

Familial occurrence and heritable connective tissue disorders in cervical artery dissection

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ABSTRACT

Objective: In a large series of patients with cervical artery dissection (CeAD), a major cause of ischemic stroke in young and middle-aged adults, we aimed to examine frequencies and correlates of family history of CeAD and of inherited connective tissue disorders.

Methods: We combined data from 2 large international multicenter cohorts of consecutive patients with CeAD in 23 neurologic departments participating in the CADISP-plus consortium, following a standardized protocol. Frequency of reported family history of CeAD and of inherited connective tissue disorders was assessed. Putative risk factors, baseline features, and 3-month outcome were compared between groups.

Results: Among 1,934 consecutive patients with CeAD, 20 patients (1.0%, 95% confidence interval: 0.6%–1.5%) from 17 families (0.9%, 0.5%–1.3%) had a family history of CeAD. Family history of CeAD was significantly more frequent in patients with carotid location of the dissection and elevated cholesterol levels. Two patients without a family history of CeAD had vascular Ehlers-Danlos syndrome with a mutation in *COL3A1*. This diagnosis was suspected in 2 additional patients, but *COL3A1* sequencing was negative. Two patients were diagnosed with classic and hypermobile Ehlers-Danlos syndrome, one patient with Marfan syndrome, and one with osteogenesis imperfecta, based on clinical criteria only.

Conclusions: In this largest series of patients with CeAD to date, family history of symptomatic CeAD was rare and inherited connective tissue disorders seemed exceptional. This finding supports the notion that CeAD is a multifactorial disease in the vast majority of cases.

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GLOSSARY

CADISP = Cervical Artery Dissection and Ischemic Stroke Patients; **CeAD** = cervical artery dissection; **CI** = confidence interval; **CTD** = connective tissue disorder; **EDS** = Ehlers-Danlos syndrome; **vEDS** = vascular Ehlers-Danlos syndrome.

Cervical artery dissection (CeAD), a major cause of ischemic stroke in young adults, is considered a complex disease, with multiple genetic variants and environmental factors contributing to its occurrence.^{1,2} No consistent genetic association has been found so far.¹ Given the low incidence of the disease in the general population, heritability estimates based on twin or family studies are not available, and data on family history of CeAD are scarce. Only one hospital-based study from the Mayo Clinic, published 18 years ago, systematically examined the frequency of family history of CeAD in a cohort of 200 patients with CeAD, reporting a frequency of 2.5%.³ This could be an overestimation because of a referral bias, given the single tertiary center recruitment in a highly specialized institution.

Moreover, some rare inherited connective tissue disorders (CTDs) are known to cause or to be associated with CeAD, i.e., mostly vascular Ehlers-Danlos syndrome (vEDS), and perhaps, to a lesser extent, other types of EDS, Marfan syndrome, or osteogenesis imperfecta, although the evidence for these is much weaker.^{2,4} However, the prevalence of these monogenic diseases has never been systematically assessed in large patient series. Evaluating the frequency of heritable

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CADISP-plus consortium coinvestigators are listed on the *Neurology*® Web site at Neurology.org.

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forms of CeAD in a multicenter setting could be important to guide screening and genetic counseling strategies for patients with CeAD and their families.

We aimed to examine the frequencies and correlates of family history of CeAD and of the aforementioned inherited CTD in 2 large contemporary multicenter cohorts of patients with CeAD (CADISP-plus consortium).

METHODS Study population. The multicenter CADISP-plus consortium comprised 2,021 patients with CeAD from both the CADISP clinical study (n = 983)⁵ and the Paris-Lariboisière/Zürich/Bern CeAD registry (n = 1,038).^{6,7} Structure and methods of each of these studies have been described in detail previously.^{5,7-9} Briefly, we included consecutive patients evaluated in a department of neurology with a diagnosis of CeAD, following a standardized protocol (table 1, figures e-1 and e-2, and e-Methods [on the *Neurology*[®] Web site at Neurology.org] for inclusion criteria and recruiting centers). To be included, patients with CeAD had to present with a mural hematoma, aneurysmal dilation, long tapering stenosis, intimal flap, double lumen, or occlusion >2 cm above the carotid bifurcation revealing an aneurysmal dilation or a long tapering stenosis after recanalization, in a cervical artery (internal carotid or vertebral); iatrogenic dissections were excluded. Monogenic CTDs, which were an exclusion criterion for genetic analyses, were included in the CADISP clinical study. The Paris-Lariboisière/Zürich/Bern CeAD registry included patients with first-ever CeAD only.

Between 2004 and 2009, the CADISP clinical study included all consecutive patients evaluated in several departments of neurology with a diagnosis of CeAD. Patients were recruited both prospectively and retrospectively. Retrospective patients are participants who had a qualifying event before the beginning of the study in each center and were identified through local registries of patients with CeAD. The vast majority of these had a qualifying event between 1999 and 2009 (<4% before 1999). In the Paris-Lariboisière/Zürich/Bern Registry on CeAD, patients were included prospectively between 1985 and 2013 (e-Methods).

After excluding patients without reliable information on family history, 1,934 patients with CeAD were available (CADISP study: n = 921; Paris-Lariboisière/Zürich/Bern registry: n = 1,013), from 8 countries and 23 centers (figure e-1).

Variable definition. Family history of CeAD was defined by reported history of CeAD in father, mother, siblings, children, or any other defined relative of the index patient. Whenever possible, medical records were obtained for the affected relative to confirm the diagnosis and specify the age at occurrence of CeAD, the dissection site, and presence or absence of cerebral or retinal ischemia (ischemic stroke or TIA, including transient monocular blindness). We systematically searched for history of previously diagnosed vEDS, classic or hypermobile EDS,^{10,11} Marfan syndrome,¹² or other known inherited CTD according to established criteria.⁴ When patients were aphasic or had cognitive deficits, information on personal and family history was collected from a close relative. Each patient's personal medical records were examined in detail. When an inherited CTD was suspected based on suggestive clinical features or family history, the patient was sent to a specialized genetics center for further diagnostic workup.

Presence of cerebral or retinal ischemia, of arterial occlusion, stenosis, aneurysmal dilation (e-Methods), or multiple dissections at admission, and 3-month CeAD recurrence rates were recorded.

Table 1 Participating centers

Country and city	No. (%) of patients (by country)	No. (%) patients (by center)
Argentina	8 (0.4)	
Cordoba		8 (0.4)
Belgium	34 (1.8)	
Brussels		15 (0.8)
Leuven		19 (1.0)
Switzerland	711 (36.8)	
Basel		89 (4.6)
Zürich		269 (13.9)
Bern		353 (18.3)
Germany	151 (7.8)	
Heidelberg		145 (7.5)
Ludwigshafen		6 (0.3)
France	693 (35.8)	
Lille		114 (5.9)
Paris		496 (25.6) ^a
Amiens		28 (1.5)
Dijon		35 (1.8)
Besançon		20 (1.0)
Finland	174 (9.0)	
Helsinki		174 (9.0)
Italy	161 (8.3)	
Brescia		82 (4.2)
Milano		39 (2.0) ^b
Perugia		19 (1.0)
Monza		20 (1.0)
Roma		1 (0.1)
Turkey	2 (0.1)	
Istanbul		2 (0.1)

^aOf which 56 (2.9) for Hôpital Sainte-Anne, 49 (2.5) for Hôpital Pitié-Salpêtrière, and 391 (20.2) for Hôpital Lariboisière.

^bOf which 13 (0.7) for Milano Ospedale Maggiore and 26 (1.3) for Milano Ospedale San Raffaele.

Putative risk factors (hypertension, hypercholesterolemia, migraine, infection, and trauma preceding the dissection) are defined in e-Methods.

Statistical analyses. To compare clinical and radiologic characteristics as well as risk factor distribution between CeAD patients with and without a family history of CeAD, we first performed univariate analyses using Fisher exact test for categorical and Wilcoxon-Mann-Whitney test for continuous variables. Multivariable logistic regression models were then applied, adjusting for age and sex, as well as for study (CADISP clinical study, Paris-Lariboisière/Zürich/Bern CeAD registry) in a secondary analysis. Sensitivity analyses were performed after excluding one random patient from each of the 3 related patient pairs with a family history of CeAD. In addition, we verified the stability of associations after additionally adjusting

for the retrospective vs prospective recruitment for CADISP clinical study participants. Analyses were performed using Statistical Analyses System software, version 9.2 (SAS Institute, Cary, NC).

Standard protocol approvals, registrations, and patient consents. The study protocols were approved by relevant local authorities in all participating centers and conducted according to national rules concerning ethics committee approval and informed consents.^{5,7} The CADISP study is registered with clinicaltrials.gov (NCT00657969); see also www.cadisp.com.

RESULTS Among 1,934 patients with CeAD, 20 patients (1.0%, 95% confidence interval [CI]: 0.6%–1.5%) from 17 families (0.9%, 0.5%–1.3%) had a family history of CeAD; of these, 13 patients had a family history of CeAD in a first-degree relative (0.7%, 0.3%–1.0%). Characteristics of these patients are presented in table 2. In most cases, there were only 2

affected cases per family, including the index patient. Two families had 3 affected members. In one of these, only males were affected, including 2 brothers and 1 maternal cousin, suggesting a possible X-linked inheritance pattern. For 3 families (6 patients), both affected relatives were included in the CADISP-plus study (table 2). Of the remaining 14 patients with a positive family history, details on CeAD characteristics of the affected relative could be obtained in 11 patients. These characteristics remained undetermined for 3 patients (15%).

Patients with CeAD who had a family history of CeAD more often had carotid (mostly left carotid) than vertebral dissection and more frequently had elevated total cholesterol levels (≥ 6.20 mmol/L) at admission compared to patients with CeAD without such a family history (table 3). There was also a

Table 2 Characteristics of patients with a family history of CeAD

Clinical features of index patient								Clinical features of affected relative			
Family	Patient	Country	City	Age, y	Sex	Location of dissection	Cerebral ischemia	Relative(s) with CeAD	Age, y	Location of dissection	Cerebral ischemia
1	1	Switzerland	Basel	60	F	Left carotid	1	Brother	49	Left carotid	1
2	2	Germany	Heidelberg	31	M	Left vertebral	1	Father	31	Left carotid	1
3	3	Germany	Heidelberg	43	M	Left carotid	1	Sister (patient 4)	41	Left carotid	1
3	4	Germany	Heidelberg	41	F	Left carotid	1	Brother (patient 3)	43	Left carotid	1
4	5	France	Lille	48	M	Bilateral carotid	0	Male cousin ^a	59	Left carotid	1
5	6	France	Paris	53	M	Left carotid	1	Brother	51	Left carotid	1
								Male cousin	46	Right carotid	0
6	7	France	Amiens	49	M	Left carotid	1	Sister (patient 8)	45	Right carotid	1
6	8	France	Amiens	45	F	Right carotid	1	Brother (patient 7)	49	Left carotid	1
7	9	France	Dijon	44	F	Left vertebral	1	Female cousin	50	Carotid	1
8	10	France	Paris	53	F	Left carotid	0	Male cousin	NA	NA	NA
								Male cousin	NA	NA	NA
9	11	Italy	Milan	36	F	Left carotid	1	Uncle	60	Carotid	1
10	12	France	Paris	45	M	Left carotid	1	Brother (patient 13)	50	Left carotid	1
10	13	France	Paris	50	M	Left carotid	1	Brother (patient 12)	45	Left carotid	1
11	14	France	Paris	44	M	Right carotid	1	Mother	NA	Carotid	NA
12	15	Switzerland	Bern	40	F	Left carotid	0	Sister	NA	NA	NA
13	16	Switzerland	Bern	38	M	Left carotid	0	Brother	48	Carotid	0
14	17	Switzerland	Bern	53	F	Left carotid	1	Sister	NA	Carotid	1
								Brother	NA	Carotid	1
15	18	Switzerland	Zürich	38	M	Left carotid	0	Male cousin ^b	57	Common carotid	0
16	19	Switzerland	Bern	48	F	Left carotid	1	Sister	NA	Right carotid	1
17	20	Switzerland	Bern	38	F	Bilateral carotid	1	Uncle	NA	NA	NA

Abbreviations: CeAD = cervical artery dissection; NA = not available.

Cerebral ischemia = ischemic stroke or TIA, including transient monocular blindness.

^aThis patient also had a dissection of the left subclavian artery, and the brachiocephalic artery extended to the right common carotid artery and the right vertebral artery (without aortic dissection).

^bThis patient also had aortic dissection.

Table 3 Putative risk factors, and clinical and radiologic features of patients with and without a family history of CeAD

	Family history of CeAD		p	OR (95% CI) ^a	p ^a	p ^b	p ^c
	Yes (n = 20)	No (n = 1,914)					
Age, y	44.9 ± 7.0	44.6 ± 9.8	0.94	1.00 (0.96-1.05)	0.90	0.87	0.82
Women	10 (50.0)	814 (42.5)	0.50	1.35 (0.56-3.26)	0.50	0.51	0.71
Putative risk factors^d							
Hypertension ^e	5 (25.0)	477 (25.0)	1.00	1.01 (0.35-2.87)	0.99	1.00	0.86
Hypercholesterolemia ^f	5 (41.7)	222 (17.0)	0.041	3.51 (1.07-11.44)	0.038	0.027	0.059
Total cholesterol	5.5 ± 1.0	5.1 ± 1.2	0.17	1.29 (0.83-1.99)	0.26	0.21	0.42
Triglycerides	1.1 ± 0.2	1.4 ± 1.0	0.29	0.44 (0.12-1.55)	0.20	0.21	0.23
Body mass index, kg/m ²	23.5 ± 3.1	24.4 ± 4.0	0.41	0.96 (0.84-1.11)	0.58	0.60	0.46
Current smoker	2 (10.0)	559 (29.3)	0.080	0.27 (0.06-1.17)	0.081	0.083	0.14
Infection in previous month ^g	2 (10.0)	255 (15.0)	0.76	0.63 (0.15-2.74)	0.54	0.52	0.71
Cervical trauma in previous month	7 (36.8)	552 (29.0)	0.45	1.45 (0.56-3.72)	0.44	0.50	0.20
Migraine	10 (52.6)	626 (33.5)	0.090	2.20 (0.87-5.59)	0.096	0.11	0.18
Migraine with aura	3 (15.8)	228 (12.2)	0.72	1.31 (0.38-4.58)	0.67	0.70	0.45
Migraine without aura	8 (42.1)	445 (23.8)	0.099	2.31 (0.91-5.89)	0.080	0.085	0.22
Clinical and radiologic features^h							
Cerebral ischemia at admission	15 (75.0)	1,444 (76.0)	1.00	0.96 (0.34-2.66)	0.93	0.91	0.61
ICA dissection ^h	18 (90.0)	1,231 (67.7)	0.031	4.52 (1.03-19.80)	0.045	0.043	0.083
Left ICA dissection ^h	16 (80.0)	711 (39.3)	3.08 × 10 ⁻⁴	6.39 (2.12-19.30)	0.0010	0.0010	0.0018
Right ICA dissection ^h	4 (20.0)	604 (33.5)	0.24	0.49 (0.16-1.47)	0.20	0.21	0.17
Multiple dissections	2 (10.0)	291 (15.2)	0.76	0.59 (0.14-2.60)	0.49	0.49	0.68
Arterial occlusion	7 (36.8)	615 (34.3)	0.81	1.14 (0.44-2.91)	0.79	0.79	0.77
Stenosis	12 (63.2)	1,099 (61.8)	1.00	1.05 (0.41-2.69)	0.92	0.94	0.97
Aneurysmal dilation	3 (15.8)	184 (10.3)	0.44	1.62 (0.47-5.62)	0.45	0.49	0.82
CeAD recurrence at 3 mo	0 (0)	27 (1.6)	1.00	NA	NA	NA	NA

Abbreviations: CeAD = cervical artery dissection; CI = confidence interval; ICA = internal carotid artery; NA = not available; OR = odds ratio.

Data are mean ± SD or n (%).

^aAge- and sex-adjusted.

^bAdditionally adjusted for study (CADISP clinical study or Paris-Lariboisière/Zürich/Bern CeAD registry).

^cAnalysis restricted to 17 unrelated familial cases (i.e., for families 3, 6, and 10, only one patient was included in the analyses).

^dMissing values are <2.5%, except for hypercholesterolemia (n = 12/1,304 for patients with and without family history of CeAD), total cholesterol (n = 12/1,304), triglycerides (n = 10/1,296), body mass index (n = 16/1,225), infection (n = 20/1,699), and 3-month follow-up (n = 20/1,669).

^eAssociations with hypertension were still nonsignificant after removing 308 patients from the Paris-Lariboisière/Zürich/Bern CeAD registry who were included before 2000 and in whom hypertension was defined as systolic blood pressure ≥160 mm Hg or diastolic blood pressure ≥95 mm Hg; OR (95% CI) = 0.87 (0.27-2.79), p = 0.82.

^fHypercholesterolemia was defined here as total cholesterol ≥2.4 g/L (6.21 mmol/L).

^gPrevious week for CADISP.

^hNinety-four patients with dissections both in a vertebral and a carotid artery were excluded.

nonsignificant trend toward a higher prevalence of migraine, especially migraine without aura (table 3). Patients with a family history of CeAD did not differ significantly from those without such a family history regarding other putative risk factors, baseline characteristics (especially frequency of multiple dissections), and short-term (3 months) recurrence rate (table 3). Results were substantially unchanged, although no longer reaching statistical significance, when excluding one random patient from each of the 3 related patient pairs with a family history of CeAD.

None of the patients with a family history of CeAD had been diagnosed with a known inherited CTD. Among patients with CeAD who had a family history of CeAD, 2 patients (0.1%, 0.0%–0.2%) had clinically and genetically confirmed vEDS, with mutations detected in the *COL3A1* gene. In both cases, CeAD occurred before age 30 years, and the diagnosis of vEDS was already known before the dissection, with a history of colon rupture. Characteristics of the dissection and other clinical features of vEDS in these patients are described in table 4. There were 2

Table 4 Patients with CeAD who had confirmed inherited CTD

ID	Country	City	CTD	CTD known before CeAD	Other CTD criteria	Gene with mutation	Age	Sex	CeAD location	CeAD type	Cerebral ischemia	Putative risk factors of CeAD
I	France	Paris	vEDS	Yes	Positive family history (brother, same mutation), colon rupture, thin and translucent skin, characteristic facial appearance	COL3A1, p.Gly540Arg	25	M	Carotid (bilateral)	Stenosis and contralateral occlusion	TIA	Recent infection
II	France	Paris	vEDS	Yes	Colon rupture, thin and translucent skin, easy bruising, muscle ruptures, joint dislocations, sprains	COL3A1, p.Gly571Arg	29	M	Vertebral	Occlusion	Ischemic stroke	Migraine with and without aura, hypercholesterolemia, smoker
III	Switzerland	Zürich	Classic EDS	No	Cutis hyperlaxa, thin skin, easy bruising, joint hypermobility	Not tested	43	M	Carotid	Stenosis	No	Migraine with aura, recent cervical trauma, smoker
IV	France	Paris	Hypermobile EDS	yes	Multiple sprains, joint hypermobility and 3 of 3 children with joint hypermobility, mild cutis hyperlaxa	Not tested	42	F	Carotid	Stenosis	No	Migraine without aura, hypercholesterolemia
V	France	Paris	OI	Yes	>50 fractures	Not tested	40	F	Carotid + vertebral	Stenosis + aneurysm	No	Migraine without aura, hypertension, hypercholesterolemia, current smoker
VI	France	Paris	Marfan syndrome	Yes	Positive family history (maternal grandmother, mother, sister, uncle), glaucoma, retinal detachment, spontaneous pneumothorax, aortic insufficiency, mitral valve prolapse, dilatation of ascending aorta	Not tested	24	F	Vertebral (bilateral)	Stenosis	TIA + ischemic stroke	Migraine without aura

Abbreviations: CeAD = cervical artery dissection; CTD = connective tissue disorder; EDS = Ehlers-Danlos syndrome; OI = osteogenesis imperfecta; vEDS = vascular Ehlers-Danlos syndrome.

additional patients in whom vEDS was suspected after the CeAD, but *COL3A1* DNA sequencing was negative. A detailed description of these patients is provided in table e-1. One patient had clinical diagnosis of Marfan syndrome, because he had a positive family history and fulfilled the revised Ghent criteria, despite the absence of genetic testing (table 4).¹² Two additional patients had features of Marfan syndrome, but did not fulfill established clinical diagnostic criteria (table e-1).¹² One patient was diagnosed with classic EDS, one with hypermobile EDS and one with osteogenesis imperfecta, all without genetic confirmation, but fulfilling clinical diagnostic criteria (table 4).^{10,11,13}

DISCUSSION In the largest series of patients with CeAD to date, comprising nearly 2,000 patients recruited through departments of neurology (mean age 45 years, 57% men), family history of CeAD was very rare, and was associated with carotid location and elevated cholesterol levels. A trend toward an association of familial CeAD with migraine without aura was also observed. Underlying inherited CTDs, known to be associated with dissection, were exceptional, and all occurred in patients without family history of CeAD. Two patients had clinically and genetically confirmed vEDS. One patient had Marfan syndrome, one was diagnosed with classic EDS, one with hypermobile EDS, and one with osteogenesis imperfecta, based on clinical criteria.

In the only previous study to our knowledge that systematically addressed the frequency of family history of CeAD in 200 patients with CeAD,³ 10 patients from 8 families had a family history of dissection. Of these, 5 patients (2.5%, 0.3%–4.7%) from 3 families (1.5%, 0%–3.2%) had a family history of dissection in the cervical arteries (the remaining being in intracranial arteries, aorta, or renal artery) and in 4 patients, the family history of CeAD was in a first-degree relative (2.0%, 0.1%–3.9%).³ The slightly higher prevalence of familial CeAD compared with our series could be explained by sampling fluctuation (CIs overlap), or selection bias, because recruitment through a single tertiary center could have led to an overrepresentation of unusual, familial cases,³ while our multicenter recruitment may be more representative of the community. Although rare, the observed frequency of family history of CeAD is higher than expected by chance given the low disease incidence. Indeed, based on an estimated CeAD prevalence of 1/1,000,^{14,15} the probability for a patient with CeAD with 1 sibling and 2 children of having a first-degree relative who had a CeAD by mere chance is <0.5% (e-Methods).

Although power is limited by the small number of familial cases, we describe some differences in

characteristics of patients with and without a family history of CeAD, with a higher frequency of carotid dissection (90% vs 68%) and of hypercholesterolemia (42% vs 17%) in the former. These findings suggest that genetic determinants of CeAD may differ according to the dissection site. The more marked familial clustering for carotid dissection, which was suggested previously in a study comparing patients with CeAD who had a family history of CeAD with published findings from patients with sporadic CeAD,¹⁶ could point to a more important contribution of genetic factors in this vessel location. Most patients with a family history of CeAD had a dissection in the left carotid artery, suggesting that inherited anatomical factors might have a role. The higher frequency of hypercholesterolemia in patients with CeAD who had a positive family history is intriguing, because we have previously shown that patients with CeAD have a significantly lower prevalence of hypercholesterolemia than healthy controls or patients with an ischemic stroke of another etiology matched on age and sex.⁹ This may reflect that familial CeAD has different underlying mechanisms from sporadic CeAD, and may also point to shared pathways or shared genetic variation between CeAD and lipid metabolism, with allelic heterogeneity. Of note, for patients in whom detailed information was available, most relatives had a dissection in the same artery type as the index patients (17/19); age at CeAD occurrence was often similar within families, as previously described.¹⁵

Only 2 patients with CeAD (without family history of CeAD) had a genetically confirmed diagnosis of vEDS, which was known before the CeAD. From a clinical perspective, our findings suggest that clinically obvious inherited CTDs are extremely rare in patients with CeAD, because only 0.1% of our patients had a diagnosis of vEDS that was clinically evident and genetically confirmed. vEDS is a very rare condition, with a prevalence estimated at 0.2–1/100,000,¹⁷ and although CeAD is one of its classic complications, it was described in only 2% of the patients in the largest, partly retrospective series of patients with genetically confirmed vEDS.^{18,19} The first major complication of vEDS was shown to occur before age 40 in 80% of 220 patients,¹⁹ and the reported mean age at occurrence of the first cerebrovascular complication was 28 years.¹⁸ In agreement with these reports, CeAD occurred before age 30 in both patients with vEDS in our series. One of 1,934 patients was previously known to have Marfan syndrome, which is close to the prevalence of this disease in the general population, estimated between 1/3,000 and 1/5,000.²⁰ Three patients, who had their dissection between 2001 and 2006, had been diagnosed beforehand with classic or hypermobile EDS and

with osteogenesis imperfecta (prevalence for these diseases range between approximately 1/100,000 and 1/20,000), without molecular confirmation, but the genetic investigation of these disorders was challenging before the advent of next-generation sequencing, and not thought to be a requirement for diagnosis. Clinical implications are less dramatic because these diseases do not expose to an increased risk of life-threatening complications, such as vascular or hollow organ rupture, as is the case for vEDS.⁴ Overall, inherited CTDs, including EDS, Marfan syndrome, and osteogenesis imperfecta, appeared very rare in this large multicenter series of patients with CeAD, and CeAD was typically not the first symptom revealing the inherited disorder.

Our study has limitations. Only short-term clinical follow-up was available at this stage, so that we could not verify the previously reported association of CeAD family history with long-term CeAD recurrence.³ The number of patients with a family history of CeAD being small, association estimates have wide CIs and require confirmation in independent samples. Family members with a history of CeAD were not all included in CADISP-plus, therefore precluding detailed clinical description, although minimal information on CeAD characteristics could be obtained in the majority of cases. The diagnosis of CeAD could not formally be verified in 17% of the affected relatives. An underestimation of familial CeAD cannot be excluded, because (1) many CeADs causing strokes among family members remained undiagnosed in the last century because of lack of knowledge and proper imaging equipment, (2) CeAD with minor or no clinical symptoms, or leading to very severe rapidly fatal stroke, is probably still underdiagnosed, (3) some patients may have limited knowledge of their relatives' health. However, history of symptomatic CeAD is clinically more relevant and, while a systematic screening of CeAD in all first-degree relatives of patients with CeAD with arterial imaging might increase the diagnostic yield by potentially capturing some cases of asymptomatic CeAD, it would be unrealistic and ethically challenging to perform on such a large sample. Patients with CeAD who had inherited CTDs were diagnosed only in centers from Paris (1.0% of all Paris patients) and Zürich (0.4% of all Zürich patients). Although these were among the cities with the largest recruitment, it could point to an underestimation of such disorders in other centers. In France, many national referral centers for rare vascular disorders are located in Paris, which could lead to a recruitment and ascertainment bias. However, the proportion of patients with CeAD with inherited CTD remains small ($\leq 1.0\%$), even in the cities with the largest number of diagnosed cases. Because patients with severe inherited CTDs, such as

vEDS, often benefit from close multidisciplinary follow-up in highly specialized referral centers, they may also be hospitalized there when they have a CeAD, and may therefore not have been included in our study. However, given the low prevalence of these disorders, this is unlikely to have led to a major underestimation of their frequency among patients with CeAD at population level. Finally, we cannot formally exclude mild forms of inherited CTD with incomplete penetrance or CeAD as the first isolated symptom,^{15,21} because patients were not systematically screened for mutations in genes such as *COL3A1*, *FBN1*, *TGFBR1*, or *TGFBR2*, responsible for vEDS,¹⁹ Marfan syndrome,¹² and Loey-Dietz syndrome.²² In earlier studies, systematic search for mutations in *COL3A1* among 53 patients with CeAD,^{23–26} and in *TGFBR1* and *TGFBR2* among 56 consecutive patients with CeAD,²¹ identified potentially deleterious mutations in *COL3A1* among 2 cousins with CeAD,²³ and in *TGFBR2* in 2 unrelated patients with CeAD,²¹ but none of them fulfilled the clinical diagnostic criteria of vEDS or Loey-Dietz syndrome, possibly pointing to mutations with incomplete penetrance.^{10,11,22} Whether identifying such mutations is clinically relevant, especially regarding risk of CeAD recurrence, other vascular complications, and familial risk, is unclear to date. Noteworthy, skin biopsies performed in series of 7 to 65 patients with CeAD have shown that about half of these patients have ultrastructural skin connective tissue abnormalities on electron microscopy, the most common pattern being described as composite fibrils within collagen bundles and elastic fiber abnormalities with minicalcifications and fragmentation.^{2,27–30} Moreover, skin biopsies performed in healthy relatives of 3 index patients with CeAD (from 3 distinct families) have suggested that these ultrastructural skin connective tissue changes may be inherited according to an autosomal dominant pattern, but linkage studies were inconclusive.³¹ Similar pathologic changes in the wall of temporal arteries were also described in discordant identical twin pairs, both in the affected and unaffected twin.³² These findings could suggest underlying connective tissue fragility in patients with CeAD, which may in some cases be inherited, perhaps as part of uncharacterized inherited CTD with incomplete penetrance.

In 2 large multicenter cohorts of patients with CeAD, both family history of symptomatic CeAD and known inherited CTDs were very rare. In clinical practice, given the psychological distress and anxiety that is often generated by the occurrence of CeAD,³³ which usually affects young individuals with few or no vascular risk factors,⁹ this is important information for patients and their families. Based on current knowledge, we believe that systematic screening for

mutations in genes responsible for inherited CTDs is not clinically justified in monosymptomatic cases.⁴ For research purposes, our findings justify ongoing efforts to identify genetic susceptibility factors for CeAD by genetic association studies,⁴ or next-generation sequencing, rather than a family-based linkage approach, except for the very rare families with multiple cases.

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