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Determinants and outcome of multiple and early recurrent cervical artery dissections

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Abstract

Objective

To assess putative risk factors and outcome of multiple and early recurrent cervical artery dissection (CeAD).

Methods

We combined data from 2 multicenter cohorts and compared patients with multiple CeAD at initial diagnosis, early recurrent CeAD within 3 to 6 months, and single nonrecurrent CeAD. Putative risk factors, clinical characteristics, functional outcome, and risk of recurrent ischemic events were assessed.

Results

Of 1,958 patients with CeAD (mean ± SD age 44.3 ± 10 years, 43.9% women), 1,588 (81.1%) had single nonrecurrent CeAD, 340 (17.4%) had multiple CeAD, and 30 (1.5%) presented with single CeAD at admission and had early recurrent CeAD. Patients with multiple or early recurrent CeAD did not significantly differ with respect to putative risk factors, clinical presentation, and outcome. In multivariable analyses, patients with multiple or early recurrent CeAD more often had recent infection (odds ratio [OR] 1.81, 95% confidence interval [CI] 1.29–2.53), vertebral artery dissection (OR 1.82, 95% CI 1.34–2.46), family history of stroke (OR 1.55, 95% CI 1.06–2.25), cervical pain (OR 1.36, 95% CI 1.01–1.84), and subarachnoid hemorrhage (OR 2.85, 95% CI 1.01–8.04) at initial presentation compared to patients with single nonrecurrent CeAD. Patients with multiple or early recurrent CeAD also had a higher incidence of cerebral ischemia (hazard ratio 2.77, 95% CI 1.49–5.14) at 3 to 6 months but no difference in functional outcome compared to patients with single nonrecurrent CeAD.

Conclusion

Patients with multiple and early recurrent CeAD share similar risk factors, clinical characteristics, and functional outcome. Compared to patients with single nonrecurrent CeAD, they are more likely to have recurrent cerebral ischemia at 3 to 6 months, possibly reflecting an underlying transient vasculopathy.

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CADISP-plus coinvestigators are listed at links.lww.com/WNL/A638.

Glossary

CADISP = Cervical Artery Dissection and Ischemic Stroke Patients; **CeAD** = cervical artery dissection; **CI** = confidence interval; **HR** = hazard ratio; **OR** = odds ratio; **SAH** = subarachnoid hemorrhage.

Cervical artery dissection (CeAD) is a common cause of stroke in young and middle-aged adults. In 15% to 20% of patients with CeAD, multiple dissections are found at presentation.[1–7] CeAD recurrences are rare; estimates range between 0% and 25% in hospital-based series, with the largest cohorts reporting recurrence rates of ≈3% at 3 to 6 months.[8] Long-term recurrences, beyond the first months after the initial event, are more seldom (≈1%/y),[9] although studies with very long-term follow-up are lacking.[8,9] The distinction between multiple and early recurrent dissections is a matter of debate. It depends partly on the delay between symptom onset and diagnosis by cervical artery imaging, with a longer delay resulting in a higher frequency of multiple CeAD and a lower rate of early recurrent CeAD.[10]

Little is known about the determinants and prognosis of multiple and early recurrent CeAD. We aimed to explore the risk factors, characteristics, and outcome of multiple and early recurrent CeAD in 2 large, international, hospital-based cohort studies and hypothesized that they would differ from patients with single nonrecurrent CeAD.

Methods

Study population

The Cervical Artery Dissection and Ischemic Stroke Patients (CADISP)-plus Consortium gathered clinical information on 2,145 patients with CeAD from the multicenter CADISP study (n = 983) and the Paris-Lariboisière/Zürich/Bern cohort studies (n = 1,162) (figure 1). Methods of the CADISP-plus Consortium[11] have been described previously.[1,3,12]

In the CADISP study, we prospectively included all consecutive patients evaluated in neurology departments with a diagnosis of CeAD between 2004 and 2009.[13] In addition, retrospective patients who had a qualifying event before the start of the study (mostly between 1999 and 2009) and were identified through local CeAD registries were included. The Paris-Lariboisière/Zürich/Bern registry prospectively included consecutive patients with a first-ever CeAD between 1985 and 2014. In both studies, iatrogenic dissections were excluded, and patients with CeAD were evaluated following a standardized protocol. For the current study, patients with a single CeAD without follow-up at 3 to 6 months were excluded from further analyses because we could not determine whether they had experienced a recurrent CeAD (n = 187, 8.7%). Overall, 1,958 patients with CeAD (n = 952 from CADISP, n = 1,006 from the Paris-Lariboisière/Zürich/Bern study, figure 2) were available for the present analysis, recruited in 8 countries and 23 centers (figure 1).

Standard protocol approvals, registrations, and patient consents

Study protocols were approved by local authorities in all participating centers.

Definition of multiple and early recurrent CeAD

All centers applied the same diagnostic criteria for CeAD.[11,14] The dissection of a cervical carotid or vertebral artery had to be radiologically confirmed by the presence of a mural hematoma, a dissecting aneurysm, a long tapering stenosis, an intimal flap, a double lumen, or an occlusion >2 cm above the carotid bifurcation revealing a dissecting aneurysm or a long tapering stenosis after recanalization.

Multiple CeAD was defined as the simultaneous presence of >1 CeAD at the initial diagnosis. Early recurrent dissection was defined as a new, radiologically confirmed diagnosis of CeAD at follow-up occurring within 6 months after the first CeAD symptoms (the delay between symptom onset and follow-up was variable given the observational setting). Patients with both multiple and early recurrent CeAD were included in the group with multiple dissections for statistical analyses.

Study variables

Clinical characteristics and radiologic characteristics

Presence of cerebral ischemia (ischemic stroke or TIA) and other presenting clinical characteristics were recorded. All patients had their cervical arteries assessed by CT, magnetic resonance, or digital subtraction angiography. Treatment could consist of thrombolytic therapy (IV or intra-arterial) and/or antithrombotic therapy (antiplatelet agents, vitamin K antagonists or heparin, or a combination of the aforementioned therapies) based on the treating physician's judgement. Clinical follow-up with assessment of recurrent events was obtained through neurologic examination or telephone interview and chart review between 3 and 6 months after the initial event.

Putative risk factors

Hypertension was defined as a history of elevated blood pressure (systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive drug intake). In the Paris-Lariboisière/Zürich/Bern registry, the older World Health Organization threshold for hypertension (≥160/95 mm Hg) was used for patients included before 2000. The variable hypercholesterolemia was defined as a total fasting cholesterol ≥6.20 mmol/L at admission. A positive family history of stroke was characterized by at least 1 first-

Figure 1 CADISP-plus centers

Centers in London, UK, and Munich, Germany, participated in the Cervical Artery Dissection and Ischemic Stroke Patients (CADISP)-genetics study but not the CADISP clinical study.

degree family member with a positive history of stroke. Migraine was defined according to the International Classification of Headache Disorders.[15,16] An infection in the week preceding the dissection (or the preceding month for the Paris-Lariboisière/Zürich/Bern registry) was characterized by the presence of at least 1 typical symptom of infection, in combination with fever (temperature ≥38°C) or corresponding serologic, cultural, or radiologic findings indicating an acute infection or the combination of at least 2 typical corresponding symptoms of infection.[3] The occurrence of a cervical trauma in the month preceding the dissection (defined as severe if leading to medical examination or hospitalization[17]) and the presence of a known connective tissue disorder (e.g., vascular Ehlers-Danlos syndrome, or Marfan syndrome) were recorded.

Outcome

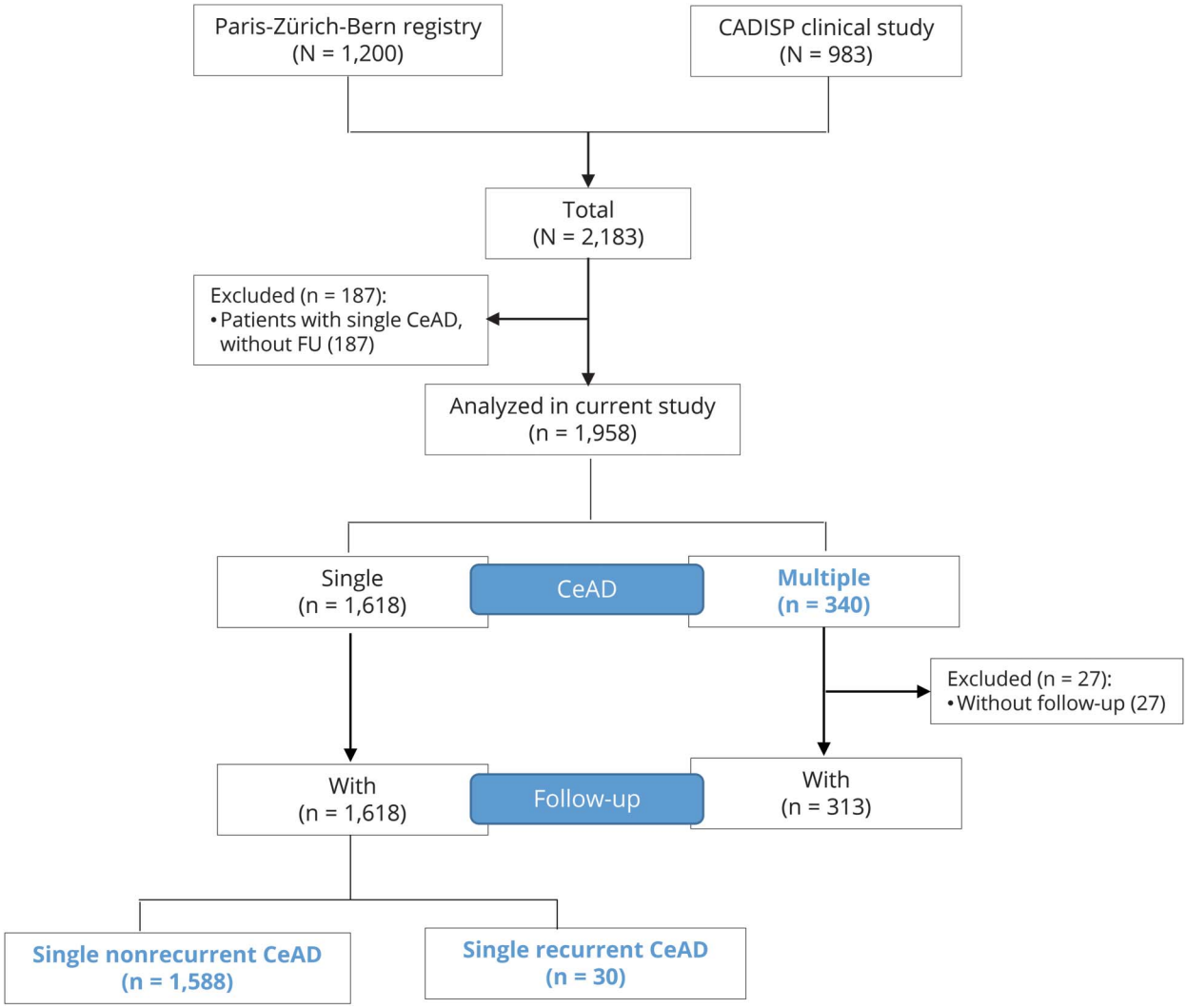
Outcome measures were good functional outcome, defined as modified Rankin Scale score ≤1, and occurrence of TIA, ischemic stroke, cerebral ischemia (TIA or ischemic stroke), or death after admission and within 3 to 6 months after initial CeAD diagnosis. In the Paris-Lariboisière/Zürich/Bern study, an ischemic event was defined as a stroke if neurologic symptoms of sudden onset lasted >24 hours and as a TIA if the duration of symptoms was <24 hours. In the CADISP study, patients with symptoms lasting <24 hours but a relevant acute ischemic lesion on imaging qualified as ischemic stroke.

Statistical analyses

Patients with a single nonrecurrent CeAD made up the reference group, with which we compared patients with multiple CeAD at initial diagnosis and patients with single CeAD experiencing an early recurrent CeAD.

Logistic regression was used to compare (1) putative risk factors of multiple vs single CeAD and early recurrent vs single CeAD with multivariable models adjusted for all putative risk factors with values of $p < 0.05$ in univariable analyses and (2) clinical characteristics of multiple vs single and early recurrent vs single CeAD with multivariable models being adjusted for all putative risk factors with values of $p <$

Figure 2 Flowchart of the study population



CADISP = Cervical Artery Dissection and Ischemic Stroke Patients; CeAD = cervical artery dissection; FU = follow-up.

0.05. For analyses of putative risk factors and clinical characteristics, we also compared patients with multiple CeAD to patients with early recurrent CeAD. In the absence of significant differences, patients with multiple or early recurrent CeAD were studied together and compared to patients with single nonrecurrent CeAD in multivariable analyses, given the small sample size for early recurrent CeAD. All logistic regression analyses were stratified by study type.

We performed a Cox regression to compare the risk of incident ischemic stroke, TIA, and death within 3 to 6 months between patients with multiple or early recurrent CeAD and patients with single nonrecurrent CeAD after verifying the proportional hazards assumption (using proportionality tests assessing the significance of an interaction term between time and each variable in the model). Multivariable analyses were adjusted for age, sex, study type, and any other relevant baseline characteristics significantly associated with multiple or early recurrent CeAD. Finally, the frequency of good functional outcome at 3 to 6 months was compared between patients with multiple or early recurrent CeAD and patients with single nonrecurrent CeAD with univariate logistic regression stratified by study type.

Sensitivity analyses were performed by repeating all analyses after the exclusion of patients with a preceding major trauma (n = 55).

Data availability

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

Results

We included 1,958 patients with CeAD from 23 centers in 8 countries (figure 1). The mean ± SD age of the study

population was 44.3 ± 10.0 years, and 859 (43.9%) were women. At the time of diagnosis, 1,406 patients (71.8%) had cerebral ischemia and 25 patients (1.3%) had a subarachnoid hemorrhage (SAH). CeAD affected predominantly the carotid artery (1,336 patients, 68.2%), with 109 patients (5.6%) having both carotid and vertebral CeAD.

Of 1,958 patients with CeAD, 1,588 (81.1%) had a single nonrecurrent CeAD, 340 (17.4%) had multiple CeAD, and 30 (1.5%) presented with single CeAD and had an early recurrent CeAD within 3 to 6 months after symptom onset. Among the 340 patients with multiple CeAD, 7 (2.0%) also had an early recurrent CeAD and were included by design in the multiple dissection group for subsequent analyses. The risk of early recurrent CeAD did not differ significantly between patients with multiple and those with single CeAD at the time of diagnosis (odds ratio [OR] 1.23, 95% confidence interval [CI] 0.53–2.82, $p = 0.63$). In patients with an early recurrent dissection, the mean interval between symptom onset and recurrent CeAD was 1.45 ± 1.09 months, and 18 of 37 early CeAD recurrences (48.6%) occurred within the first month after symptom onset (figure 3).

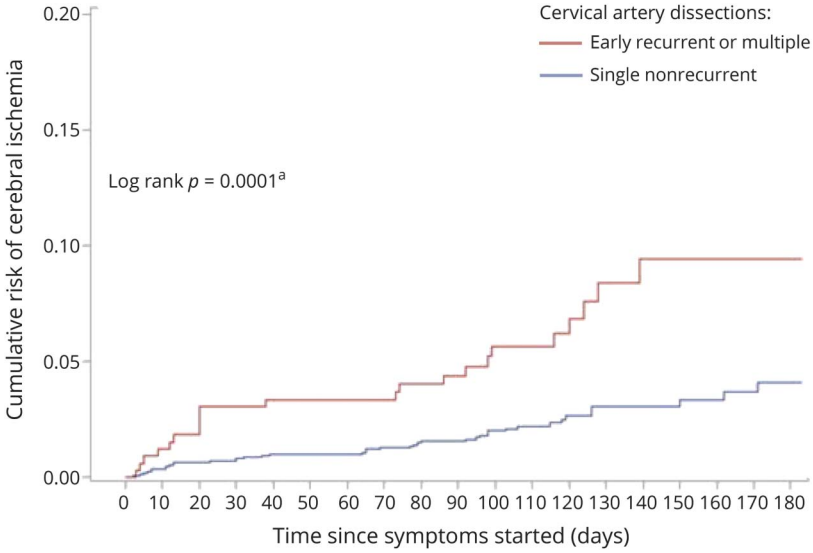
Regarding putative risk factors, in univariable analyses, patients with multiple CeAD were younger, more often women, less often smokers, and more frequently had vertebral artery dissection, a family history of stroke, migraine, and recent infection compared to patients with nonrecurrent single CeAD (table 1). In multivariable analyses, multiple CeAD remained significantly associated with vertebral artery dissection (OR 2.02, 95% CI 1.47–2.77), recent infection (OR 1.76, 95% CI 1.23–2.52), female sex (OR 1.41, 95% CI 1.02–1.94), and family history of stroke (OR 1.50, 95% CI 1.00–2.23) (table 1). Because the distribution of putative risk factors did not differ between patients with multiple and early recurrent CeAD (table 1), we ran multivariable analyses combining both patient groups and comparing them to patients with single nonrecurrent CeAD. Putative risk factors associated with multiple or early recurrent CeAD were mostly similar to those associated with multiple CeAD alone, except that the association with sex was no longer significant (table 1 and figure 4).

In a comparison of baseline clinical features between groups in univariable analyses, patients with multiple CeAD more often had cervical pain and SAH than patients with nonrecurrent single CeAD. In multivariable analyses adjusted for the aforementioned risk factors for multiple CeAD, only the association with SAH remained significant (OR 3.20, 95% CI 1.13–9.08) (table 2). Patients with nonrecurrent single CeAD presented less often with cerebral ischemia compared to patients with early recurrent single CeAD (OR 0.42, 95% CI 0.20–0.89). Because baseline clinical features did not differ significantly between patients with multiple and early recurrent CeAD, we ran multivariable analyses combining both patient groups, showing a significant association with cervical pain (OR 1.36, 95% CI 1.01–1.84) and SAH (OR 2.85, 95% CI 1.01–8.04) compared to single nonrecurrent CeAD (table 2 and figure 4).

Acute-phase treatment did not differ between any of the patient groups.

Follow-up information (3–6 months after symptom onset, mean duration 3.9 ± 1.2 months) was available in 1,931 patients. Twelve patients (0.6%) died during follow-up; all

Figure 3 Kaplan-Meier curve for risk of cerebral ischemia during follow-up



[a] *p* Value for difference in cerebral ischemia occurrence between patients with early recurrent or multiple cervical artery dissection (CeAD) vs patients with single nonrecurrent CeAD with the log-rank test.

Table 1 Association of putative risk factors with multiple and early recurrent CeAD

				Univariate			Multivariable[c]	
	Multiple CeAD (n = 340)	Recurrent CeAD (n = 30)	Single nonrecurrent CeAD (n = 1,588)	OR (95% CI) and *p* value, multiple vs single CeAD	OR (95% CI) and *p* value, recurrent vs single CeAD	OR (95% CI) and *p* value, multiple vs recurrent CeAD	OR (95% CI) and *p* value, multiple vs single CeAD	OR (95% CI) and *p* value, multiple or recurrent vs single CeAD
Dissection site, n (%)[a]								
Carotid	125/340 (36.8)	22/30 (73.3)	1,080/1,587 (68.1)	Referent	Referent	Referent	Referent	Referent
Vertebral	106/340 (31.2)	8/30 (26.7)	507/1,587 (31.9)	1.81 (1.37–2.39)	0.77 (0.34–1.73)	2.28 (0.97–5.32)	2.02 (1.47–2.77)	1.82 (1.34–2.46)
				3.34×10^{-5}	0.521	0.057	1.50×10^{-5}	1.04×10^{-4}
Vertebral and carotid	109/340 (32.0)	0/30 (0.0)	0/1,587 (0.0)	NA	NA	NA	NA	NA
				0.967	NA	0.989	0.967	0.964
Demographic characteristics								
Age, mean (SD), y	42.8 (9.7)	42.6 (9.2)	44.6 (10.1)	0.98 (0.97–0.99)	0.98 (0.95–1.02)	1.00 (0.96–1.04)	0.99 (0.97–1.01)	0.99 (0.97–1.00)
				0.002	0.277	0.873	0.215	0.111
Women, n (%)	193/339 (56.9)	12/30 (40.0)	654/1,588 (41.2)	1.88 (1.49–2.39)	0.94 (0.45–1.98)	1.83 (0.85–3.95)	1.41 (1.02–1.94)	1.30 (0.96–1.77)
				1.66×10^{-7}	0.881	0.122	0.039	0.093
Putative risk factors, n (%)								
Current smoking	75/338 (22.2)	8/28 (28.6)	458/1,575 (29.1)	0.69 (0.53–0.92)	0.98 (0.43–2.23)	0.70 (0.30–1.66)	0.76 (0.53–1.09)	0.79 (0.56–1.10)
				0.010	0.955	0.419	0.137	0.161
Hypertension	79/339 (23.3)	7/29 (24.1)	379/1,579 (24.0)	0.97 (0.74–1.29)	0.99 (0.42–2.35)	1.02 (0.42–2.49)		
				0.855	0.989	0.962		
Diabetes mellitus	6/339 (1.8)	1/29 (3.4)	37/1,583 (2.3)	0.75 (0.31–1.78)	1.55 (0.20–11.72)	0.63 (0.07–5.50)		
				0.509	0.670	0.678		
Hypercholesterolemia	24/235 (10.2)	0/19 (0.0)	139/1,105 (12.6)	0.75 (0.46–1.21)	NA	NA		
				0.233	0.991	0.992		
Family history of stroke	61/327 (18.6)	7/28 (25.0)	217/1,533 (14.1)	1.41 (1.03–1.92)	2.00 (0.84–4.75)	0.75 (0.30–1.85)	1.50 (1.00–2.23)	1.55 (1.06–2.25)
				0.033	0.118	0.530	0.047	0.022
Migraine	137/333 (41.1)	9/29 (31.0)	489/1,545 (31.6)	1.55 (1.21–2.0)	0.93 (0.42–2.07)	1.54 (0.68–3.49)	1.15 (0.83–1.58)	1.09 (0.80–1.48)
				4.64×10^{-4}	0.858	0.299	0.41	0.59

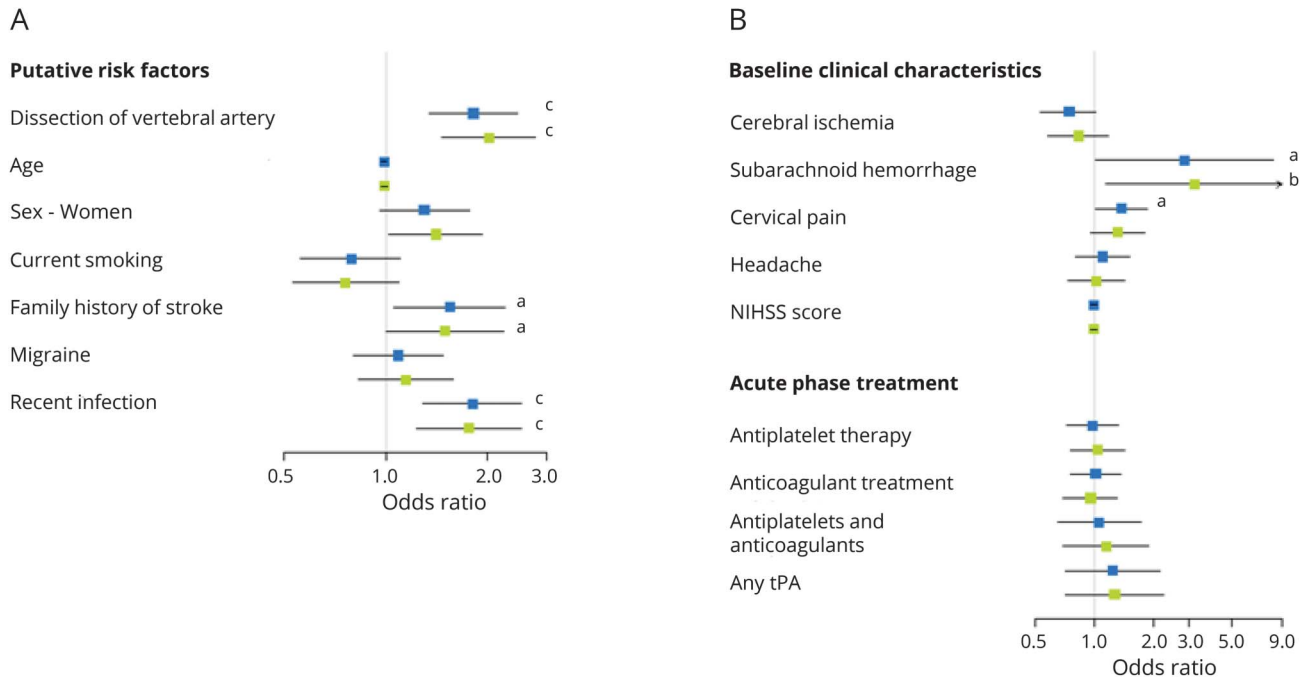
Continued

Table 1 Association of putative risk factors with multiple and early recurrent CeAD *(continued)*

				Univariate			Multivariable[c]	
	Multiple CeAD (n = 340)	Recurrent CeAD (n = 30)	Single nonrecurrent CeAD (n = 1,588)	OR (95% CI) and *p* value, multiple vs single CeAD	OR (95% CI) and *p* value, recurrent vs single CeAD	OR (95% CI) and *p* value, multiple vs recurrent CeAD	OR (95% CI) and *p* value, multiple vs single CeAD	OR (95% CI) and *p* value, multiple or recurrent vs single CeAD
Migraine without aura	98/333 (29.4)	6/29 (20.7)	344/1,546 (22.2)	1.47 (1.13–1.92)	0.89 (0.36–2.20)	1.55 (0.61–3.92)		
				0.004	0.798	0.356		
Migraine with aura	49/334 (14.7)	4/29 (13.8)	170/1,545 (11.0)	1.42 (1.01–2.00)	1.25 (0.43–3.63)	1.06 (0.35–3.18)		
				0.046	0.687	0.915		
Hormonal contraception[b]	58/165 (35.1)	2/12 (16.7)	177/508 (34.8)	1.06 (0.73–1.53)	0.37 (0.08–1.73)	2.70 (0.57–12.69)		
				0.774	0.207	0.208		
Preceding trauma	119/337 (35.3)	13/28 (46.4)	492/1,574 (31.2)	1.27 (0.98–1.63)	1.83 (0.85–3.93)	0.68 (0.31–1.50)		
				0.066	0.122	0.341		
Recent infection	78/311 (25.1)	9/28 (32.1)	255/1,448 (17.6)	1.57 (1.18–2.10)	2.20 (0.99–4.92)	0.71 (0.31–1.64)	1.76 (1.23–2.52)	1.81 (1.29–2.53)
				0.002	0.054	0.428	0.002	5.98×10^{-4}
Connective tissue disorder	8/334 (2.4)	0/27 (0.0)	16/1,532 (1.0)	2.12 (0.89–5.01)	NA	NA		
				0.088	0.988	0.989		

Abbreviations: CeAD = cervical artery dissection; CI = confidence interval; NA = not applicable; OR = odds ratio .
[a] At initial presentation.
[b] In 698 women under <50 years of age.
[c] Multivariable logistic regression analyses are adjusted for all putative risk factors with $p < 0.05$ in univariable analyses. Hypertension is defined by systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or antihypertensive drug intake. In the Paris-Lariboisière/Zürich/Bern registry, the older World Health Organization threshold for hypertension (≥160/95 mm Hg) was used for patients included before 2000. Hypercholesterolemia was defined as a total fasting cholesterol ≥6.20 mmol/L at admission. A positive family history of stroke was characterized by at least 1 first-degree family member with a positive history of stroke. Migraine was defined according to the International Classification of Headache Disorders.[15,16] An infection in the week preceding the dissection (or the preceding month for the Paris-Lariboisière/Zürich/Bern registry) was characterized by the presence of at least 1 typical symptom of infection, in combination with fever (temperature ≥38°C) or with corresponding serologic, cultural, or radiologic findings indicating an acute infection or the combination of at least 2 typical corresponding symptoms of infection.[3] The occurrence of a cervical trauma in the month preceding the dissection and the presence of a known connective tissue disorder (e.g., vascular Ehlers-Danlos syndrome or Marfan syndrome) were recorded.

Figure 4 Association of risk factors, characteristics, and treatment with multiple and early recurrent CeAD



Associations of (A) putative risk factors or clinical characteristics and (B) acute-phase treatment with multiple or early recurrent cervical artery dissection (CeAD; blue) or multiple CeAD only (green) compared to single nonrecurrent CeAD. Forest plots display odds ratios and 95% confidence intervals obtained in multivariable logistic regression (table 2). [a]$p < 0.05$; [b]$p < 0.01$; [c]$p < 0.001$. NIHSS = NIH Stroke Scale; tPA = tissue plasminogen activator.

had a single nonrecurrent CeAD. Sixty patients (3.1%) had new-onset cerebral ischemia during follow-up; 33 patients (1.7%) had an ischemic stroke; and 32 patients (1.7%) had a TIA.

Compared to patients with single nonrecurrent CeAD, patients with multiple CeAD were at significantly increased risk of cerebral ischemia (hazard ratio [HR] 2.86, 95% CI 1.49–5.48), ischemic stroke (HR 2.70, 95% CI 1.11–6.55), and TIA (HR 2.89, 95% CI 1.19–7.03) (table 3). Results remained unchanged in multivariable models adjusted for age, sex, study type, previous infection, dissection site, family history of stroke, and presence of SAH or cerebral ischemia at baseline (table 3). Among the 30 patients with an early recurrent CeAD, 2 (7%) had cerebral ischemia in relation with the CeAD recurrence. Combining patients with multiple and early recurrent CeAD yielded an increased risk of incident cerebral ischemia similar to that for multiple CeAD only compared to patients with single nonrecurrent CeAD (table 3 and figure 3).

At follow-up, 1,414 patients (73.2%) had a good functional outcome defined as a modified Rankin Scale score ≤1. The likelihood of having a good functional outcome did not differ significantly between patients with multiple or early recurrent CeAD and patients with single nonrecurrent CeAD (OR 1.28, 95% CI 0.95–1.72 and OR 1.75, 95% CI 0.66–4.59), even in the subgroup of patients who had a stroke at baseline (OR 1.28, 95% CI 0.91–1.80 and OR 1.00, 95% CI 0.28–3.59).

In sensitivity analyses excluding patients with a preceding major trauma (n = 55), results remained essentially unchanged (data not shown).

Discussion

In this large multicenter study of 1,958 patients with CeAD with a mean follow-up of 3.9 ± 1.2 months, we found that 81.1% of patients had a single nonrecurrent CeAD, 17.4% had multiple CeAD at initial presentation (2% of whom had early recurrent CeAD), and 1.5% had a single CeAD at baseline with early recurrence. Patients with multiple and early recurrent CeAD did not differ with respect to risk factors, clinical presentation, and outcome. Compared to patients with single nonrecurrent CeAD, patients with multiple or early recurrent CeAD more often had vertebral artery dissection, recent infection, and a family history of stroke. They also more frequently had SAH and cervical pain at initial presentation. During follow-up, 3.0% of patients had new cerebral ischemia, with a nearly tripling of risk in patients with multiple or early recurrent CeAD compared to patients with single CeAD. Three-quarters of all patients had a good functional outcome, with no significant differences among patients with single, multiple, and early recurrent CeAD.

The prevalence of multiple CeAD is in line with previous reports on subsets of the present sample[3] and slightly lower than in a previous independent study of 200 patients with

Table 3 Association of multiple or early recurrent CeAD with risk of new-onset ischemic events at 3 to 6 months

	Multiple CeAD (n = 313), n (%)	Recurrent CeAD (n = 30), n (%)	Single nonrecurrent CeAD (n = 1,588), n (%)	HR (95% CI), multiple vs single CeAD	*p* Value	HR (95% CI), multiple or recurrent vs single CeAD	*p* Value
Model 1, univariate							
Cerebral ischemia	20/311 (6.4)	2/30 (6.7)	38/1,566 (2.4)	2.86 (1.49–5.48)	0.002	2.99 (1.61–5.54)	5.4×10^{-4}
Ischemic stroke	10/311 (3.2)	1/30 (3.3)	22/1,567 (1.4)	2.70 (1.11–6.55)	0.028	2.81 (1.21–6.53)	0.01
TIA	11/311 (3.5)	1/30 (3.3)	20/1,567 (1.3)	2.89 (1.19–7.03)	0.019	3.00 (1.28–6.98)	0.011
Model 2, adjusted for age, sex, study type, dissection site, family history of stroke, and previous infection							
Cerebral ischemia				2.69 (1.40–5.16)	0.003	2.77 (1.49–5.14)	0.001
Ischemic stroke				2.53 (1.04–6.13)	0.040	2.62 (1.13–6.08)	0.025
TIA				2.74 (1.12–6.69)	0.027	2.79 (1.20–6.53)	0.018
Model 3, like model 2 with additional adjustment for SAH at baseline							
Cerebral ischemia				2.76 (1.43–5.30)	0.002	2.83 (1.52–5.26)	0.001
Ischemic stroke				2.58 (1.06–6.26)	0.037	2.67 (1.15–6.20)	0.023
TIA				2.83 (1.16–6.91)	0.023	2.86 (1.22–6.70)	0.015
Model 4, like model 2 with additional adjustment for cerebral ischemia at baseline							
Cerebral ischemia				2.70 (1.41–5.18)	0.003	2.83 (1.53–5.24)	0.001
Ischemic stroke				2.54 (1.05–6.15)	0.038	2.68 (1.16–6.21)	0.021
TIA				2.75 (1.13–6.68)	0.026	2.84 (1.22–6.64)	0.016

Abbreviations: CeAD = cervical artery dissection; CI = confidence interval; HR = hazard ratio; NA = not applicable; SAH = subarachnoid hemorrhage .

CeAD recruited in a single tertiary center (28%), with a possible recruitment bias toward more severe cases.[9] CeAD recurrence rates in former independent studies (of 200 patients at most) varied widely, which can be partly ascribed to differences in follow-up duration, ranging between 6 months and 9.3 years.[6,9,18–26] Most studies reported CeAD recurrence rates ≤5%,[8] except for 2 studies that reported 7.0% and 8.3% of CeAD recurrences at 7.4 and 9.3 years[9] and 1 study of 36 patients reporting a CeAD recurrence rate of 25% at 7 months.[26] We found that early recurrent CeAD tended to cluster very early within the first month after the initial CeAD.[9] Moreover, no significant differences in patient characteristics, putative risk factors, and outcome were found between patients with multiple and early recurrent CeAD, suggesting common pathogenic mechanisms compatible with the hypothesis that a transient vasculopathy or vulnerability of the arterial wall could underlie both multiple and early recurrent CeAD.[8,27]

The association we found between multiple or early recurrent CeAD and preceding infection remained highly significant after adjustment for potential confounders. One could speculate that this association might reflect an underlying transient vasculopathy caused by the concomitant infection, rendering the cervical arteries more vulnerable to dissection. The mechanism underlying this association could hypothetically involve secretion of proinflammatory cytokines, free radicals, and proteases; direct presence of infectious agents within the vessel wall; or possibly small vessel vasculitis of the vasa vasorum.[28–31] Supporting this theory, a pilot study of 37 patients with CeAD found that patients with multiple CeAD more often had imaging features of vessel wall inflammation such as perivascular contrast enhancement in high-resolution MRI and increased perivascular [^{18}F]-fluorodeoxyglucose uptake in PET.[32] Alternatively, certain anti-infective agents may play a role because an increased risk of aortic aneurysms and dissections was, for instance, reported in patients taking fluoroquinolones.[33] In the present study, we could not conduct analyses of the type of infection associated with multiple and early recurrent CeAD. Moreover, patients were not systematically screened for covert infections such as chronic sinusitis or dental infections. There is increasing interest in the role of latent infections, including dental infection, and of oral and gut microbiome in the occurrence of cerebrovascular disease, which may also be relevant to explore in relation to CeAD.[34–37] Ongoing large-scale genomic studies may also provide insight into potential interactions between recent infection and genetic susceptibility to CeAD.[38]

The higher frequency of family history of stroke in patients with multiple or early recurrent CeAD compared to those with single nonrecurrent CeAD may suggest an increased

familial liability to cervico-cerebral artery disease or may be partly explained by recall bias. Whether the family history of stroke was related to familial CeAD cannot be determined by the current data. In line with previous studies, patients with multiple or early recurrent CeAD more frequently had vertebral CeAD,[3,4,39] possibly related in part to the more subtle and less specific symptoms of vertebral compared to carotid CeAD, complicating the diagnosis in isolated vertebral artery CeAD.

From a clinical perspective, the most striking findings are the higher frequency of SAH at presentation in patients with multiple CeAD and the nearly tripled risk of incident cerebral ischemic events at 3 to 6 months in patients with multiple or early recurrent CeAD.[5,10] Although absolute numbers remain low (3.0% of SAH at diagnosis and 6.4% of incident cerebral ischemia in patients with multiple or early recurrent CeAD), more extensive workup and monitoring may be warranted in these patients. The fact that these associations do not translate into a significantly lower rate of good functional outcome is reassuring but does not diminish the need for close monitoring of these patients.

The association of multiple CeAD with a higher frequency of SAH may partly reflect that patients with multiple CeAD are at higher risk of having at least 1 dissection extending intracranially, especially given the frequent involvement of the vertebral artery, which is more prone to intracranial extension.[40] SAH may also occur in reversible cerebral vasoconstriction syndrome, more commonly seen in patients with CeAD, especially vertebral artery dissection,[41] or could be the consequence of an underlying transient vasculopathy making the arteries more prone to rupture. The higher risk of incident cerebral ischemia may again reflect an underlying, possibly transient vasculopathy and the increased likelihood of thrombus formation and embolism in at least 1 of the dissected arteries. The association of multiple or early recurrent CeAD with the risk of incident cerebral ischemia was independent of preceding infection, suggesting that a prothrombotic state caused by an underlying infection is not a major mediator.[30] Our findings regarding the nearly tripled risk of incident cerebral ischemia in patients with multiple or early recurrent CeAD raise the question of whether more intensive antithrombotic treatment (e.g., anticoagulants vs antiplatelets) should be prescribed to patients with multiple or early recurrent CeAD in the absence of SAH. Analyses focusing on patients with multiple or early recurrent CeAD within completed[42] and ongoing trials (NCT02046460) that compare different antithrombotic strategies in patients with CeAD could be of interest.

To the best of our knowledge, this is the largest series to date of patients with CeAD with detailed information on multiple and early recurrent dissections. Despite the overall large sample size, we had limited power for analyses of association with early recurrent dissections. Most patients were recruited in tertiary referral centers, which may have introduced a referral bias, but this is mitigated by the multicenter design. Standardized follow-up imaging has not been performed in all patients; therefore, we cannot exclude that some asymptomatic recurrent CeADs have been missed. Very early recurrences before 3 months may also have been missed. Future studies with systematic and standardized follow-up imaging in large series of consecutive patients with CeAD might be warranted, although cost and clinical relevance should be balanced against the relatively low risk of recurrent symptomatic CeAD.

The present findings should prompt careful workup and monitoring of patients with multiple and early recurrent CeAD, considering the nearly tripled risk of cerebral ischemia. Additional research is required to determine whether multiple and early recurrent dissections are facilitated by an underlying vasculopathy and to characterize it. Further studies are also needed to explore the effect of antithrombotic treatment type on the risk of stroke in patients with multiple or early recurrent CeAD.

Author contributions

Study concept or design: Compter, Schilling, Bousser, Arnold, and Debette. Acquisition of data: Compter, Vaineau, Goeggel-Simonetti, Metso, Southerland, Pezzini, Kloss, Touzé, Worrall, Thijs, Bejot, Reiner, Grond-Ginsbach, Bersano, Brandt, Caso, Lyrer, Traenka, Lichy, Martin, Leys, Sarikaya, Baumgartner, Jung, Fischer, Engelter, Chabriat, Tatlisumak, Bousser, and Arnold. Analysis or interpretation of data: Compter, Schilling, Vaineau, Goeggel-Simonetti, Metso, Southerland, Pezzini, Kloss, Touzé, Worrall, Thijs, Bejot, Reiner, Grond-Ginsbach, Bersano, Brandt, Caso, Lyrer, Traenka, Lichy, Martin, Leys, Sarikaya, Baumgartner, Jung, Fischer, Engelter, Dallongeville, Chabriat, Tatlisumak, Bousser, and Arnold. Drafting/revising the manuscript for content: Compter, Schilling, Vaineau, Goeggel-Simonetti, Metso, Southerland, Pezzini, Kloss, Touzé, Worrall, Thijs, Bejot, Reiner, Grond-Ginsbach, Bersano, Brandt, Caso, Lyrer, Traenka, Lichy, Martin, Leys, Sarikaya, Baumgartner, Jung, Fischer, Engelter, Dallongeville, Chabriat, Tatlisumak, Bousser, Arnold, and Debette. Statistical analysis: Compter, Schilling, and Debette. Obtaining funding: Debette. Study supervision or coordination: Bousser, Arnold, and Debette.

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Disclosure

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