Cervical artery dissection: An atypical presentation with Ehlers–Danlos-like collagen pathology?

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Cervical artery dissection

An atypical presentation with Ehlers–Danlos-like collagen pathology?

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Abstract—The authors took skin biopsies of the macroscopically normal skin of seven consecutive patients with spontaneous cervical artery dissection (SCAD). Histologically, alterations of the collagen and elastic fiber networks were found in six patients. In five, the histologic, immunohistochemical, and ultrastructural changes were similar to those usually found in Ehlers–Danlos syndrome (EDS). This suggests that SCAD is frequently associated with the dermal alterations seen in EDS.

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Spontaneous cervical artery dissection (SCAD) is the most frequent cause of stroke in young adults.[1] Risk factors for SCAD include minor trauma, migraine, hyperhomocysteinemia, and rare disorders such as fibromuscular dysplasia, Marfan syndrome, or Ehlers–Danlos syndrome (EDS), especially the type IV (vascular variant).[2] Vessel wall and uterine ruptures predominantly express the latter type, and affected individuals are prone to SCAD.[3] Pathologically altered skin collagen recently has been demonstrated in patients with SCAD lacking clinical evidence for any specific connective tissue disorder (CTD).[4] We designed the present prospective study to further explore the skin collagen structure in SCAD.

Patients and methods. In a primary care hospital, seven consecutive patients were treated for SCAD from October 1999 to September 2002. The diagnosis was based on clinical (local symptoms and stroke) and paraclinical findings (Duplex ultrasound, MRI, and angiography). The patients were four women and three men aged from 29 to 48 years (mean, 39 years). There was no history of major trauma or vascular risk factors, including the intake of sympathomimetic drugs. We applied the Villefranche criteria for EDS for clinical diagnosis of CTD.[5] Skin biopsies (SBs) taken from the mid-dermis were assessed by light microscopy (staining techniques: hematoxylin-eosin, orcein-Giemsa, Warthin–Starry, Sirius red, Masson trichrome, periodic acid-Schiff–colloidal iron), immunohistochemistry for factor XIIIa (dermal dendrocyte), and electron microscopy.

Five patients gave written consent, and two globally aphasic patients with agraphia and alexia gave witnessed oral consent.

Results. Five of the patients did not fulfill clinical criteria for the known EDS subtypes, Marfan syndrome, pseudoxanthoma elasticum, and any other CTD. One patient had clinical features suggestive of EDS I, and the clinical course of another patient with two radial artery dissections caused by repeated puncture during her stay in the intensive care unit fitted to EDS IV. There was no inflammation, no hyperhomocysteinemia, and no evidence of fibromuscular dysplasia on angiography (table). Peculiar microscopic changes were disclosed in the dermis of six patients. Four patients displayed a disorganized pattern of elastic fibers, two of them having a fragmented ultrastructural aspect of these fibers. Collagen bundles were thin and oriented in a haphazard pattern (n = 4). Electron microscopy showed twisted collagen fibrils of various diameters, loose bundles with irregular interfibrillar spaces, and excessive amorphous matrix (n = 5). In four patients, the endoplasmic reticulum of fibroblasts was dilated and enriched in granular material (see table and figure). These aspects were consistent with EDS IV in two patients, unclassifiable EDS in three, borderline atypical elastopathy in one, and normal connective tissue in one. Histologically, the skin microvasculature was normal. The density in dermal dendrocytes ranged from low ($<50/mm^2$) to normal (75 to $95/mm^2$). The histologic phenotype of the patients with clinical findings suggestive of EDS did not differ from those without stigmata.

Discussion. In six of seven patients with SCAD, the skin contained an abnormal connective tissue matrix. This suggests a causal link between SCAD and an abnormal structure of the connective tissue. Brandt et al.[4] described a comparable connection in their selected, retrospective, and laboratory-based series. Pathologic collagen structures appeared in 31 of 55 of their SCAD cases (56.3%).[4] Minor risk factors, normally insufficient to induce arterial wall rupture alone, could thus facilitate SCAD in a fragile, but previously asymptomatic, vessel wall.

It has not escaped our attention that the present series carries a high frequency of pathologic changes commonly seen in clinically obvious EDS even in patients devoid of EDS stigmata. This implies that there may be a yet-unrecognized EDS type prone to

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Table *Patients treated for SCAD from October 1999 to September 2002*

No./ age, y/ sex	Site of dissection/ lesion	Trauma, risk factors/preceding symptoms	Symptoms	Signs of CTD	Light microscopy/ immunohistochemistry	Electron microscopy	Conclusion
1/44/F	Occlusion of the right ICA. Incomplete right MCA stroke.	No. Occurred while jogging. Raeder syndrome on the left 4 years before.	Left hemiparesis, supramodal hemineglect, disturbed body scheme.	Dissections of both radial arteries during her hospital stay following repeated punctures. Dilated aorta.	Disorganized collagen bundles and elastic fibers. Normal density in dendrocytes.	(1) Collagen: twisted fibrils with variable diameter, bundles of variable size; (2) fibroblasts: dilated ER filled with granular material; (3) interstitium: enlarged; (4) elastic fibers: normal structure, excessive amount; (5) excessive amorphous matrix.	Possible EDS IV.
2/44/F	Bilateral ICA forming pseudo aneurysms and stenosis left > right; left ACA stroke.	No. Occurred when doing standard dancing. Migraine.	Short-lasting akinetic mutism.	No.	Disorganized collagen bundles and elastic fibers; rare dendrocytes.	(1) Collagen: fibrils of variable diameter, disorganized thin bundles; (2) fibroblasts: dilated ER filled with granular material; (3) excessive amorphous matrix; (4) elastic fibers: fragmented or "moth-eaten."	EDS.
3/29/M	Left VA, small stroke of the left dorsolateral medulla oblongata.	No. Overhead work the week before.	Wallenberg syndrome.	No.	Normal.	(1) Collagen: small bundles, irregular interfibrillar spaces, small diameter fibrils; (2) excessive amorphous matrix; (3) elastic fibers: focal fragmentation.	Possible EDS IV.
4/34/M	Left ICA. Superficial left MCA stroke.	No.	Global aphasia, ideomotor apraxia.	Hypermobile joints and skin, molluscoids.	Disorganized collagen bundles and elastic fibers. Rare dendrocytes.	(1) Collagen: bundles of variable sizes, small diameter fibrils, disorganized bundles; (2) fibroblasts; dilated ER filled with granular material; (3) excessive diffuse matrix with granular deposits; (4) elastic fibers: normal.	EDS.
5/34/F	ICA bilateral with left stenosis, parietal left MCA stroke.	No. Occurred during supper. Left-sided facial pain and malaise the weeks before.	Fluent mixed aphasia when challenged (orthostatically, stress).	No.	Normal.	Normal.	Normal.
6/45/F	Left ICA. No stenosis, no stroke.	Chiropraxia 3 weeks before. Migraine.	Local pain, ipsilateral Horner syndrome.	No.	Disorganized collagen and elastic fibers; normal looking dendrocytes.	(1) Collagen: bundles of variable sizes, twisted fibrils, irregular interfibrillar spaces; (2) fibroblasts: dilated ER; (3) elastic fibers: normal.	EDS.
7/48/M	Left ICA, subtotal MCA- and AChA-stroke.	No.	Global aphasia, apraxia, left sensorimotor hemiplegia.	No.	Clumps of elastic fibers with uneven sizes.	Normal.	Elastopathy.

CTD = connective tissue disorder; ICA = internal carotid artery; MCA = middle cerebral artery; ER = endoplasmic reticulum; EDS = Ehlers-Danlos syndrome; ACA = anterior cerebral artery; AChA = anterior choroidal artery; VA = vertebral artery.

SCAD. EDS encompasses a heterogeneous group of CTDs chiefly characterized by various combinations of cutaneous hyperextensibility and fragility, joint laxity, vascular and visceral ruptures, and skeletal deformities. Obviously, the Villefranche classification does not yet recognize EDS variants with other manifestations that can be identified by objective morphologic, functional, and instrumental quantifications.[6-8] Cross-sectional studies of full-blown EDS type IV indicate a SCAD risk for ~2% of the patients, which seems low for EDS IV but elevated regarding SCAD.[3] These EDS-like changes indicate a fragile collagen. Although the prevalence of these dermal changes in the general population is unknown, a pure coincidence is merely probable. It remains open whether we are dealing with a variant of EDS IV or a new variant of CTD. We did not attempt genetic analysis because the results in several studies investigating genes causing CTD were negative in patients with SCAD.[2,9] The data on EDS IV suggest that despite following an autosomal-dominant trait, phenotype and age of presentation can vary considerably.[3] New mutations may occur in up to 50%. These data need to be validated by a study that blinds the pathologist to the clinical presentation and includes genetic analysis.

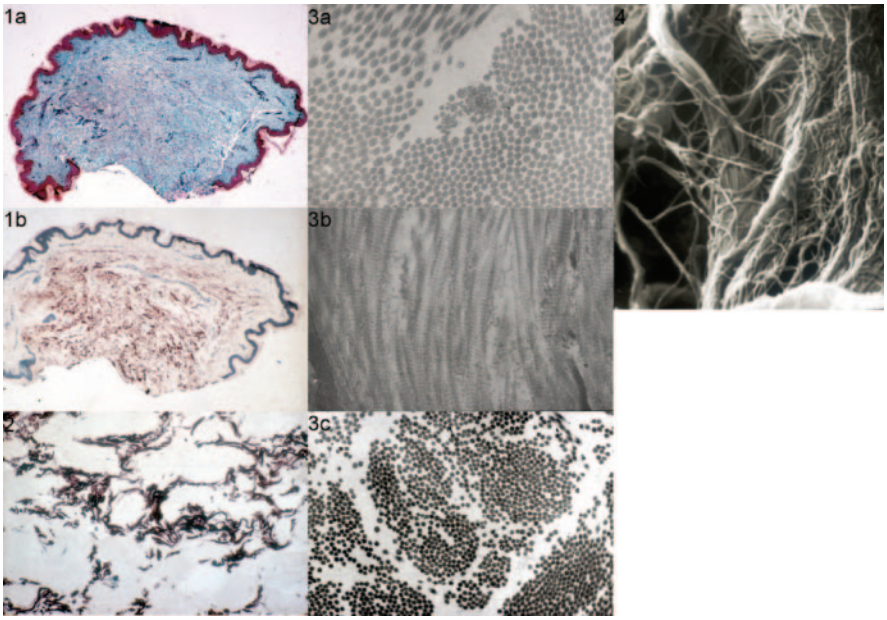

Figure. (1) Typical retraction in the deep layers of a skin biopsy in Ehlers–Danlos syndrome: (a) Masson trichrome coloration disclosing irregular collagen; and (b) orcein coloration showing irregular and dense net of elastic fibers. (2) Abnormal elastic fibers. (3) Electron microscopy: (a) with an abnormal collagen fibril ("cauliflower-like"); (b) twisted collagen fibrils with granulofilamentous deposits; and (c) small collagen bundles with irregular interfibrillar spaces. (4) Scanning electron microscopy: loose-packed arrangement of the collagen fibrils.

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