Connective tissue anomalies in patients with spontaneous cervical artery dissection

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ABSTRACT

Objective: To investigate the prevalence of connective tissue abnormalities in patients with spontaneous cervical artery dissections (sCeAD).

Methods: We systematically assessed clinically detectable signs of connective tissue aberration in a series of consecutive patients with sCeAD and of age- and sex-matched patients with ischemic stroke unrelated to CeAD (non-CeAD IS) by a standard examination protocol including 68 items, and performed extensive molecular investigation for hereditary connective tissue disorders in all patients with sCeAD.

Results: The study group included 84 patients with sCeAD (mean age, 44.5 ± 7.8 years; 66.7% men) and 84 patients with non-CeAD IS. None of the patients with sCeAD met clinical or molecular diagnostic criteria for established hereditary connective tissue disorder. Connective tissue abnormalities were detected more frequently in the group of patients with sCeAD than in the group of those with non-CeAD IS (mean number of pathologic findings, 4.5 ± 3.5 vs 1.9 ± 2.3 ; $p < 0.001$). Eighty-one patients (96.4%) in the sCeAD group had at least one detectable sign compared with 55 patients (66.7%) in the group with non-CeAD IS ($p < 0.001$). Skeletal, ocular, and skin abnormalities, as well as craniofacial dysmorphisms, were the clinical signs more strongly associated with sCeAD. Signs suggesting connective tissue abnormality were also more frequently represented in patients with sCeAD than in patients with traumatic CeAD (28.6%, $p < 0.001$; mean number of pathologic findings, 1.7 ± 3.7 , $p = 0.045$).

Conclusions: Connective tissue abnormalities are frequent in patients with sCeAD. This reinforces the hypothesis that systemic aberrations of the connective tissue might be implicated in the pathogenesis of the disease. *Neurology*® 2014;83:2032–2037

GLOSSARY

HCTD = hereditary connective tissue disorder; IS = ischemic stroke; sCeAD = spontaneous cervical artery dissection.

The pathogenesis of spontaneous cervical artery dissection (sCeAD), the most frequent cause of ischemic stroke in young and middle-aged adults, is still unclear. The finding of composite collagen fibrils and fragmented elastic fibers on electron microscopic examination of skin biopsy specimens in more than half of patients with sCeAD is an argument in favor of the hypothesis that connective tissue aberrations might have a causative role.^{1,2} However, whether such morphologic alterations represent subclinical phenotypes of a generalized disorder of the connective tissue remains to be determined. Hereditary connective tissue disorders (HCTDs) have been rarely diagnosed among patients with CeAD and external stigmata of connective tissue abnormalities inconsistently detected.^{3,4} These observations cast doubts on the assumption of a primary disorder of the connective tissue. Therefore, although the hypothesis of an underlying arteriopathy leading to structural instability of the vessel wall is likely and generally accepted, the exact nature of this disorder is still matter of debate.¹ To further investigate this

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Table 1 Items included in the standard examination protocol**Skeletal features**

1. Pectus carinatum: protrusion of the sternum/adjacent ribs
2. Reduced upper to lower segment ratio or arm span to height ratio >1.05
3. Walker-Murdoch sign (wrist sign): instruct the patient to grip his wrist with his opposite hand. If thumb and fifth finger of the hand overlap with each other, this represents a positive sign.
4. Steinberg sign (thumb sign): instruct the patient to hold the thumb across the palm of the same hand. If the entire thumb nail protrudes beyond the ulnar border of hand, this represents a positive sign
5. Scoliosis: radiographically defined as a lateral curvature of the spine $>20^\circ$ in the coronal plane
6. Spondylolysis/spondylolisthesis: radiographically defined
7. Reduced extension of the elbow ($<170^\circ$)
8. Pes planus (flat foot): medial displacement of the medial malleolus so that the instep of the foot comes in contact with the ground when standing
9. Talipes equinovarus (clubfoot): the foot is rotated internally at the ankle
10. Pectus excavatum: depression of the sternum/adjacent ribs
11. Joint hypermobility: Beighton score ≥ 5
12. Complications of joint hypermobility (sprains, dislocations/subluxations)
13. Small joints hypermobility: hyperextensibility of the joints of the forefinger and middle finger (so-called "telescoping")
14. Tendon/muscle ruptures
15. Arachnodactyly: long slender fingers and toes. It is scored when the middle finger length exceeds the palm length
16. Camptodactyly: fixed flexion deformity of the proximal interphalangeal joints
17. Polydactyly (hyperdactyly)
18. Increased bone fragility (multiple bone fractures)
19. Chronic joint/limb pain
20. Joint contractures: stiffness of the joint preventing full extension
21. Congenital dislocation of the hips
22. Beighton score
 - Thumb: ability to passively touch the forearm with the thumb, while flexing the wrist
 - Fifth finger (Gorling sign): ability to passively extend the fifth finger to 90° or more
 - Elbow recurvatum: hyperextension of the elbow beyond 10°
 - Genu recurvatum: hyperextension of the knee beyond 10°
 - Forward flexion of the trunk with knees fully extended so that the palms of the hands rest flat on the floor
23. Marfan-like habitus: dolichostenomelia, long slender fingers, pectus deformity

Ocular features

24. Enophthalmos: the posterior displacement of the eye within the orbit
25. Down-slanting palpebral fissures: when the outer canthus is positioned lower than usual
26. Hypoplastic iris or ciliary muscle causing decreased miosis
27. Exotropia
28. Ptosis: the forward displacement of the eye
29. Blue sclera
30. Myopia
31. Epicanthus: a fold of skin extending from the upper eyelid to or over the inner canthus of the eye
32. Deep-set eyes

Cutaneous features

33. Striae atrophicae (not associated with marked weight loss or pregnancy or repetitive stress)
34. Thin, translucent skin (especially noticeable on the chest/abdomen)
35. Easy bruising: (1) reported by patient, but no visible hematoma, (2) fewer than 5 visible skin hematomas, and (3) more than 5 visible skin hematomas. Spontaneous ecchymoses, frequently recurring in the same areas and causing characteristic brownish discoloration

Continued

Table 1 Continued

36. Acrogeria (aged appearance to the extremities, particularly the hands)
37. Yellow cobblestone lesions in flexural locations
38. Redundant skin folds
39. Prominent skin creases of the forehead, chin, and at the corner of the mouth
40. Soft, velvety texture
41. Skin hyperextensibility (laxity)
Mild hyperextensibility: skin extensibility of >2 cm but <4 cm on the ulnar side of the volar forearm 4 cm above the wrist on manual testing
Severe hyperextensibility: skin extensibility of >4 cm on the ulnar side of the volar forearm 4 cm above the wrist on manual testing
42. Widened atrophic scars (dystrophic scars): scars are found mostly on pressure points (i.e., knee, elbow, forehead, or chin) and have a thin, atrophic, papyraceous appearance. Frequently, the scars become wide and discolored. Wound healing is impaired
43. Piezogenic papules: painful or asymptomatic papules of the feet and wrists that result from herniation of fat through the dermis
Craniofacial features
44. High-arched palate with crowding of teeth
45. Malar hypoplasia (micrognathism)
46. Retrognathia: abnormal posterior positioning of the mandible or, less frequently, the maxilla
47. Decrease of subcutaneous adipose tissue (face and limbs: tight skin, hollow cheeks, prominent staring eyes because of the paucity of adipose tissue)
48. Gingival recession (exposure in the roots of the teeth)
49. (Ocular) hypertelorism: defined as a canthal index >42
50. Bifid/broad uvula
51. Cleft palate
52. Cleft lips
53. Craniosynostosis
54. Dentinogenesis imperfecta: teeth are discolored (most often a blue-gray or yellow-brown color) and translucent. Teeth are also weaker than normal, making them prone to rapid wear, breakage, and loss
55. Thin lips
56. Absent lingual frenulum
57. Absent labial frenulum
58. Short philtrum
59. Dolichocephaly
60. Firm, lobeless ears
Other features
61. Recurrent or incisional hernias: inguinal, umbilical, crural or jatal hernia, or diastasis rectus either detected during physical examination or in the medical history
62. Pelvic floor prolapse (involving bladder, uterus, or bowel)
63. Arterial, uterine, intestinal fragility or rupture
64. Early-onset varicose veins
65. Mental retardation (developmental delay)
66. Congenital heart disease
67. Hearing impairment
68. History of pneumothorax/pneumohemothorax

issue, we systematically searched for clinical signs of connective tissue anomalies in a cohort of patients with CeAD and control subjects.

METHODS We undertook a hospital-based case-control study of consecutive patients with CeAD and patients with non-CeAD ischemic stroke (non-CeAD IS) prospectively recruited during a 44-month period (between March 2010 and November 2013). Patients in the CeAD group were those whose diagnosis was

confirmed by MRI/magnetic resonance angiography or conventional angiography,⁵ with or without stroke.

Dissections occurring as an immediate consequence of a major trauma were labeled “traumatic” (for definition, see e-Methods on the *Neurology*[®] Web site at Neurology.org). The group of control subjects was selected from a cohort of patients with first-ever cerebral ischemia, after exclusion of the subgroup with CeAD-related infarction. Non-CeAD IS patients were frequency-matched with CeAD patients on sex and age (in 3-year intervals). Clinically detectable signs of connective tissue abnormalities were systematically investigated in each subject by 2

raters, a neurologist (A.G.) and a geneticist (M. Colombi), expert in the assessment of connective tissue signs, to ensure a homogeneous evaluation. This standardized examination included the assessment of 68 signs reflecting the spectrum of the clinical features observed in the Ehlers-Danlos syndrome vascular type, Marfan syndrome, pseudoxanthoma elasticum, osteogenesis imperfecta, arterial tortuosity syndrome, and Loeys-Dietz syndrome (table 1).^{e3–e13} Each sign was counted as an all-or-none variable (present vs absent), resulting in an individual connective score and a mean number of pathologic findings for each group (mean score). The 2 raters were blinded to the status of the patients. Interrater reliability was assessed by having the 2 examiners categorize the same set of 68 signs in all patients and was evaluated using the κ statistic, according to the method described by Cohen.⁶ We categorized these signs according to the specific organ or system involved into (1) skin abnormalities, (2) ocular abnormalities, (3) skeletal abnormalities, (4) craniofacial dysmorphisms, and (5) abnormalities involving other organs.

All patients with CeAD underwent direct sequencing of *TGFBR1* and *TGFBR2* genes,⁷ 62 of *SMAD3* and *TGFBR2* genes, while only in selected cases, *COL3A1* (n = 10), *SLC2A10* (n = 3), *FBN1* (n = 2), and *ACTA2* (n = 2) genes were analyzed, based on individual characteristics. To test the hypothesis that connective tissue disorders have a major role also in the pathogenesis of sporadic CeAD cases, we planned to exclude from the present analysis those patients whose clinical features had eventually fulfilled the diagnostic criteria for one of the monogenic disorders reported above and/or in whom molecular screening revealed causative mutations.

Standard protocol approvals, registrations, and patient consents. The study was approved by relevant local authorities. Written informed consent was obtained from all patients (or next of kin).

RESULTS The study group was composed of 84 patients with sCeAD (mean age, 44.5 ± 7.8 years; 66.7% men) and 84 patients with non-CeAD IS (mean age, 44.0 ± 8.7 years; 66.7% men). Compared to patients with non-CeAD IS, patients with sCeAD had a lower prevalence of hypercholesterolemia, a higher prevalence of migraine, particularly without aura, tended to be taller and thinner, and less frequently hypertensive, smokers, and diabetics (table 2).

Short-lasting triggering factors preceding the occurrence of the vascular event were also detected more often in the group of patients with sCeAD than in the group of patients with non-CeAD IS (table e-1). None of the patients with sCeAD met clinical diagnostic criteria or carried causal mutations for established HCTD. Interrater agreement for the assessment of connective signs was high with 80 of the 84 patients rated identically by the 2 raters ($\kappa = 0.84$). Signs suggesting connective tissue abnormalities were detected more frequently in the group of patients with sCeAD than in the group of those with non-CeAD IS (mean score, 4.5 ± 3.5 vs 1.9 ± 2.3 ; $p < 0.001$; figure e-1). Eighty-one patients (96.4%) in the sCeAD group had at least one detectable sign compared with 55 patients (66.7%) in the group with non-CeAD IS ($p < 0.001$). Overall, skeletal, ocular, and skin abnormalities, as well as

Table 2 Demographic and clinical characteristics of the study group

	CeAD (n = 84)	non-CeAD IS (n = 84)	p Value
Age, y	44.5 $\pm$ 7.8	44.0 $\pm$ 8.7	0.718
Sex, male	56 (66.7)	56 (66.7)	1.000
Height, cm	171.6 $\pm$ 8.9	169.3 $\pm$ 8.5	0.085
Weight, kg	70.3 $\pm$ 13.3	74.6 $\pm$ 14.7	0.052
Hypertension	19 (22.6)	28 (33.3)	0.122
Diabetes mellitus	1 (1.29)	5 (6.0)	0.210
Hypercholesterolemia	11 (13.1)	29 (34.5)	0.001
Smoking	22 (26.2)	30 (35.7)	0.182
Any migraine	36 (42.8)	13 (15.5)	<0.001
MO	31 (36.9)	8 (9.5)	<0.001
MA	5 (6.0)	5 (6.0)	1.000
Dissected vessel			
Internal carotid artery	48 (57.1)		
Vertebral artery	18 (21.4)		
Multiple vessels ^a	15 (17.8)		
Fibromuscular dysplasia	4 (4.8)	0 (0.0)	0.121
Presenting symptom			
Stroke	62 (73.8)		
TIA	6 (7.1)		
Local symptoms ^b	43 (51.1)		
Retinal ischemia	0 (0.0)		
SAH	0 (0.0)		
Cause of stroke ^c			
Large vessel disease		8 (9.5)	
Cardiac embolism		35 (41.7)	
Small vessel disease		4 (4.8)	
Other determined etiology	52 (83.9)	9 (10.7)	
Undetermined origin			
Multiple possible etiologies	10 (16.1)	1 (1.1)	
Complete evaluation		27 (32.1)	
Incomplete evaluation		0 (0.0)	

Abbreviations: CeAD = cervical artery dissection; IS = ischemic stroke; MA = migraine with aura; MO = migraine without aura; SAH = subarachnoid hemorrhage.

Data are mean $\pm$ SD or n (%). See e-Methods for risk factor definition.

^a More than one vessel involved.

^b Including Horner syndrome, cranial nerve palsies, head or neck pain, or pulsatile tinnitus.

^c According to TOAST (Trial of Org 10172 in Acute Stroke Treatment) criteria.

craniofacial dysmorphisms, were more frequently observed in the group of patients with sCeAD, as opposed to the abnormalities involving other organs, which were equally distributed in the 2 groups. Facial appearance of patients with sCeAD was more often characterized by tight skin, hollow cheeks, and prominent staring eyes as a consequence of paucity of adipose tissue. The most prominent skeletal features were scoliosis and mild pectus excavatum, while the most prominent skin feature was mild hyperextension. Hypermobility/laxity of some joints was also more frequently observed in the group of patients with sCeAD (Beighton score⁸ ≥ 2 in 16.7% vs 3.6% [$p = 0.009$]; mean score, 0.6 ± 1.1 vs 0.1 ± 0.5 [$p = 0.001$]; table 3).

We also studied 7 patients whose CeAD was obviously due to a major trauma, during the same study period. Signs suggesting connective tissue abnormality were less frequently represented in this group compared to the group of patients with sCeAD (traumatic CeADs with at least one detectable sign, 28.6%, $p < 0.001$; mean score, 1.7 ± 3.7 , $p = 0.045$).

DISCUSSION Our findings indicate that clinically detectable connective tissue abnormalities, frequently

observed in patients with HCTD, are also highly prevalent in patients with sCeAD. This provides indirect support to the “connective hypothesis” of the disease. Structural deviations in the main components of connective tissue, collagen and elastic fibers, may lead to functional impairment of the mechanical stability and elasticity of the arterial wall, predisposing to dissection at given points of minor resistance. Similar to other previous studies, we did not diagnose a definite HCTD in any of the patients included in our series, despite the extensive clinical and molecular investigation.⁹ Whether this implicates the existence of a milder form of connective tissue disorder predisposing to CeAD remains unknown, even though it seems plausible. The low prevalence of clinically recognizable connective signs in patients with traumatic CeAD, as opposed to spontaneous cases, is a further argument in favor of this view. Overall, our findings are in line with the prevailing theory that sCeAD represents a multifactorial disease and the end result of a synergistic interplay between an underlying constitutional arteriopathy and short-lasting environmental factors. These triggering factors, normally insufficient to induce arterial wall rupture alone, could transiently facilitate dissection in a fragile, previously asymptomatic, vessel wall. Obviously, we cannot but speculate on the relation between the clinical signs of connective tissue abnormality we detected and a generalized disorder of the connective tissue. In this regard, our findings need to be validated by a study that correlates patient phenotype with pathologic data. Notably, the only study in which clinical signs of connective tissue abnormalities were systematically assessed by standard examination found no preponderance of these stigmata in patients with CeAD and argued against a connective tissue disorder underlying the disease. However, the 25 clinical items used in that analysis reflect the spectrum of signs mainly found in Marfan and Ehlers-Danlos syndromes, and it is unclear why authors did not include specific features of other HCTDs in their standardized examination protocol.⁴ Difference in sample size and the lack of patients’ molecular characterization should also be considered when comparing the results of that study with ours, because they might contribute to explain some discrepancies.

The most relevant shortcoming of both analyses, as well as of others previously reported,^{2,3} is that they rely heavily on the identification and subjective interpretation of signs that are qualitative or semiquantitative (i.e., skin extensibility, joint hypermobility, tissue fragility, and bruising), and for which, therefore, normal standards are unavailable. However, the excellent interrater agreement in the assessment of these items makes this drawback unlikely in our analysis. Clinically detectable signs of connective tissue abnormalities are subtle in most patients with sCeAD and, therefore,

Table 3 Distribution of connective tissue anomalies in patients with sCeAD and non-CeAD IS

Connective abnormalities	sCeAD (n = 84)	non-CeAD IS (n = 84)	p Value
At least 1	81 (96.4)	55 (66.7)	<0.001
Sum score	4.5 ± 3.5	1.9 ± 2.3	<0.001
Organ involvement			
Bone and joints ^a	57 (67.9)	28 (33.3)	<0.001
Gorling sign	8 (9.5)	1 (1.2)	0.034
Elbow recurvatum	14 (16.7)	5 (6.0)	0.049
Scoliosis	19 (22.6)	4 (4.8)	0.001
Pectus excavatum	14 (16.7)	1 (1.2)	<0.001
Beighton score ^b			
Mean $\pm$ SD	0.6 ± 1.1	0.1 ± 0.5	0.001
≥ 2	14 (16.7)	3 (3.6)	0.009
Marfan-like habitus	15 (17.9)	5 (6.0)	0.030
Skin ^a	35 (41.7)	20 (23.8)	0.014
Mild skin hyperextension	16 (19.0)	6 (7.1)	0.038
Eye ^a	39 (46.4)	25 (29.8)	0.026
Craniofacial dysmorphisms ^a	41 (48.8)	20 (23.8)	0.001
Decrease of subcutaneous adipose tissue	16 (19.0)	4 (4.8)	0.07
Thin lips	9 (10.7)	2 (2.4)	0.05
Other organs ^a	14 (16.7)	7 (8.3)	0.160

Abbreviations: IS = ischemic stroke; sCeAD = spontaneous cervical artery dissection. Data are mean $\pm$ SD or n (%).

^aNo. of patients with at least one sign involving the specific organ or system.

^bIndividual score values range, 0–9 (0–1 point for each item).

they might remain undetected because they can only be recognized by experienced examiners. This represents an obvious limitation to the possibility of applying such a standardized approach in everyday clinical practice when trying to detect patients at higher risk of dissection. Nevertheless, in the absence of rigorous histopathologic studies, the demonstration of a distinctive connective tissue phenotype in patients with sCeAD reinforces the hypothesis that the disorder implicated in the pathogenesis of the disease is probably not limited to the vascular bed, and that the connective tissue is the most likely target organ.

AUTHOR CONTRIBUTIONS

Dr. Giossi: manuscript drafting/revising, study design, data analysis and interpretation, data acquisition. Marco Ritelli, Paolo Costa, Andrea Morotti, Loris Poli, Elisabetta Del Zotto, Irene Volonghi, Nicola Chiarelli, Massimo Gamba, Paolo Bovi, Giampaolo Tomelleri, Monica Carletti, Nicoletta Checcarelli, Giorgio Meneghetti, Michele Morra, Mauro Chinaglia, Valeria De Giuli, Marina Colombi: manuscript drafting/revising, data acquisition. Alessandro Padovani: manuscript drafting/revising, study supervision. Dr. Pezzini: manuscript drafting/revising, study design, data analysis and interpretation, data acquisition, statistical analysis, study supervision.

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