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Spontaneous Carotid-Cavernous Fistula in a Patient With Ehlers-Danlos Syndrome Type IV

—Case Report—

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Abstract

A 30-year-old female complained of sudden onset of severe proptosis, chemosis, diplopia, and bruit. Right carotid angiography showed a high-flow direct carotid-cavernous fistula (CCF) draining into the engorged superior ophthalmic vein, inferior petrosal sinus, and pterygoid plexus. The patient experienced retroperitoneal bleeding from a ruptured right renal artery after undergoing cerebral angiography. We suspected Ehlers-Danlos syndrome (EDS) type IV, which was confirmed by showing cultured fibroblasts failed to secrete procollagen type III. Endovascular surgery cannot be considered the treatment method of choice in view of the fragility of the arteries and veins in patients with EDS type IV. We treated our patient with extracranial internal carotid artery ligation. Currently, there is no ideal treatment for CCF in patients with EDS type IV. Since CCF is rarely life-threatening, the investigative approach and course of treatment must consider the associated vascular fragility.

Key words: carotid-cavernous fistula, Ehlers-Danlos syndrome type IV, procollagen type III, treatment

Introduction

Ehlers-Danlos syndrome (EDS) is a familial hereditary connective tissue disorder characterized by joint hypermobility, hyperextensible skin, easy bruising, and abnormal scarring.[3,28,30] Ten subtypes have been recognized based on clinical and genetic differencies.[2,6,12,18] EDS type IV was first described by Barbaras in 1967.[1] EDS type IV is the so-called ''vascular type'' accounting for 4% of all EDS cases, and is the most severe form of the disease, with patients frequently dying at a young age, following arterial or myocardial rupture, aortic dissection, or bowel perforation.[6,14,18] Spontaneous carotid-cavernous fistula (CCF) is the most frequent neurovascular complication associated with EDS type IV. We successfully treated a patient with spontaneous CCF associated with EDS type IV by extracranial internal carotid artery (ICA) ligation.

Case Report

A 30-year-old woman complained of sudden onset of severe proptosis, chemosis, and bruit in her head. On admission to another hospital, computed tomography (CT) and magnetic resonance (MR) imaging showed remarkable enlargement of the right superior ophthalmic vein. Cerebral angiography was performed given the suspicion of CCF based on clinical symptoms and neuroimaging. Right carotid angiography showed a high-flow direct CCF draining into the engorged superior ophthalmic vein, inferior petrosal sinus, and pterygoid plexus (Fig. 1). After undergoing cerebral angiography, the patient suddenly complained of severe low back pains, and her blood pressure fell. Abdominal CT showed retroperitoneal hematoma. Abdominal angiography indicated that the source of bleeding was rupture of the right renal artery. The patient underwent transarterial embolization, after which her condition stabilized. She was then trans-

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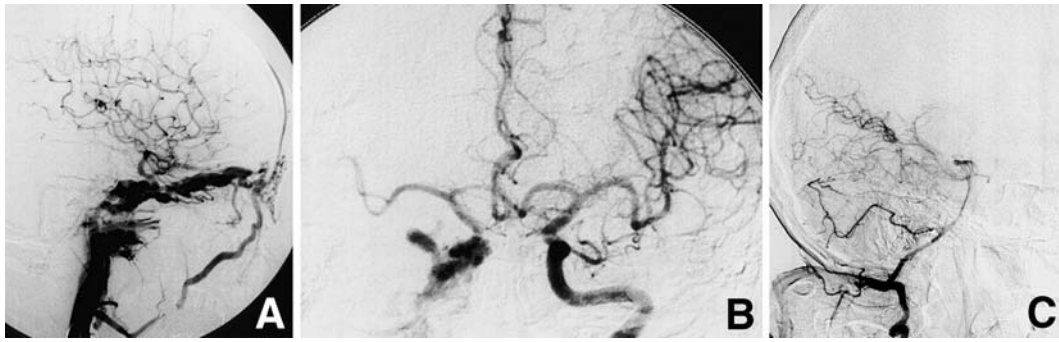

Fig. 1 **A: Right carotid angiogram showing a high-flow direct carotid-cavernous fistula draining into the superior ophthalmic vein, inferior petrosal sinus, pterygoid plexus, and facial veins. B: Left carotid angiogram with compression of the right carotid artery showing the right anterior cerebral artery and right middle cerebral artery filled through the anterior communicating artery. C: Right vertebral angiogram with compression of the right carotid artery (Allcock method) showing the poor blood supply through the posterior communicating artery.**

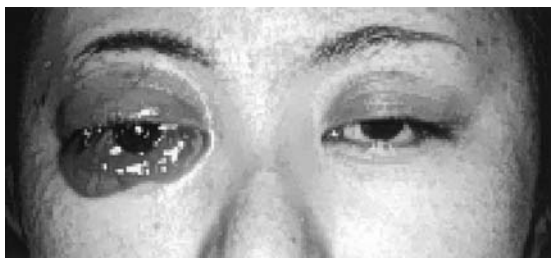

Fig. 2 **Photograph showing the patient's face at presentation to our department.**

ferred to our hospital for treatment of the CCF.

On admission, the patient was alert and fully oriented. Her right eye protruded and pulsated synchronously with her pulse, and the conjunctiva was red and edematous (Fig. 2). A bruit was audible over the whole head, and was loudest over the right fronto-orbital area. Ophthalmological examination indicated uncorrected visual acuity of 0.2/0.7. Bilateral Amsler grid testing indicated no abnormalities at any point in either visual field. The right eye was markedly red with dilated irregular conjunctival and subconjunctival vessels. Hess chart testing indicated abducens nerve paralysis. Ophthalmoscopy revealed somewhat hyperemic optic discs, and dilated retinal vessels, more marked on the left than the right, with no evidence of disc atrophy, and no hemorrhage or exudates in either fundus.

MR imaging showed enlargement of the right cavernous sinus and a prominent high-velocity signal void. The superior ophthalmic vein was enlarged and the right globe was proptotic (Fig. 3).

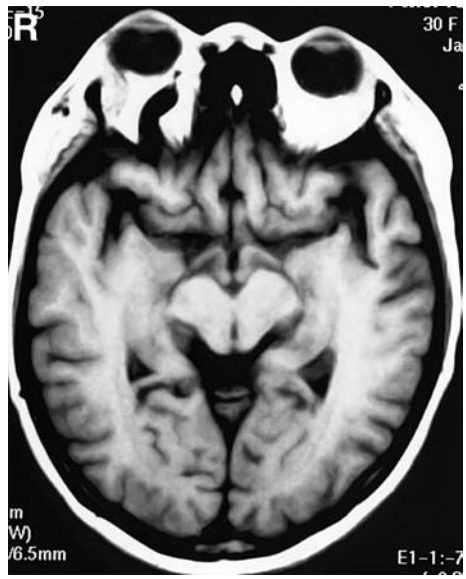

Fig. 3 **T_1-weighted magnetic resonance image showing a high-velocity signal void in the superior ophthalmic vein, and the proptotic right globe.**

The patient had a history of varicose veins. She bruised easily, had thin skin, and hyperextensible joints. Based on the patient's history and the clinical symptoms, we suspected that the right high-flow CCF was caused by ruptured intracavernous sinus aneurysms. Fibroblasts cultured from a skin biopsy failed to secrete procollagen type III (Fig. 4). The diagnosis was EDS type IV.

We considered the risks of interventional radiology under a diagnosis of EDS type IV, and chose

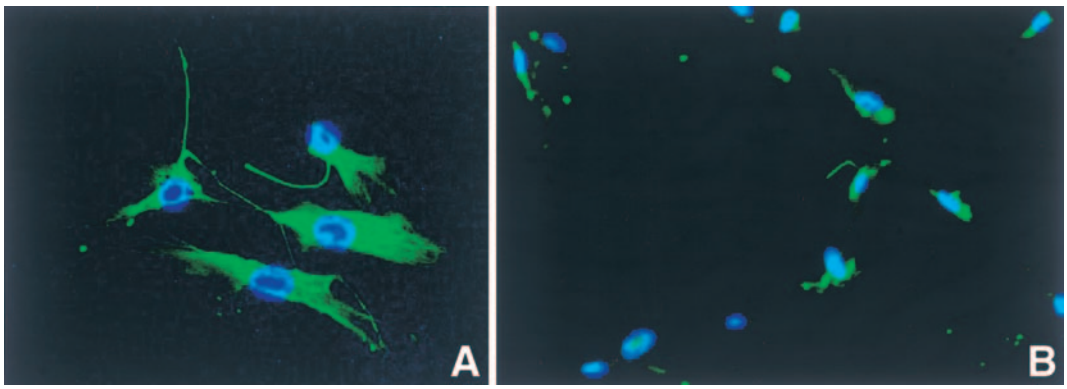

Fig. 4 Photomicrographs showing immunostaining for procollagen type III. A: control fibroblast (×400), B: patient's fibroblast (×200).

conservative treatment, although retroperitoneum bleeding occurred once again at our hospital. Fortunately, the patient's bleeding stopped, and the patient recovered. Right eyeball damage was possible following such an episode of high-flow CCF, and the patient strongly desired to regain her normal appearance. No neurological deficits were provoked by a manual Matas procedure before surgery. No cerebral blood flow study was done because of the fragile vessels. The patient gave informed consent for right ICA ligation in the neck. Since intravascular treatment carried a higher risk than surgery because of the basic disease, and the first priority was avoiding risk, right carotid ligation was performed under general anesthesia. Therefore, the method of carotid ligation after performing test clamping under local anesthesia was not used. She developed transient left hemi-motor weakness during the postoperative period and cerebral infarction was recognized in the external capsule and watershed area in the right hemisphere on MR imaging, but she made a full recovery, with complete resolution of all symptoms. Now, 4 years following the episode, she is leading a normal everyday life as a homemaker. The latest follow-up MR imaging showed only old infarction in the right watershed area and external capsule remained. No obvious new lesion was recognized (Fig. 5).

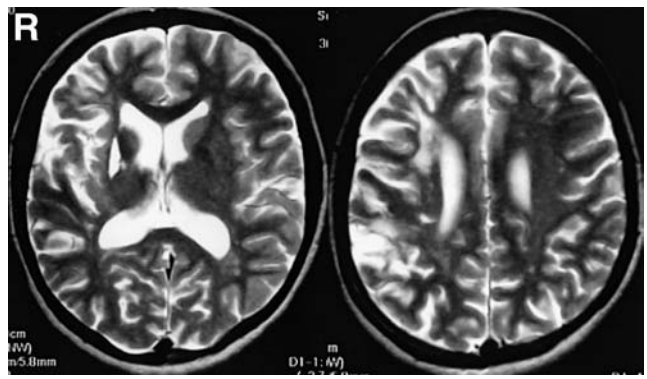

Fig. 5 Follow-up T_2-weighted magnetic resonance images 4 years after surgery, showing old cerebral infarction in the right hemisphere, especially the watershed area and the external capsule.

Discussion

The vessels in patients with EDS type IV have reduced total collagen content, thin walls with irregular elastic fibrils, and reduced cross-sectional areas.[13] Patients with EDS type IV are biochemically characterized by a decrease or absence of type III collagen.[11] EDS type IV is the consequence of mutations in the COL3A1 gene, located on chromosome 2, that alter the metabolism of type III collagen, a major constituent of the walls of blood vessels, the hollow organs of the gastrointestinal tract, and the uterus.[3,24,29] EDS type IV disorder is pathologically heterogenous, and is inherited as autosomal dominant in some families, and as autosomal recessive in the others.[2,22] The clinical diagnosis is confirmed by biochemical assays of type III procollagen synthesized from cultured skin fibroblasts and/or confirmation of mutation in the COL3A1 gene. In our patient, cultured skin fibroblasts produced very low levels of type III procollagen.

Including the present case, only 33 cases of EDS type IV with CCF have been reported since 1955 (Table 1).[2,5–7,9,11,13,14,16,17,21,23,25,26] The age at which the syndrome manifested ranged from 17 to 52 years (mean 31.8 years). The patients were predominantly female (male:female ratio of 1:5.4). Angiography

Table 1 Summary of the clinical course and treatment of 33 patients with Ehlers-Danlos syndrome type IV and carotid-cavernous fistula

Case No.	Author (Year)	Age/ Sex	Side	Treatment	Outcome
1	Francois et al. (1955)[23]	52/F	rt	conservative	blindness
2	Graf et al. (1965)[21]	24/F	lt	1st: graded occlusion	no change
				2nd: extracranial ICA clamping	initial improvement
				3rd: CCA ligation	no change
				4th: ocular enucleation	died 19 days later of cardiac rupture
3		37/F	lt	CCA ligation	no change in vision; died 6 yrs later of rupture of the splenic artery
4		30/M	lt	extracranial ICA ligation	good
5	Schoolman and Kepes (1967)[26]	39/F	lt	extracranial ligation of ICA, ECA, and CCA	initial improvement; died of aortic laceration caused by angiography
6	Julien and De Boucaud (1971)[14]	50/F	rt	NR	died from epistaxis
7	Maugery et al. (1972)[23]	17/F	lt	1st: conservative	spontaneous resolution; recurrence 10 yrs later
				2nd attempt at extracranial ligation	no change in vision, otherwise improved
				3rd: ICA ligation	
8	Farley et al. (1983)[6]	22/F	lt	1st: transvenous balloon embolization	no change
				2nd: transvenous balloon embolization	died 4 days later of pontine hemorrhage
9	Guiolet et al. (1984)[23]	31/F	lt	conservative	spontaneous resolution
10	Dany et al. (1986)[23]	29/F	rt	ICA ligation	died 3 yrs later of hemoperitoneum
11	Lach and Nair (1987)[17]	43/F	lt	attempted transarterial balloon embolization	died 15 days later of right common iliac artery laceration
12	Peacemen et al. (1987)[23]	27/F	NR	NR	died 3 yrs later of renal artery rupture
13	Fox et al. (1988)[23]	20/M	lt	transarterial balloon embolization	good
14	Dean et al. (1989)[23]	27/M	lt	NR	died 2 wks later of ruptured ICA aneurysm
15	Halbach et al. (1990)[11]	19/NR	NR	direct surgical repair	good
16		22/F	lt	1st: transvenous balloon embolization	improved ocular movement
				2nd: transvenous balloon embolization	pontine hemorrhage 4 days later
17	Halbach et al. (1991)[9]	39/F	lt	1st: transarterial balloon embolization	initial improvement
				2nd: transarterial balloon embolization	
				3rd: transvenous injection of liquid adhesive	good
18		49/F	rt	transarterial balloon, platinum coils and silk suture	good
19	Schievink et al. (1991)[25]	17/F	lt	intracranial ICA and CCA ligation and muscle embolization	good
20		20/F	rt	1st: attempted at transarterial balloon embolization	
				2nd: CCA clamping	good
21	Pope et al. (1991)[21]	22/M	lt	transarterial balloon embolization	good
22		25/F	lt	transarterial balloon embolization	proptosis and chemosis resolved with residual lt sixth cranial nerve paresis
23		45/F	rt	transarterial balloon embolization	good
24		27/F	lt	attempted transarterial balloon embolization	died 2 wks later of ruptured rt ICA aneurysm
25	Kashiwagi et al. (1993)[16]	22/M	lt	attempted transvenous balloon embolization, transarterial balloon embolization	good
26	Forlodou et al. (1996)[7]	40/F	rt	transarterial balloon embolization	6 mos later paralysis of the rt sixth cranial nerve regressed
27	Debrun et al. (1996)[5]	39/F	rt	1st: transarterial balloon embolization	proptosis and chemosis subsided within 1 wk
				2nd: transvenous balloon embolization	died 1 yr later of massive intestinal hemorrhage
28		39/F	lt	transarterial balloon embolization	good
29		39/F	lt	1st: transarterial balloon embolization	recurrence 6 hrs later
				2nd: transarterial balloon embolization and ICA occlusion	good
30	Bashir et al. (1999)[2]	50/F	lt	transvenous GDC embolization	died 4 days later of hemothorax and abdominal aortic rupture
31	Horowitz et al. (2000)[13]	18/F	lt	transvenous GDC embolization	died 21 days later of ruptured cardiac posteromedial papillary muscle
32		40/F	rt	transvenous GDC embolization	symptoms resolved but died the same day of iliac artery perforation
33	Present case	30/F	rt	extracranial ICA ligation	good

CCA: common carotid artery, ECA: external carotid artery, GDC: Guglielmi detachable coil, ICA: internal carotid artery, NR: not reported.

demonstrated a direct type CCF in all cases examined. The cause of direct CCF associated with EDS type IV may be rupture of a cavernous aneurysm. Weakness of the cavernous sinus wall, as well as of the arterial wall, is associated with aneurysm formation of the ICA, and subsequent rupture leads to the formation of CCF.[14]

Transarterial angiography has been associated with aortic ruptures, and arterial tearing and dissection in the aorta and renal, hepatic, subclavian, splenic, and iliac arteries, and massive hemorrhaging along the route of the catheter from the arterial puncture site, even if the diagnosis had been established prior to the examination and the appropriate precautions taken.[17,26,27] The morbidity was 36% and the mortality was 12% for 25 angiographic procedures in patients with EDS type IV.[25] Diagnostic procedures requiring arterial punctures should be avoided, except in extreme circumstances.[13] Transvenous angiography or MR imaging are advocated as the initial investigative method.[2] In our case, the risks were emphasized by the two episodes of bleeding following angiography. Patients with possible EDS type IV warrant a low-risk initial investigative approach.

The treatment of CCF in a patient with EDS type IV is more hazardous than usual due to the fragility of the vessels.[15] Three cases were treated conservatively, eight with proximal ligation of the extracranial ICA or common carotid artery, and 26 were treated via an endovascular approach (14 cases involving a transarterial approach, 8 involving a transvenous approach). Among these cases, 13 cases reported in detail had a good outcome. Ten patients died during the perioperative period. Five patients treated by an endovascular approach died during the perioperative period.[2,6,13,17,21] The fragility of the tissues and vessels in patients with EDS type IV may contraindicate endovascular treatment for spontaneous CCF, because of the increased risk of tearing. Endovascular treatment is widely used as the treatment of choice for CCF, but neurosurgeons should be fully aware of the potential hazards of the procedure in patients with EDS type IV.

We chose extracranial carotid ligation, because no deaths occurred during the perioperative period among eight cases involving whole ligation of the extracranial ICA or common carotid artery.[4,10,23,31] In this case, it was judged that the risk of performing intravascular catheter operation by the fragile of a vessel wall was very high. We gave up performing some inspection of monitoring before operation, such as cerebral blood flow study with balloon occlusion examination, and so on. Extracranial ICA ligation carries the risk of aneurysm secondary to hemodynamic changes.[5] Recurrence of CCF was also reported after carotid ligation.[8,20] However, we believe that these risks of aneurysm formation and recurrence of CCF were outweighed by the 51% mortality before the age of 40 years in patients with EDS type IV.[2,5]

Patients suffering from EDS type IV face the risk of fatal complications associated with the aneurysm rupture, arterial dissection, or rupture of hollow organs. There is currently no ideal approach to the treatment of CCF associated with EDS type IV.[19] Since CCF is rarely life-threatening, vascular fragility must be considered when selecting the course of investigation and treatment.

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