is present in some patients with EDS IV and many patients have a pronounced tendency to bruise. These features are helpful in establishing an early diagnosis. Mitral valve prolapse, spontaneous pneumothorax, and varicose veins may also be clues to the diagnosis, but these abnormalities are less specific. The characteristic facial appearance of EDS IV was first reported by Graf [6], a neurosurgeon, and many striking examples have since been published [4,7]. These facial features consist of the following: 1) large expressive eyes with the sclera clearly visible around the iris, 2) a thin pinched nose, 3) thin lips, especially the upper lip, and 4) lobeless ears. The thin and fragile skin sometimes almost appears translucent, allowing subcutaneous veins to be clearly visible, particularly over the anterior chest and abdomen (Fig. 1). Scarring is often abnormal, and both papyraceous scars as well as keloids may be observed. Excessive bruising is mainly due to tissue and capillary fragility, and tests for hemostasis are usually normal. Identifying patients with EDS IV is extremely important because the vascular fragility associated with the syndrome may make any invasive procedure a hazardous undertaking. The diagnosis of EDS IV should be confirmed by analysis of type III procollagen produced by skin fibroblasts, and a mutation in the *COL3A1* gene can be identified in the great majority of patients.

CEREBROVASCULAR MANIFESTATIONS

The three main cerebrovascular complications of EDS IV are 1) carotid cavernous fistulas, 2) cervical arterial dissections, and 3) intracranial aneurysms. Among 419 patients with EDS IV identified at the University of Washington, 43 (11%) had cerebrovascular manifestations [3••]. Among 19 patients with EDS IV and cerebrovascular complications evaluated by the same group of investigators, six had carotid cavernous fistulas, four had intracranial aneurysms, four had intracranial hemorrhages suspected to be due to intracranial aneurysms, four had spontaneous internal carotid artery or vertebral artery dissections, and one was suspected of having had vertebral artery dissections [8].

Treatment

Carotid cavernous fistula

- Carotid cavernous fistulas are abnormal communications between the internal carotid artery or its branches and the cavernous sinus. Spontaneous carotid cavernous fistulas have been divided into direct and dural fistulas. Direct spontaneous carotid cavernous fistulas are due to rupture of an intracavernous internal carotid artery aneurysm or a tear of the internal carotid artery. EDS IV should be suspected in all patients with a spontaneous direct carotid cavernous fistula, particularly in young adults and in those with bilateral carotid cavernous fistulas [9,10]. However, patients with EDS IV in the sixth decade of life with carotid cavernous fistulas have also been reported. Four patients with EDS IV were identified by the University of California San Francisco group among 212 patients with direct carotid cavernous fistulas, the great majority of which were traumatic in nature [11]. Although a spontaneous carotid cavernous fistula is rarely a life-threatening condition, there is a definite threat to the patient's vision and treatment should be expeditiously instituted, even though the reported mortality rate for treatment of this type of fistula in EDS IV has been as high as 50%.
- Endovascular treatment is the first choice, mainly because surgical treatment of carotid cavernous fistulas is a major undertaking regardless of the presence of an underlying connective tissue disease. Usually, endovascular treatment takes place through a transarterial route, but because of the marked vascular fragility in EDS IV a transvenous route is probably preferable [10]. Another advantage of the transvenous route in closing carotid cavernous fistulas in patients with EDS IV is that it avoids the ectasia and tortuosity of the cervical arteries that is so common in patients with this syndrome. When percutaneous endovascular treatment of a carotid cavernous fistula is planned in a patient with EDS IV, it should be carried out with complete anesthetic and surgical services ready for emergency interventions should severe bleeding occur. Treatment with soft coils is preferable to treatment of the carotid cavernous fistula with balloons. Finally, simple ligation of the cervical internal carotid artery may be the safest option for some patients with EDS IV, although the increased flow through the remaining cervical arteries may increase the risk of aneurysm formation or dissection.

Spontaneous cervical artery dissections

- Dissections of the carotid and vertebral arteries usually arise from an intimal tear, allowing blood under arterial pressure to enter the wall of the artery forming an intramural hematoma. The dissection may result in stenosis, occlusion, or the formation of an aneurysmal dilatation, the so-called dissecting aneurysm. It is possible that some dissections are the result of a primary intramural hematoma. Heritable connective tissue disorders are probably common in patients with spontaneous artery dissections, but the exact type often remains elusive. However, EDS IV is foremost among the heritable connective tissue disorders associated with an increased risk of spontaneous dissection of the carotid and vertebral arteries [12]. Large series of patients with spontaneous cervical artery dissections often include one or two patients with recognized EDS IV.
- To prevent thromboembolic complications, anticoagulation with intravenous heparin followed by oral warfarin is usually recommended for patients with acute dissections of the carotid or vertebral arteries. However, I consider EDS IV to be a contraindication for systemic anticoagula-

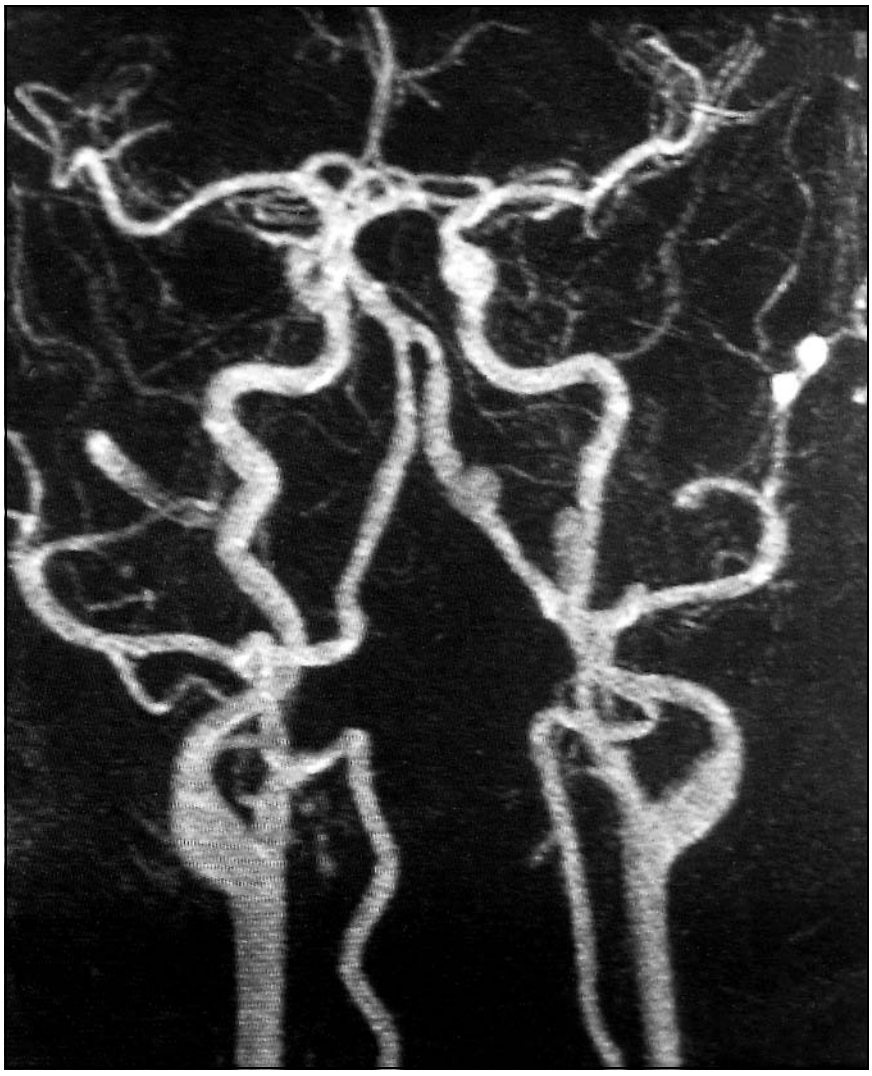

Figure 2. Magnetic resonance angiogram of a 25-year-old man with Ehlers-Danlos syndrome type IV and dissecting aneurysms of the left internal carotid and vertebral arteries.

tion. Treatment with platelet inhibitors, such as aspirin, is probably a better option. Nevertheless, marked bleeding may also occur in patients with EDS IV who are treated with aspirin [13]. Fortunately, a very small minority of patients with dissections require treatment beyond anticoagulation or antiplatelet therapy. Surgical and endovascular treatment should really only be reserved for those patients with EDS who have repeated persistent symptoms of cerebral or retinal ischemia despite maximal tolerated medical treatment.

- Patients with EDS IV and dissections are usually in their second or third decade of life and multiple dissections are common (Fig. 2). In addition, there is an increased risk of recurrence of a spontaneous artery dissection.

Intracranial aneurysms

- Intracranial aneurysms are acquired lesions that are most commonly located at the branching points of the major arteries at the base of the brain. In patients with EDS IV, both saccular as well as dissecting intracranial aneurysms have been reported. There have been no adequate studies delineating the frequency of EDS IV among patients with intracranial aneurysms. In the International Study of Unruptured Intracranial Aneurysms comprising 4060 patients, there were no patients with EDS, compared to

four with neurofibromatosis type I, and 71 with autosomal-dominant polycystic kidney disease [14••]. In my experience, I would estimate that about one in 500 patients with intracranial aneurysms has clinically apparent EDS IV.

- The risk of performing intracranial aneurysm surgery in patients with EDS IV is high. Vascular fragility is the most important cause of catastrophic intraoperative complication [15]. Thus, it is important to observe more than the usual precautions for proximal vascular control. For example, patients with EDS IV who have a posterior communicating artery aneurysm should also have their internal carotid artery exposed in the neck prior to craniotomy. The risk of endovascular coiling is probably as high, if not higher, than surgical clipping in patients with EDS IV. Not only does vascular fragility increase the morbidity and mortality rate of endovascular coiling, the arterial tortuosity may prevent adequate endovascular access and the administration of intravenous heparin, which is performed in most endovascular procedures, may greatly exacerbate the bleeding tendency in these patients.
- Screening is generally not recommended for patients with EDS IV because of the high risk of performing surgery and the shortened life span. However, there appears to be a subgroup of patients and families with EDS IV who have a milder form of the disease and screening should be considered for those individuals. Also, treatment of aneurysms may be better tolerated in this patient population. Unfortunately, there are no known clinical or radiographic parameters predictive of a high surgical risk and, similarly, there is no correlation between a specific mutation in the *COL3A1* gene and the type of frequency of major complications.

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