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# Cerebrovascular Disease in Ehlers-Danlos Syndrome Type IV

Wouter I. Schievink, MD, Martien Limburg, MD, Johanna W.E. Oorthuys, MD, Paul Fleury, MD, PhD, and F. Michael Pope, MD, FRCP

**We describe two patients with cerebrovascular complications of Ehlers-Danlos syndrome type IV. A 16-year-old girl with spontaneous internal carotid artery dissection and a 46-year-old woman with aneurysmal subarachnoid hemorrhage and multiple aortic dissections were both deficient in collagen type III, analyzed in cultured skin fibroblasts. To our knowledge, spontaneous carotid artery dissection associated with collagen type III deficiency has not been reported previously. Early clinical recognition of this syndrome is of great importance in view of the hazards of angiography and surgery. Collagen type III deficiency plays a role in the pathogenesis of intracranial saccular aneurysms and may also be involved in the pathogenesis of carotid cavernous fistulas and dissections of the cervical arteries. (*Stroke* 1990;21:626–632)**

Ehlers-Danlos syndrome (EDS) is a group of connective tissue disorders with features that include variable degrees of joint hypermobility, hyperextensible skin, easy bruising, and abnormal scarring.[1-3] EDS was first described in 1668 by the Dutch surgeon Job van Meek'ren,[4] who had observed a 23-year-old man with "extraordinary elasticity of the skin." Nine types and several subtypes of EDS have been recognized on the basis of clinical, genetic, and biochemical characteristics.[5]

The underlying defect of EDS type IV (EDS-IV: arterial, ecchymotic, or Sack-Barabas type) is an abnormality of collagen type III.[3,6-8] This substance is a major component of distensible tissues, such as blood vessels, hollow viscera, and skin.[9] Consequently, a person with typical EDS-IV has a propensity toward arterial rupture or aneurysm formation, intestinal perforation, pneumothoraces, and certain cutaneous features, such as unusually thin and fragile skin with prominent veins, severe bruising, and premature aging.[1-3,7,10-12] Hyperextensibility of the skin, however, is variable, and loose-jointedness is often limited to the digits. The typical facial appearance includes large eyes, thin nose and lips, and lobeless ears.[7,12-14] Both autosomal dominant and recessive inheritance have been described, and sporadic mutations frequently occur.[5,7,12-14]

EDS-IV is of special importance to neurologists and neurosurgeons because of the wide variety of cerebral vascular pathology that may be encountered in such patients, including intracranial aneurysms,[15-23] carotid cavernous fistulas,[21,22,24-33] fusiform aneurysms of the cervical arteries,[22,34,35] and postarteriographic dissection of the internal carotid artery.[30] In most such cases EDS was diagnosed by clinical and histologic criteria. In only two instances was biochemical confirmation obtained.[23,32] Indirectly, aortic dissection and mitral valve prolapse (features associated with EDS-IV[1,36]) may cause cerebrovascular symptoms. Recognition of the disorder is complicated by the fact that clinical features may be subtle. We describe two patients with previously undiagnosed EDS-IV who presented with cerebrovascular abnormalities. Biochemical studies confirmed abnormalities of collagen type III.

## Case Reports

### *Case 1*

In March 1985, this 16-year-old girl developed a continuous right temporal headache. Four days later she collapsed with an accompanying transient left-sided facial weakness. A few hours later she was admitted to our hospital after another collapse. Her medical history included spontaneous bruising since early childhood, and at the age of 3 years she had been hospitalized for a dislocated shoulder. The family history was unremarkable.

On examination, a left-sided central facial paresis was observed and the left plantar response was extensor. These abnormalities disappeared within 30 minutes, and the remainder of the neurologic exam-

From the Departments of Neurology (W.I.S., M.L., P.F.) and Pediatrics (J.W.E.O.) and the Institute of Human Genetics (J.W.E.O.), University of Amsterdam, Academisch Medisch Centrum, Amsterdam, The Netherlands, and the MRC Clinical Research Centre, Harrow (F.M.P.), United Kingdom.

Address for reprints: M. Limburg, MD, Department of Neurology H2.214, Academisch Medisch Centrum, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.

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FIGURE 1. *Facial appearance of patient 1. Note large eyes, thin nose, thin lips, lobeless ears, and abnormal scars on forehead.*

ination was unremarkable. She showed a characteristic facies with prominent eyes, a thin nose, thin lips, and lobeless ears. Abnormal scars were present on her forehead (Figure 1). Her skin was thin and translucent, especially over the chest, where a venous network was clearly visible. There were numerous ecchymoses on her legs, and a few wide scars were found over both knees. Mild hypermobility of the elbow and finger joints was noted.

A computed tomogram (CT scan) showed a small low-density lesion of the right external capsule, consistent with an old infarct. The results of coagulation studies were normal. The patient was started on aspirin. Arteriography revealed changes characteristic of an "in and out" dissection of the right cervical internal carotid artery (Figure 2). The remainder of the cervical and intracranial arteries were normal. A chest roentgenogram demonstrated a left-sided partial pneumothorax. A clinical diagnosis of EDS-IV was made. Histologic examination of a skin biopsy showed changes compatible with EDS-IV, with a reduction in the density of collagen fibers and an increased abundance of elastic fibers. The diagnosis was confirmed by collagen type III analysis in cultured fibroblasts, which showed only 50% of the normal amount (partial deficiency) (Figure 3). Messenger ribonucleic acid (mRNA) studies of $\alpha_1$(III) collagen showed normal abundance. These results may be explained by a mutation, either inhibiting mRNA translation from one allele or resulting in a structurally abnormal protein. Collagen type III analysis of her parents was normal.

After 2 months, aspirin was discontinued because of a marked increase in spontaneous bruising. Between 1985 and 1986 three episodes of spontaneous dislocation of the right shoulder occurred, which were treated conservatively. The patient has had no recurrence of neurologic symptoms during 4 years of follow-up.

*Case 2*

In February 1986, this 46-year-old woman suddenly developed a severe headache during coitus and vomited several times.

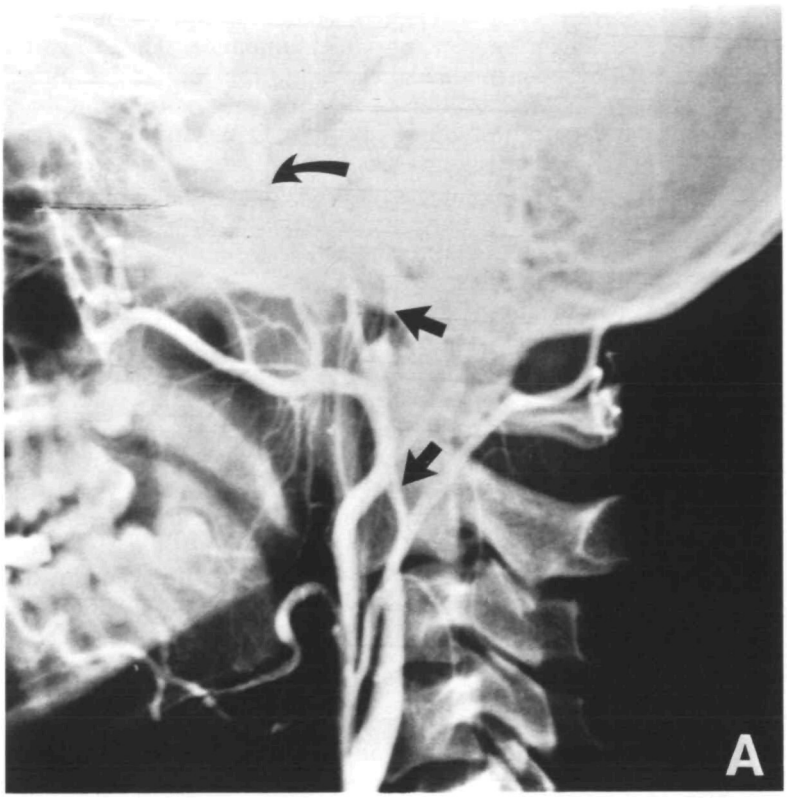
Her medical history included easy bruising and an abdominal aortic dissecting aneurysm in February 1981, at the age of 41 years. At laparotomy, extensive retroperitoneal fibrosis prevented an aortic graft. Ten months later, after a hemorrhage into a mesenteric cyst, a second attempt at aortic grafting was unsuccessful. In September 1983, an aneurysm of the aortic bifurcation was found on routine venous digital subtraction angiography. In May 1985, an aneurysm near the origin of the gastric artery leaked, causing a right-sided hemoperitoneum and hemothorax, which were treated conservatively. This episode was complicated by a small myocardial infarction.

The family history was revealing (Figure 4). Subjects $I_2$ and $II_4$ are likely to have had a subarachnoid hemorrhage at a young age; subject $II_1$ suffered an intracranial hemorrhage at the age of 79 years.

On admission to our hospital patient 2 was oriented but unaware of what had happened. She had a pointed face, prominent eyes, and thin lips and looked prematurely aged. During the next few hours meningeal irritation developed, and subsequent CT scanning showed blood in the basal cisterns. Arteriography disclosed a multiloculated aneurysm of the left internal carotid artery near the origin of the ophthalmic artery. There were extensive irregularities in the walls of all large arteries, including both carotid and vertebral arteries. An angiogram of the right internal carotid artery showed an aneurysm at the base of the skull but no further abnormalities of the intracranial arteries. At craniotomy the next day a very thin-walled saccular aneurysm with visible turbulences was clipped. There was a striking fragility of the fibrous tissues, in which stitches barely held. After an uneventful postoperative recovery the patient was discharged in good health.

Strongly suspected by the clinical signs and family history, the diagnosis of EDS-IV was confirmed by analysis of radiolabeled fibroblast collagens, showing a reduced collagen type III:total collagen ratio of only 6% (normal values 14–19%) (Figure 5).

In June 1988, after sudden and severe chest and back pain caused by a dissection of the descending aorta, patient 2 died in hypovolemic shock. At autopsy



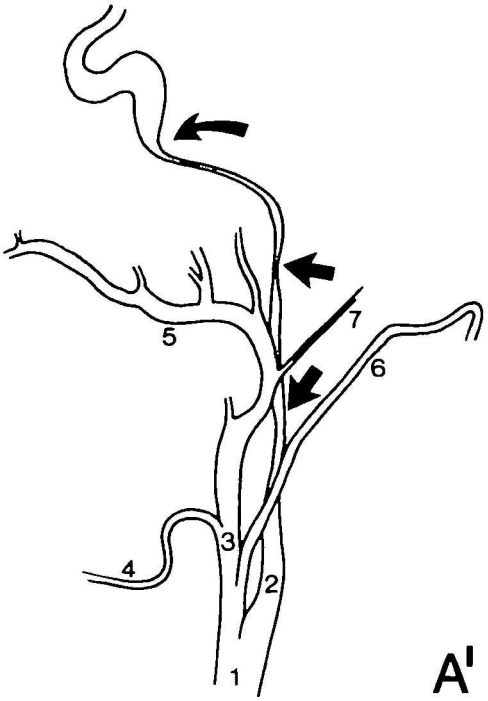





FIGURE 2. *Transfemoral cerebral arteriograms in patient 1. Right lateral* (A) *and anteroposterior* (B) *views demonstrating severe segmental narrowing (straight arrows) with irregularities of internal carotid artery beginning approximately 4 cm distal to bifurcation and ending below carotid siphon (curved arrow).* A': *Schematic representation of right lateral view. 1, common carotid artery; 2, internal carotid artery; 3, external carotid artery; 4, facial artery; 5, maxillary artery; 6, occipital artery; 7, posterior auricular artery.*

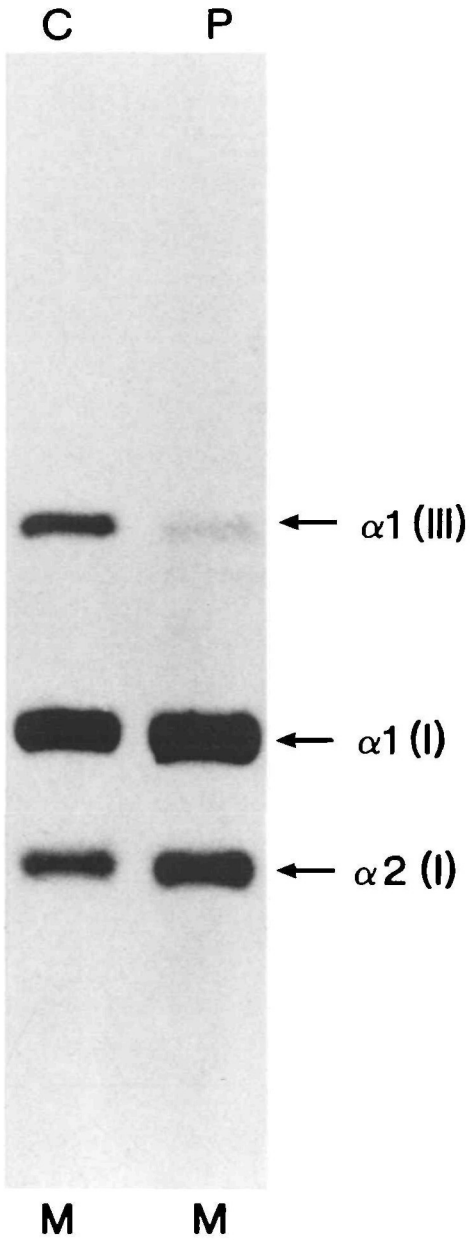



FIGURE 3. *Radiolabeled profiles of medium (M) collagens. After reduction with mercaptoethanol, pepsinized collagens show decrease of approximately 50% of $\alpha_1$(III) monomer in patient 1 (P) compared with normal control (C).*

several old dissections of the abdominal aorta and iliac vessels were seen. A recent dissection was present from the left subclavian artery down to the abdominal aorta, with a left-sided hemothorax. Unfortunately, the carotid vessels were not available for study.

## Discussion

Several abnormalities of collagen type III have been observed in patients with EDS-IV.[3,6–8] Cultured skin fibroblasts of these patients often secrete little or no collagen type III into the medium, and abnormal quantities are retained intracellularly.[3,6–8] Occasionally, qualitative defects of collagen type III molecules occur.[3,7,8] Histology of the arteries from affected patients shows mild, nonspecific abnormalities such as fragmentation of the internal elastic lamina and abnormal arrangement of elastic fibers in the tunica media of elastic and muscular arteries.[15,16,20,25,26,30] In contrast, skin histology is often diagnostic in patients with more severe forms of the disease.[7]

Clinically, EDS-IV is heterogeneous and its manifestations range from defective collagen type III with minimal phenotypic expression to lethal arterial rupture at an early age.[1,3,7,12,14,37] Our first patient presented with a rare vascular complication of EDS-IV at a particularly young age. Her transparent skin and characteristic facies strongly suggested the diagnosis. Her family was unaffected, and this patient represents a sporadic case. To our knowledge spontaneous carotid artery dissection associated with collagen type III deficiency has not been reported previously. Our second patient suffered multiple arterial complications with a three-generation autosomal transmission of the mutant gene, but she remained undiagnosed for 5 years despite multiple abdominal aortic aneurysms.

Suspicion of collagen type III disorders has important implications for the clinical management of these patients because of the severe and often lethal complications of various investigative or surgical procedures. Cikrit et al[38] reviewed 36 patients with EDS-IV; of 12 patients undergoing arteriography, eight had severe complications, including two deaths, and seven deaths were noted in 29 vascular surgical procedures. Transfemoral arteriography of such patients has been complicated by expanding hematomas at the puncture site and tearing of the aorta and medium-sized arteries.[20,26,30,33,39,40] Direct puncture of the carotid artery has resulted in large hematomas severe enough to obstruct the airway, requiring intubation.[25,30] Two patients with carotid cavernous fistulas suffered massive epistaxis following arteriography.[25,27] Intravenous digital subtraction angiography has been advocated as a safe alternative to arterial angiography[35,38]; in one patient, however, rupture of the superior vena cava occurred during manipulation of the catheter.[41] Attempts at balloon embolization of carotid cavernous fistulas by transarterial[30,32] and transvenous[21,33] routes have both been complicated by lethal hemorrhages.[21,30,33] In only one reported instance could the fistula be safely occluded.[32]

Surgeons have described the tissues of affected patients as resembling "wet blotting paper",[1] "cold porridge",[42] or "wet cotton",[25] and tissue friability was a particular problem in various operations in our patient 2. Arteries and veins tear easily due to the flimsiness of their walls, literally crumbling in the surgeon's hands.[15,34,39,42–44] Clamps and sutures often break loose or sever the vessel walls.[1,34,43–45] Wound dehiscence, thin papyraceous scars, and keloid formation all occur,[7,11–13,34,45] but abdominal and cutaneous incisions usually heal reasonably well.

The exact pathogenesis of spontaneous dissection of the cervical arteries in general is unknown, but it

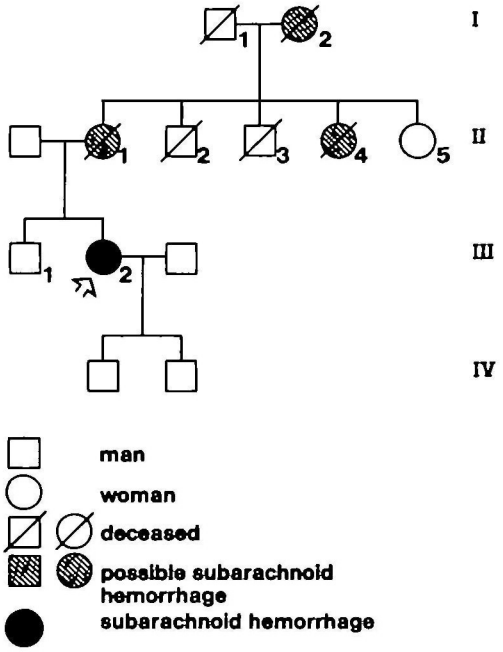



FIGURE 4. *Pedigree of patient 2. $I_1$: deceased, "something" in the head; $I_2$: deceased, 40 years old, cerebral hemorrhage; $II_1$: deceased, 79 years old, cerebral hemorrhage; $II_2$: deceased, 60 years old, cardiac cause; $II_3$: deceased, 60 years old, cardiac cause; $II_4$: deceased, 40 years old, cerebral hemorrhage; $II_5$: in good health, 80 years old; $III_1$: in good health, 49 years old; $III_2$: proposita.*

could include mechanical factors and intrinsic structural defects of the vessel wall.[46–48] Angiographic findings of fibromuscular dysplasia occur in approximately 15% of cases.[48] Other recognized causes include Marfan's syndrome[47] and cystic medial degeneration.[47] However, histologic examination of the arteries involved usually shows no preexistent abnormalities, and in the majority of cases the primary arterial defect remains unknown.[46–48] Patient 1 had a collagen type III deficiency combined with the typical clinical and angiographic characteristics of internal carotid artery dissection.

Pope and coworkers[49,50] followed by Ostergaard and Oxlund[51] have found a deficiency of collagen type III in about half of patients with aneurysmal subarachnoid hemorrhage unassociated with EDS-IV. We suggest that collagen type III mutations and arterial wall abnormalities may be relatively common in patients suffering carotid cavernous fistulas or dissection of the cervical arteries. Recently, Mokri et al[52] reported a familial clustering of spontaneous internal carotid artery dissection in which no obvious underlying defect was established. In those cases in particular, collagen type III analysis would be of interest.

In conclusion, the early clinical recognition of EDS-IV is of the utmost importance due to the high complication rate of various procedures requiring arterial puncture or surgery. These procedures should therefore be undertaken only on the most strict indication. Young and middle-aged patients

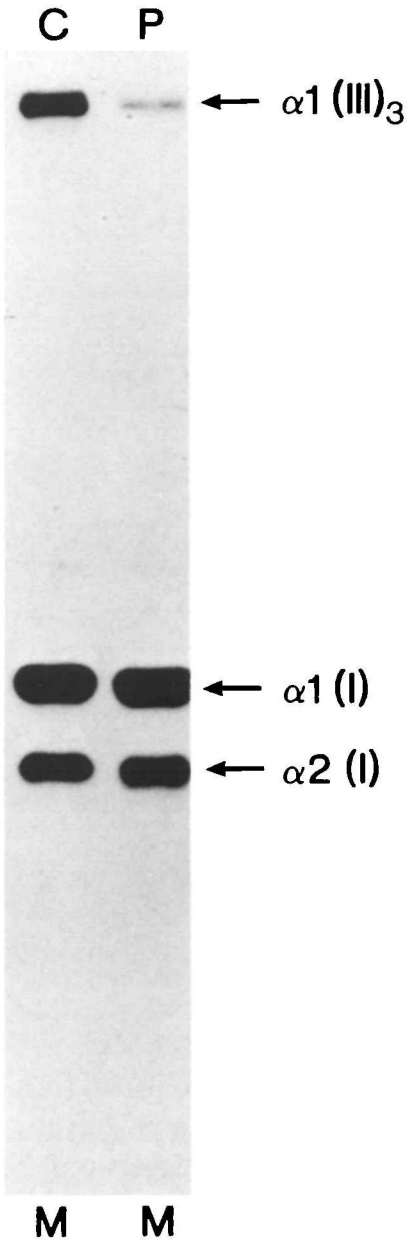



FIGURE 5. *Radiolabeled profiles of medium (M) collagens. Unreduced pepsinized collagens show marked reduction of $\alpha_1(III)_3$ in patient 2 (P) compared with normal control (C). Type III collagen:total collagen ratio was estimated by scanning to be approximately 6% compared with normal control values of 14–19%.*

with cervical artery dissections, carotid cavernous fistulas, and any large or medium-sized arterial aneurysms should be suspected of collagen type III mutations. This can usually be easily proved by fibroblast culture and collagen protein analysis or by gene linkage studies in suitable families. Prenatal diagnosis and prevention are theoretically possible in all patients with detectable mutations.

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KEY WORDS • aneurysm, dissecting • cerebrovascular disorders • Ehlers-Danlos syndrome