Spontaneous carotid-cavernous fistula and multiple arterial dissections in Type IV Ehlers-Danlos syndrome

Case report

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A 43-year-old woman without phenotypic expression of Ehlers-Danlos syndrome developed a spontaneous unilateral carotid-cavernous fistula (CCF). Attempts at balloon occlusion of the CCF were unsuccessful, and caused multiple arterial dissections and lacerations eventually leading to massive retroperitoneal hemorrhage and death. The CCF was demonstrated during postmortem studies. In addition, the patient had independent dissections of the internal carotid artery at the site of the fistula and an intracavernous aneurysm of the contralateral internal carotid artery. Despite widespread dissections, the major arteries showed only mild histological abnormalities. Morphometric analysis of collagen from the aorta revealed an increase in large-sized fibers, consistent with deficiency of Type III collagen.

KEY WORDS: carotid-cavernous fistula • Ehlers-Danlos syndrome • collagen disorder

Ehlers-Danlos syndrome (EDS) encompasses a group of inherited disorders of connective tissue, all of which have abnormalities of collagen composition. It is manifested by a wide spectrum of clinical presentations. At least 10 distinct types have been described on the basis of clinical and genetic differences.10-35 Type IV EDS is characterized by a deficiency of Type III collagen, resulting in fragility of blood vessels and intestines. Complications may include arterial dissections, bowel rupture, and intracranial aneurysms.1-3,5,9,16,25,26,29,37,43 An association with spontaneous carotid-cavernous fistula (CCF) has also been reported.12,14,16,17,23,39

This paper describes the clinical, pathological, and ultrastructural findings in a patient with previously undiagnosed Type IV EDS who developed a spontaneous CCF and subsequently died as a result of multiple arterial dissections.

Case Report

This 43-year-old white woman was admitted to the hospital on February 9, 1982, complaining of swelling around her left eye and noise in her head. She had been healthy until approximately 16 hours previously, when she had suddenly developed a roaring noise in her head. Within 30 to 60 minutes, her left eye became protuberant and red. There was no history of trauma. She had always had a tendency to bruise easily, but had had two uncomplicated pregnancies and no problems with superficial cuts or with dental extractions. Her family history was unremarkable except for the fact that her mother was said to have died of an "aneurysm." No further details regarding this were known.

Examination. The patient was alert and fully oriented. Her left eye protruded and pulsated synchronously with her pulse. The conjunctiva was red and edematous. Periorbital ecchymosis was present. The left pupil was 4 mm (right pupil 3 mm) in diameter and reacted sluggishly to light. There was a complete left ophthalmoplegia. A bruit was heard over the whole head, being loudest over the left fronto-orbital area. The remainder of the examination was normal.

Routine blood count, serum electrolytes, urinalysis, prothrombin time, partial thromboplastin test, and platelet count were normal. Radiographs of the chest and skull and a computerized tomography scan of the head without contrast enhancement were normal. Four-vessel cerebral angiography revealed a left CCF that
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![Diagram](image)

**FIG. 1.** Sections of the left carotid artery showing continuous dissection of the common carotid artery (lower row) and internal carotid artery (ICA, upper row). The arrow points to the origin of dissection. A small intramural hematoma is also present at the site of the catheter insertion (arrowhead).

filled only from the left carotid artery injection. There was poor filling of the left carotid artery and its branches distal to the fistula. The right carotid and vertebral arterial systems were normal. There was good filling of the distal left carotid arterial system via collateral vessels when the right carotid and left vertebral arteries were injected.

**Hospital Course.** By February 11, 1982, vision had deteriorated in the left eye to finger-counting only. Percutaneous balloon catheter occlusion of the fistula was attempted under neuroleptanalgesia and local anesthesia. A catheter was inserted in the left common carotid artery (CCA) via a No. 14 Angiocath.* Repeated attempts to manipulate the catheter through the intrapetrous portion of the internal carotid artery (ICA) failed and the procedure was abandoned. Despite the application of pressure for 10 minutes, bleeding from the arterial puncture site persisted and a hematoma developed which caused upper airway obstruction. This necessitated endotracheal intubation for 24 hours.

On February 15, repeat left carotid angiography again demonstrated the left CCF. This procedure was followed by recurrence of the hematoma in the soft tissues of the neck. Reintubation was necessary for airway protection. After several days the patient recovered and, except for the continued presence of the fistula, was well enough to be transferred to a regular hospital room. On February 23, she suddenly became hypotensive and developed signs of severe hypovolemic shock and marked abdominal distention. Peritoneal lavage disclosed the presence of blood.

*No. 14 Angiocath catheter manufactured by the Deseret Co., Sandy, Utah.

**Operation.** At laparotomy a small amount of free blood was found within the peritoneal cavity. In the retroperitoneal space there was a huge hematoma, the source of which was a 1 × 1.5-cm tear in the aorta just proximal to the origin of the left common iliac artery. The damaged aorta and proximal iliac artery were excised and a knitted Dacron graft was interposed between the aorta and both iliac arteries. The surgeon commented upon the extreme friability of the tissues.

**Postoperative Course.** After surgery the patient had persistent hypotension and tachycardia, which were unresponsive to volume replacement. The patient suffered cardiac arrest on February 26, but was resuscitated. Chest radiographs showed a widened mediastinum, a large collection of fluid in the left hemithorax, and a smaller collection in the right hemithorax. Bilateral drainage tubes were inserted and blood was obtained from each side. While preparations were being made for an aortic arch angiogram, the patient suffered another cardiac arrest. Attempts at resuscitation were unsuccessful.

**Postmortem Examination.** Autopsy was performed 18 hours post mortem. External inspection revealed numerous ecchymoses about the eyes, right groin, and lower abdomen. During dissection, the soft tissues and vessels were extremely fragile. In the left CCA there was a continuous 10-cm dissection, starting approximately 2 cm above the site of the catheter insertion and extending to the highest level of the extracranial segment of the ICA (Fig. 1). The lumen of the ICA was displaced and compressed by an intramural hematoma. The left cavernous sinus was thrombosed. Other dissections with thromboses in their false lumina were present in the
right renal, external iliac, and femoral arteries. The aorta wall was paper-thin. There was a 2-cm laceration in the right common iliac artery 1 cm below the graft, which was responsible for a retroperitoneal hematoma of 1.5 liters (the angiographic catheter had been inserted via the right femoral artery). The pleural cavities contained a total of 3 liters of hemorrhagic fluid. On the left side there was also a solid clot weighing 650 gm. Both lungs were atelectatic and there were small hemorrhagic foci in the left lung. Foci of hemorrhagic necrosis were present in the myocardium and epicardial fat of the ventricles. The pericardial sac contained 100 ml of blood. In the middle and inferior gyri of the frontal lobe there was recent hemorrhagic infarction measuring 5 × 5 cm.

Pathological Examination. The entire length of the left carotid artery and multiple sections of the aorta and right carotid, iliac, femoral, and renal arteries, plus sections of all organs, were examined after formalin fixation. The base of the skull containing the cavernous sinuses and carotid arteries was removed in one block and cut semi-serially 2 mm apart. Paraffin-embedded tissues were stained by standard histological methods. For electron microscopic examination, formalin-fixed pieces of the lower abdominal and thoracic aorta were processed for glutaraldehyde post-fixation and Epon embedding. Corresponding levels of the aorta from an age- and sex-matched patient served as control material. Morphometric analysis was performed on 200 collagen fibers from the aortas of the patient and the control subject.

In the intracavernous left ICA there was a transmural tear communicating with the cavernous sinus (Fig. 2). There were also multiple short dissections extending outward to the adventitia. In the intracavernous right ICA a rupture of the internal and external elastic laminae was visible, with formation of a small laterally placed aneurysm (Fig. 3). The left ophthalmic artery was thrombosed, but the right ophthalmic artery was not identified after en bloc processing of the specimen. The other intracranial arteries were normal.

A localized hematoma was found in the CCA at the site of catheter insertion. Approximately 2 cm above this, there was a rupture of the intima, internal elastic lamina, and most of the media, with a dissection extending approximately 1 cm downward and 10 cm upward (Fig. 1). In the areas of dissection, reduction in the amount of elastic tissue, fragmentation of the internal elastic lamina, and marked proliferation of the intimal cells were revealed. Grossly normal CCA and ICA segments showed focal breaks in the internal elastic lamina with fibrosis, proliferation of smooth-muscle cells, and marked intimal cell hyperplasia. There was no continuity between the ICA dissection and the area of rupture that had caused the CCF. Widespread focal abnormalities in the distribution of smooth muscle and elastic fibers, beyond the grossly apparent dissec-
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Fig. 4. Electron micrograph showing collagen in the abdominal aorta of a control patient (upper) and of our patient with Type IV Ehlers-Danlos syndrome (EDSIV, lower). Note the smaller size of the collagen fibers in the control section compared to the EDSIV section. × 80,000.

Fig. 5. Block graph showing distribution of collagen fibers according to their size. Black blocks indicate fibers in the normal control subject, and white blocks indicate fibers in the present patient. There is significant reduction in the number of small-sized collagen fibers in the patient compared with the control material. The fibers in both patients were measured under × 180,000 magnification.

sections and lacerations, were present in all major extracranial vessels. None showed cystic medial necrosis or atherosclerosis. Dissection of the right renal artery extended microscopically into several intraparenchymal branches. In the brain, there were anoxic-ischemic changes restricted to Sommer’s sector and the hemorrhagic infarction in the left frontal lobe seen previously.

Electron microscopic examination of the thoracic and abdominal aorta revealed no morphological abnormalities in the smooth muscles, endothelium, or fibroblasts. Arrangements of collagen fibers appeared slightly looser and more disorganized in our patient than in the control material. The diameter of collagen fibers in the aorta of our patient was larger than in the control subject (Fig. 4). Also, morphometric analysis revealed a reduction in the number of small fibers sized 140 to 250 Å, and marked increase in the number of large fibers sized 300 to 400 Å (Fig. 5).

Discussion

Type IV EDS is a group of heterogeneous disorders characterized by a diminished synthesis and defective secretion of Type III collagen or pro-collagen, or a production of structurally abnormal pro-collagen molecules. Pope, et al., described several distinct subtypes of Type IV EDS differing in the degree of collagen deficiency, clinical manifestations, and inheritance patterns. Autosomal recessive cases demonstrated absence of Type III pro-collagen and collagen in the tissue and cultured skin fibroblasts, as well as lethal arterial complications. The two other subtypes of Type IV EDS had decreased levels of Type III collagen in the tissue and a milder clinical course.

Apart from a history of easy bruising, our patient had none of the external stigmata of Type IV EDS. Pope, et al., described patients of entirely “normal” appearance who had low levels of Type III collagen in the skin, episodes of spontaneous bleeding, and increased aortic extensibility. Our patient most likely belonged to this type, a diagnostically difficult category of Type IV EDS without the usual phenotypic expressions. Her relatively long period of survival, apparently fragile soft tissues, angiographic complications, and spontaneous arterial dissections are all similar to the clinical findings in previously reported cases of typical Type IV EDS.

At least eight cases of CCF associated with Type IV EDS have been reported; however, descriptions of the postmortem findings are limited to individual cases. The only report of bilateral CCF is also the only one in which the site of rupture of the carotid artery is described. The communication between the left ICA and the cavernous sinus in our patient is demonstrated in Fig. 2. The morphology of the intra-
cavernous carotid aneurysm on the contralateral side indicates that CCF may be preceded by segmental weakness and disruption of the tunica elastica (Fig. 3). The association of Type IV EDS and intracranial aneurysms has been reported previously.\textsuperscript{16,37} It has also been shown that some patients with a typical berry aneurysm may have abnormalities of Type III collagen in their skin and blood vessels.\textsuperscript{34} In our patient, the aneurysm in the right ICA morphologically resembled the "posttraumatic" type rather than the "saccular" or "congenital" aneurysms that are seen on the bifurcation of intracranial arteries.

Histochemical and biochemical studies of Type IV EDS have demonstrated reduced collagen content in the aorta, skin, and subcutaneous tissue,\textsuperscript{9,18,20,31} as well as a loss of collagen and an increase in elastic tissue in the lungs.\textsuperscript{10} Medium-sized arteries may reveal disorganization of the architecture with intimal fibrosis and discontinuities or reduplication of the internal elastic laminae.\textsuperscript{16,18,39} The media and adventitia may appear normal even in the presence of arterial dissections.\textsuperscript{56} This discrepancy between relatively mild histological abnormalities and disastrous clinical complications supports the hypothesis that submicroscopic defects in the collagen network cause weakening of the affected tissues.\textsuperscript{22,34,41}

Electron microscopic studies of skin collagen in Type IV EDS have demonstrated a 40% decrease in the size of collagen fibers,\textsuperscript{9,20} marked variation in the diameter with bi-modal size distribution,\textsuperscript{21} or a normal appearance despite chemically demonstrated deficiency of Type III collagen.\textsuperscript{5,36} These results contradict other studies which show that Type III collagen fibers (200 to 400 \(\mu\)m in diameter) are smaller than Type I collagen fibers (450 to 1800 \(\mu\)m in diameter).\textsuperscript{13,15,19} Thus, one should expect an increased rather than a decreased mean diameter of the collagen fibers in Type IV EDS. However, considering the polymorphism of collagen fibers and the wide range of diameters within the specific types, classification or quantitation of collagens on an ultrastructural basis is rather a difficult task.

Morphometric analysis of collagen showed no clear differences in the fiber population between our patient and the control subject. Neither was there bi-modal size distribution as reported in skin collagen of patients with Type IV EDS.\textsuperscript{9,20} However, there was a definite increase in the number of large fibers and a noticeable deficiency in small fibers 160 to 120 \(\mu\)m in size as compared to the control material. It may be postulated that most of the Type III collagen had been replaced by a population of fibers that is present in the aorta in normal conditions, such as Type I and its precursors or abnormal "mutant" collagens.\textsuperscript{19,30,33} Our electron microscopic studies were performed on aortas prefixed in formalin, and confirmation of the results must await immunoelectron microscopic studies of tissues properly processed for this method.

Although only a small group, patients with CCF and Type IV EDS present major management problems.\textsuperscript{22} Six of the eight reported patients died of systemic vascular complications.\textsuperscript{2,12,14,16,23,39} Because of blood vessel fragility, the performance of arteriography and vascular surgery is extremely dangerous. Since CCF is rarely life-threatening, investigation and treatment is aimed at preserving vision and relieving ocular symptoms.\textsuperscript{27,38} This was the rationale in the management of our patient: her vision was deteriorating and the existence of Type IV EDS was unsuspected. Obliteration of the CCF by balloon catheters via the cervical carotid artery has proven safe and effective.\textsuperscript{11,35,40} However, in patients with Type IV EDS the transarterial passage of such a catheter is contraindicated. We could not negotiate the balloon into the cavernous carotid artery because the vessel's fragile wall dissected and a false passage was created. In such patients it is safer to attack the fistula from the venous side using a technique such as transjugular balloon occlusion described by Mullan.\textsuperscript{24}

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