Stroke

ORIGINAL CONTRIBUTION

Recurrent Cervical Artery Dissection Prevalence and Predictors: A Secondary Analysis of the STOP-CAD Study

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BACKGROUND: Patients with cervical artery dissection (CeAD) may experience a recurrent dissection, but its frequency, risk factors, and clinical implications are not well defined. We aimed to determine the risk, associated factors, and clinical impact of recurrent CeAD.

METHODS: The STOP-CAD study was a multicenter international retrospective observational study of patients with CeAD treated between January 2015 and June 2022. Recurrent dissection was defined as a CeAD occurring at least 7 days after the diagnosis of the index event that affects a different artery or a different segment of the same artery. Patients were followed from day 7 up to 2 years. The absolute risk of recurrent CeAD over time was calculated using Kaplan-Meier survival estimates. Multivariable logistic and Cox regression models were used to assess predictors of CeAD recurrence.

RESULTS: Of the 4023 patients included in STOP-CAD, 3836 (median age 46 years, 45% females) were eligible for this analysis. During a median (interquartile range) follow-up of 295 (97–720) days, 88 (2.29%) patients had a CeAD recurrence. Median time-to-recurrent CeAD was 53 (interquartile range, 18–157) days. The estimated risk of recurrent CeAD at 2 years was 3.22% (95% CI, 2.59%–4.00%). In multivariable analyses, younger age (adjusted odds ratios, 0.98 [95% CI, 0.96–0.99]), migraine (adjusted odds ratio, 1.88 [95% CI, 1.14–3.07]), and fibromuscular dysplasia (adjusted odds ratio, 2.90 [95% CI, 1.66–5.06]) were associated with CeAD recurrence, while presenting with an ischemic stroke was associated with a lower likelihood of recurrence (adjusted odds ratio, 0.47 [95% CI, 0.29–0.75]). These associations with CeAD recurrence over time were confirmed by Cox regression analyses. Among the 88 patients with recurrent CeAD, only 5 had accompanying ischemic events (3 strokes, 2 transient ischemic attacks).

CONCLUSIONS: In this retrospective study, recurrent CeAD was uncommon, approximately half of the events were diagnosed within the first 2 months of the index event, and recurrent events rarely caused new ischemic events. Younger age, migraine, absence of ischemic stroke at presentation, and signs of fibromuscular dysplasia may help identify high-risk patients.

GRAPHIC ABSTRACT: A graphic abstract is available for this article.

Key Words: arteries ■ fibromuscular dysplasia ■ ischemic stroke ■ migraine disorders ■ risk actors

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Nonstandard Abbreviations and Acronyms

aOR	adjusted odds ratios
CeAD	cervical artery dissection
FMD	fibromuscular dysplasia

Cervical artery dissection (CeAD) is a frequent cause of stroke in young adults.[1,2] Although patients may experience CeAD recurrence, its estimated risk, associated factors, and clinical impact are incompletely understood.[3]

Current evidence suggests that the long-term risk of CeAD recurrences is ≈0.3% to 1% per year.[4–7] Some studies, however, have suggested a higher risk during the early phase (within the first month), during which recurrent events may occur in up to 25% of patients.[5,8] Nonetheless, differences in recurrent CeAD definition, duration of follow-up, and lack of systematic neuroimaging follow-up protocols hinder accurate risk estimation of recurrent CeAD.

Various predictors of recurrent CeAD have been proposed, including younger age, migraine, recent infection, family history of stroke, vertebral artery dissection, and a diagnosis of fibromuscular dysplasia (FMD), although some of these associations have been inconsistently reported across previous studies.[5,6,9–11]

Notably, recurrent CeAD is often asymptomatic (even without local symptoms), with rates of new subsequent ischemic events ranging from 6.7 to 23.1%.[6,8–10,12]

A recent analysis of the STOP-CAD study focused on characteristics and outcomes of patients with versus without FMD found an increased risk of recurrent dissection in patients with FMD; however, other predictors of recurrent dissection, as well as the interaction between FMD and these predictors, remain unknown.[11]

In our study, we aimed to add further knowledge on the estimated risk, predictors, and clinical consequences of recurrent CeAD using data from a large, international, multicenter cohort of patients with spontaneous CeAD.

METHODS

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Standard Protocol Approvals, Registrations, and Patient Consents

This analysis was conducted in accordance with ethical guidelines of the original STOP-CAD study, which received institutional review board approval. As this is a secondary analysis of deidentified data, additional institutional review board approval was waived by the Lifespan Institutional Review Board.

Study Design and Patient Population

This study represents a preplanned secondary analysis of the STOP-CAD study. The STOP-CAD study was a multicenter international (16 countries, 63 sites) retrospective observational study of nonmajor trauma-related patients with CeAD. Methodological details from STOP-CeAD have been previously described.[13] For the purpose of this study, a follow-up period up to 2 years was considered. This study is reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[14]

Recurrent Dissection Definition

A dissection was defined as recurrent if it was diagnosed by neuroimaging at least 7 days after the index dissection and either involved a different artery or a noncontiguous region of the originally affected artery, meaning that the new dissection needs to be separated from all prior dissection–related changes by an intervening segment of normal-appearing vessel. Patients were only included after 7 days to reduce the risk of misclassifying patients with multivessel dissection as having recurrent events. Site principal investigators reviewed all recurrent CeAD according to predefined outcome definitions. Imaging reports were included in the database when available and reviewed by neurologists from the lead site to help confirm the occurrence of recurrent CeAD. In addition, before data set finalization, site principal investigators were asked to readjudicate outcomes and confirm that events were in keeping with study-specific definitions. For all patients, decisions regarding follow-up imaging, frequency, and time interval were made according to local standards and treating physician's decision.

Study Variables

Selected variables reported for the STOP-CAD study were used. Further details are present in the primary STOP-CAD publication.[13] For this substudy, we used the after covariates from the STOP-CAD-data set: (1) demographics: age, sex, race (White, Black, Asian, and other); (2) comorbidities: migraine, hypertension, diabetes, hyperlipidemia, active smoking, recent upper respiratory infection, recent nonmajor neck trauma, previous CeAD, cerebral aneurysms, aortic aneurysms, and connective tissue disorders; (3) clinical presentation: presence of focal neurological symptoms/signs (presentation as ischemic stroke versus nonischemic stroke presentation) and days from symptom onset to dissection diagnosis; (4) baseline imaging: location and number of dissected artery (carotid, vertebral, or multiple), intracranial extension, presence of occlusion at the dissection site, signs of FMD and presence of pseudoaneurysm. Antithrombotic treatment (none, single antiplatelet, dual antiplatelet, anticoagulation) at the time of recurrence was also reviewed.

Recurrent CeAD Clinical Impact

For the purpose of this study, every case of recurrent dissection was reassessed by the primary investigators of STOP-CAD. Recurrent dissections were classified as with or without subsequent ischemic events (ischemic stroke or transient ischemic attack).

Statistical Analysis

Descriptive statistics were summarized using median (interquartile range) for continuous variables and frequencies

(percentages) for categorical variables. Kaplan-Meier estimates were used to calculate cumulative risks of recurrent CeAD at 1, 3, 6, 12, and 24 months, beginning from 7 days after the initial CeAD diagnosis. Patients were censored at the time of recurrence, death, or last available follow-up, whichever came first.

Comparisons between groups (patients with versus without recurrent CeAD and early [7–30 days] versus late [>30 days] recurrence) were performed using χ^2 or Fisher exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. Multivariable logistic regression analyses were conducted to identify independent predictors of CeAD recurrence, including variables with a univariate significance level (*P* value) below 0.05 from the univariable analyses. Adjusted odds ratios (aOR) with 95% CIs were reported.

Cox proportional hazards regression analysis was used to validate independent predictors identified in the logistic model, with hazard ratios and 95% CI presented. Kaplan-Meier curves stratified by significant predictors (age dichotomized at 45 years, migraine, and FMD) were plotted to illustrate recurrence risk differences visually. Age was dichotomized at 45 years based on previous literature[5] and supported by the approximate median age in this study.

Sensitivity analyses restricted the cohort to patients who had undergone at least 1 follow-up imaging of cervical arteries to reassess risk estimates and predictors of recurrence. After the results of our main analysis, and to assess effect modification, we fit Cox proportional hazards models for time-to-recurrent dissection comparing patients with FMD versus no-FMD within strata of ischemic presentation, reporting subgroup-specific hazard ratios and testing interaction.

No imputation was performed. Statistical significance was set at $P<0.05$ (2-sided). All analyses were conducted using Stata software version 18 (StataCorp LLC, College Station, TX).

RESULTS

Of the 4023 patients included in STOP-CAD, 182 were excluded due to an isolated intracranial artery dissection, and 5 because they had no documentation of FMD status. 3836 patients met the inclusion criteria, with a median (interquartile range) age was 46 (37–56) years, and 45.3% (n=1720) were female. During a median follow-up of 295 (97–720) days, 88 (2.3%) patients had a CeAD recurrence, of whom 36 (40.9%) patients had an early recurrence (7–30 days), and 52 (60.1%) patients had a late recurrence (>30 days). The median time-to-recurrent CeAD was 53 (18–157) days. Seventy-five (85.3%) patients had a recurrent CeAD in a different artery from the index event, whereas 13 (14.7%) had a recurrence in a noncontiguous segment of the same vessel artery. Median time-to-first follow-up imaging was 69 (13–121) days, and the median number of follow-up imaging studies during follow-up was 1 (1–2).

The absolute estimated risk of recurrent CeAD was 1.04% (95% CI, 0.75%–1.44%) at 30 days, 2.66% (95% CI, 2.13%–3.31%) at 1 year, and 3.22% (95% CI, 2.59%–4.00%) at 2 years (Table 1).

Among patients with CeAD recurrence, 5 (5.7%) were not receiving any antithrombotic treatment, 46 (52.3%) were receiving 1 antiplatelet, 11 (12.5%) were receiving dual antiplatelets, and 26 (29.5%) were receiving anticoagulation (with or without concomitant antiplatelets).

Table 1. Estimated Risk of Recurrent Cervical Artery Dissection in the Entire Cohort

Time period	Estimated risk (95% CI)	No. of events
1 mo	1.04% (0.75%–1.44%)	36
3 mo	1.73% (1.34%–2.23%)	22
6 mo	2.14% (1.69%–2.70%)	11
12 mo	2.66% (2.13%–3.30%)	11
24 mo	3.22% (2.59%–4.00%)	8

Patients with recurrent CeAD were younger (median age, 42 versus 47; $P=0.014$), more frequently female (64.8% versus 44.4%; $P<0.001$), and had a higher prevalence of migraine (34.1% versus 16.4%; $P<0.001$), history of CeAD (8.0% versus 2.5%; $P=0.001$) and FMD (21.6% versus 8.0%, $P<0.001$), whereas they had less frequently an ischemic stroke at the time of the index CeAD (42.1% versus 65.2%; $P<0.001$) or an occlusive dissection (26.1% versus 37.0%; $P=0.037$; Table 2).

In multivariable analysis, younger age (<45 years; aOR, 0.98 [95% CI, 0.96–0.99]), migraine (aOR, 1.89 [95% CI, 1.15–3.07]), and FMD diagnosis (aOR, 2.90 [95% CI, 1.66–5.06]) were independently associated with CeAD recurrence. An ischemic stroke presentation was associated with a lower likelihood of CeAD recurrence (aOR, 0.47 [95% CI, 0.29–0.75]). Full multivariable logistic regression model is presented in Table S1.

In the Cox regression model, age below 45 years (hazard ratio, 1.75 [95% CI, 1.14–2.69]), migraine (hazard ratio 2.44 [95% CI, 1.57–3.79]) and signs of FMD (hazard ratio, 3.10 [95% CI, 1.86–5.15]) were independently associated with higher risk of recurrent CeAD (Figure).

To better understand the association between ischemic stroke presentation and a lower likelihood of CeAD recurrence, an interaction analysis testing the association between FMD and recurrent dissection based on ischemic versus Nonischemic presentation was performed (Table S2). *P* value for interaction was 0.06.

Among subjects with recurrent CeAD, 5 patients (5.6%) had an ischemic event at the time of CeAD recurrence, 3 (3.4%) had an ischemic stroke, and 2 (2.3%) had a transient ischemic attack. All of these events occurred on the same day of recurrent CeAD diagnosis, and all patients were on antithrombotic therapy.

Univariate comparisons between patients with early versus late recurrent CeAD showed that patients with early recurrence tended to be younger, and numerically were more frequently female, had a higher prevalence of preceding upper tract infection and of nonmajor cervical trauma, and more often presented acute ischemic stroke and with an intracranial extension of the cervical

Table 2. Baseline Characteristics Comparing No Recurrent CeAD With Recurrent CeAD

	No recurrent CeAD (n=3748)	Recurrent CeAD (n=88)	*P* value
Demographics			
Age, y	47 (38–56)	42 (36–49)	0.014
Female sex	1663 (44.4%)	57 (64.8%)	<0.001
Race			0.182
White	2764 (73.8%)	72 (81.8%)	
Black	228 (6.1%)	1 (1.1%)	
Asian	119 (3.2%)	3 (3.4%)	
Other	557 (14.0%)	12 (13.6%)	
Risk factors and medical history			
Migraine	616 (16.4%)	30 (34.1%)	<0.001
Hypertension	1316 (35.1%)	21 (23.9%)	0.029
diabetes	323 (8.7%)	1 (1.1%)	0.013
Hyperlipidemia	856 (22.8%)	13 (14.8%)	0.074
Active smoking	723 (19.3%)	12 (13.6%)	0.183
Recent respiratory infection	242 (6.5%)	5 (5.7%)	0.770
Recent nonmajor neck trauma	834 (22.3%)	26 (29.6%)	0.105
Previous cervical artery dissection	93 (2.5%)	7 (7.9%)	0.001
Cerebral aneurysms	30 (0.8%)	2 (2.3%)	0.133
Aortic aneurysms	20 (0.5%)	1 (1.1%)	0.449
Connective tissue disorder	78 (2.1%)	3 (3.4%)	0.392
Dissection presentation			
Presentation with an acute ischemic stroke	2444 (65.2%)	37 (42.1%)	<0.001
Days from symptom onset to dissection diagnosis	1 (0–6)	2 (1–7)	0.003
Dissection localization			0.910
Carotid	1937 (51.7%)	45 (51.1%)	
Vertebral	1397 (37.3%)	32 (36.4%)	
Multivessel	414 (11.0%)	11 (12.5%)	
Occlusive dissection	1372 (37.0%)	23 (26.1%)	0.037
Intracranial extension	331(8.9%)	9 (10.2%)	0.658
Signs of fibromuscular dysplasia	299 (8.0%)	19 (21.6%)	<0.001
Presence of pseudoaneurysm	505 (13.5%)	18 (20.5%)	0.059

CeAD indicates cervical artery dissection.

dissection. The proportion of patients with signs of FMD was numerically higher in the late recurrences (Table 3). The sensitivity analysis, after excluding patients without any follow-up imaging of cervical arteries, was conducted on a total of 2861 patients. A marginal increase in the absolute estimate risk of recurrent CeAD to 3.33% (95% CI, 2.68%–4.15%) at 2 years was noted (Table S3). In multivariable analysis, the results were similar to the primary analysis, with the exception of age and female sex (Tables S4 and S5).

DISCUSSION

In this large multicenter retrospective observational study of patients with CeAD, the estimated risk of recurrent CeAD over time was low, and approximately half of the events were diagnosed within the first 2 months of the index event. Moreover, younger age, migraine, presentation without an ischemic stroke, and signs of FMD were identified as potential predictors of recurrent CeAD. Few patients with recurrent CeAD had an associated stroke or transient ischemic attack.

Previous studies reported a highly variable proportion recurrence rate of CeAD (ranging from 0.87% to 25%), although most describe rates below 5%.[3,4] Difference in definitions, the inclusion of recurrent dissections in other arterial territories, and heterogeneous neuroimaging follow-up protocols likely explain this variability.[5–10] Studies showing higher proportions of recurrence rates included a lower number of patients, suggesting a potential selection bias.[5,6,8] To our knowledge, we present the largest cohort study assessing the risk of recurrent CeAD. In comparison with the 2 previous larger cohort studies (n=1283–1618), recurrence rates were similar (1.9%–3.3%).[9,10] Focusing on the estimated risk of recurrence over time, our results are consistent with those studied with longer follow-up time.[5,6]

In line with prior findings, we also found an early high-risk period of CeAD recurrence during the first few months.[5,6,8–10] Notably, one previous study suggested a 60-fold higher risk for new events within the first month compared with long-term follow-up.[6] This clustering may reflect a true temporal risk of recurrences as well as a more frequent follow-up imaging in the early phase after the index CeAD, increasing the detection rates of asymptomatic dissections.

As previously suggested, younger age, migraine, and FMD were associated with recurrent CeAD.[5,6,10,11] Aging is associated with the beginning of atherosclerosis, which can subsequently promote arterial wall stiffness and reduce the risk of CeAD.[15] Also, increasing age may also be associated with a decreased exposure to dissection triggers, especially minor trauma associated with lifting heavy weights or contact sports.[16] Migraine may be associated with an increased risk of extracellular matrix degradation and impaired endothelium-dependent vasodilatation, which may increase the risk for arterial dissection.[17] Moreover, genetic analyses suggested that migraine and CeAD share genetic factors related to vascular structure and function.[18,19] Together, these factors may predispose individuals with migraine to a higher risk of recurrent CeAD. FMD is a systemic nonatherosclerotic and noninflammatory disease of small to medium-sized arteries. It mainly affects renal and cervical arteries, and is a well-established risk factor for arterial dissection,[20] including recurrent CeAD.[10,11,21] In a recent STOP-CAD study focusing on the differences between patients

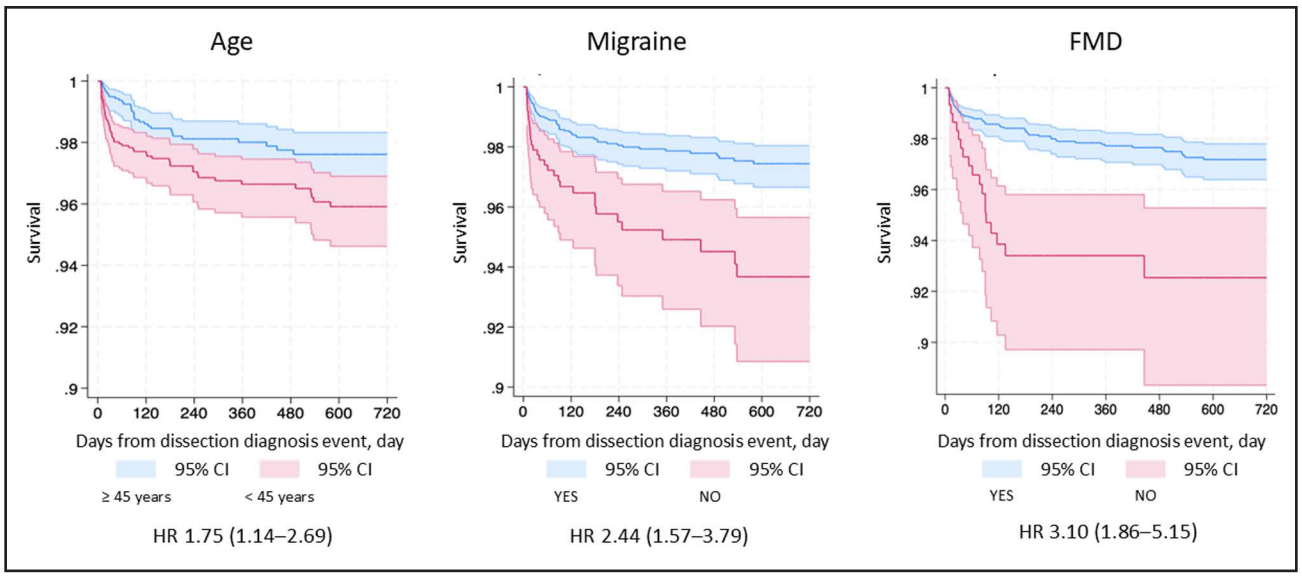

Figure. Cox regression survival curves for age, migraine, and fibromuscular dysplasia (FMD) and the risk of recurrent cervical artery dissection.
HR indicates hazard ratio.

with and without FMD, FMD was associated with recurrent CeAD, regardless of FMD definition, after excluding patients with previous CeAD, and after limiting the analysis to patients with at least one follow-up imaging.[11]

A novel finding of our study is the independent association between an initial CeAD accompanied by ischemic stroke and a reduced risk of CeAD recurrence. This hypothesis was previously suggested in univariate analysis.[9] We propose 2 potential explanations for this observation. First, FMD and connective tissue disorders—both recognized risk factors for recurrent CeAD—seem to be less frequently associated with CeAD cases that present with ischemic stroke.[10,11,21] Our interaction analysis found no significant association between FMD and recurrent dissection by ischemic versus nonischemic presentation, which may in part be due to a limited sample size. Nevertheless, these results do not support the proposed hypothesis, and alternative explanations should be considered. Second, maybe patients who experience an ischemic stroke in the context of CeAD, compared with those without stroke, may subsequently avoid dissection triggers to a greater extent.

Our results additionally suggest that a recurrent CeAD seems to be a relatively benign entity, with only a minority of patients experiencing subsequent ischemic events.[4,6,8–11] Nevertheless, an additional proportion of patients can have headache, cervical pain, or other local symptoms, ranging from 25% to 80% of cases.[6,8–11] Future prospective studies with standardized follow-up imaging protocols are required to provide accurate estimates of symptomatic recurrence rates.

Although previous studies lack clear comparisons between patients with early and late recurrent CeAD, some authors have proposed distinct underlying mechanisms. Early recurrences may share a pathophysiology similar to that of polyarterial dissections, where a temporary active process—such as an acute infection—might trigger a transient vasculopathy. In contrast, late recurrences are more likely attributable to a predominantly genetic predisposition.[6,9] Although inconclusive due to the small sample size, our exploratory comparison of patients with early versus late recurrences may support the hypothesis that different pathophysiological mechanisms underlie early versus later recurrence. Although not statistically different, it is interesting to note that recent upper respiratory tract infection and nonmajor cervical trauma were more frequently observed in patients with the early recurrence group, whereas those with late recurrence more frequently had signs of FMD.

This study has several limitations. Although this was a preplanned subanalysis, the STOP-CAD study was not specifically designed to estimate the risk, associated factors, and clinical impact of recurrent CeAD. This was a retrospective study, so there was no predefined protocol for recurrent CeAD detection or reassessment of cervical arteries. As such, and because most recurrent CeAD were asymptomatic, the absence of a systematic follow-up imaging protocol most likely contributed to an underestimation of asymptomatic recurrences. Our study provides data on a 2-year risk of recurrence after CeAD and cannot be generalized to longer follow-up periods. Because a large proportion of CeAD recurrences were not associated with new ischemic events, we cannot exclude that patients' characteristics found to be associated with recurrence actually contributed to ascertainment bias. FMD, one of the relevant predictors of recurrent CeAD, may have been underdiagnosed because only a minor proportion (12.6%) of patients

Table 3. Baseline Characteristics Comparison Between Patients With Early Versus Late Recurrent CeAD

	Early recurrent CeAD (n=36)	Late recurrent CeAD (n=52)	*P* value
Demographics			
Age, y	41 (37.0–45.5)	43 (35.0–53.5)	0.157
Female	26 (72.2%)	31 (59.6%)	0.224
Race			0.096
White	26 (72.2%)	46 (88.5%)	
Black	0 (0.0%)	1 (1.9%)	
Asian	2 (5.6%)	1 (1.9%)	
Other	8 (22.2%)	4 (7.7%)	
Risk factors and medical history			
Migraine	13 (36.1%)	17 (32.7%)	0.739
Hypertension	7 (19.4%)	14 (26.9%)	0.418
diabetes	0 (0.0%)	1 (1.9%)	0.403
Hyperlipidemia	4 (11.1%)	9 (17.3%)	0.547
Active smoking	5 (13.9%)	7 (13.5%)	1.000
Recent respiratory infection	3 (8.3%)	2 (3.9%)	0.396
Recent nonmajor neck trauma	13 (36.1%)	13 (25.0%)	0.261
Previous cervical artery dissection	3 (8.3%)	4 (7.7%)	1.000
Cerebral aneurysms	1 (2.8%)	1 (1.9%)	1.000
Aortic aneurysms	0 (0.0%)	1 (1.9%)	1.000
Connective tissue disorder	2 (5.6%)	1 (1.9%)	0.565
Dissection presentation			
Presentation with an acute ischemic stroke	18 (50.0%)	19 (36.5%)	0.208
Days from symptom onset to dissection diagnosis	3.5 (1.0–7.5)	1.0 (0.0–6.0)	0.409
Dissection localization			0.946
Carotid	18 (50.0%)	27 (51.9%)	
Vertebral	13 (36.1%)	19 (36.5%)	
Multivessel	5 (13.9%)	6 (11.5%)	
Occlusive dissection	10 (27.8%)	13 (25.0%)	0.771
Intracranial extension	6 (16.7%)	3 (5.8%)	0.151
Signs of fibromuscular dysplasia	6 (16.7%)	13 (25.0%)	0.434
Presence of pseudoaneurysm	10 (27.8%)	8 (15.4%)	0.185

CeAD indicates cervical artery dissection.

were screened for renal FMD or due to the presence of less severe or atypical subtypes.[22] Also, a detection bias cannot be excluded, as local investigators may have been more inclined to diagnose cervical FMD or screen for renal FMD after recurrent CeAD. Migraine diagnosis was based on self-report or extracted from medical records, without distinction between migraine with or without aura. Potential predictors of recurrent CeAD, such as family history of stroke/CeAD and genetic factors, were not assessed, limiting our results. Data regarding the presence of new, nonischemic symptoms are missing, therefore, limiting our evaluation of true, symptomatic, recurrent CeAD. Patients from nonwhite racial and ethnic groups and older individuals are underrepresented in our study, limiting generalizability. However, no biological differences in CeAD risk factors or pathophysiology have been established across racial groups, and a younger median age is expected in CeAD cohorts. Finally, the exploratory comparisons made between early and late patients with recurrent CeAD are limited due to low numbers and a lack of multivariable analyses.

Future prospective studies with standardized imaging protocols, centralized adjudication, systematic comorbidity assessment, and genetic testing are needed to validate and strengthen our findings.

CONCLUSIONS

In our retrospective study, the estimated risk of recurrent CeAD over a 2-year period was low, with a high-risk period during the first few months. Younger age, migraine, absence of ischemic stroke at presentation, and signs of FMD may help identify high-risk patients.

Nevertheless, patients can be reassured that, besides being rare, recurrent CeAD rarely results in a subsequent new ischemic event.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S5
STROBE Checklist

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