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Delayed Development of Aneurysmal Dilatations in Patients with Extracranial Carotid Artery Dissections

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WHAT THIS PAPER ADDS

This multicentre analysis identifies the unexplored time of onset of extracranial carotid artery aneurysms (ECAA) in patients with carotid artery dissection. The results show the delayed onset of ECAA several months after baseline in a quarter of all patients diagnosed with an ECAA with available follow up imaging. Multiple dissections and arterial tortuosity were associated with the presence of post-dissection ECAA at any time point. These novel indicators can be used in future evaluation algorithms and prediction models of ECAA development in patients with carotid dissection.

Objective: Dissection of the carotid artery (CaAD) may result in aneurysm formation. The present study was undertaken to evaluate the time of onset of post-dissection extracranial carotid artery aneurysms (ECAA) following CaAD, and to analyse independent risk factors for the development of these aneurysms.

Methods: From four European stroke centres, 360 patients with extracranial CaAD were included. The time between the estimated dissection onset and aneurysm formation was analysed, and the clinical risk factors increasing the probability of aneurysm were assessed.

Results: The median duration of follow up was 5.2 months (range 0 — 24 months). A total of 75 post-dissection ECAAs were identified in 70 patients (19.4%, 95% confidence interval [CI] 15.7 — 23.8). In 52 of 70 (74%) patients, the ECAA was diagnosed at the initial clinical work up of CaAD diagnosis, with the median estimated time of dissection onset to ECAA diagnosis being six days (interquartile range [IQR] 0 — 25). In the remaining 18 (26%) patients who had normal carotid arteries at the initial imaging, the aneurysm diagnosis was made a median of 6.2 months (189 days) from the original imaging (IQR 128 — 198). A Cox proportional hazards model showed that both multiple artery dissections (hazard ratio [HR] 2.58, 95% CI 1.54 — 4.33) and arterial tortuosity (HR 1.79, 95% CI 1.08 — 2.95) were associated with presence of ipsilateral ECAA.

Conclusion: This *post hoc* cohort analysis showed substantially delayed development of ipsilateral ECAA in patients with CaAD, months after baseline. Multiple dissections and arterial tortuosity are associated with the presence of ECAA and can be used in future prediction models of ECAA development in patients with CaAD.

Keywords: Carotid artery dissection, Extracranial carotid artery aneurysm, Post-dissection aneurysm
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INTRODUCTION

Dissection of the cervical arteries (CeAD) is an important cause of stroke in young adults.[1—3] It has been estimated that 13% — 49% of patients with CeAD will develop an ipsilateral post-dissection aneurysm over time,[4—7] predominantly in the case of a carotid artery dissection (CaAD).[2] Previous multicentre data have shown an

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increased number of extracranial carotid artery aneurysms (ECAAs) at repeat follow up imaging three months after baseline, indicating that the time of onset of ECAA varies among patients with CaAD.[5] Although the clinical course of post-dissection ECAAs is considered to be benign,[4,6,7] long term follow up imaging data in patients with CaAD are still limited. While asymptomatic ECAA are generally treated conservatively, surgical or endovascular ECAA exclusion may be considered in growing or symptomatic ECAA.[8] Better understanding of the natural history of CaAD and thus ECAA pathophysiology and associated clinical risk factors is needed for the identification of patients at risk of adverse cerebral outcomes. As separate studies for post-dissection ECAA after CaAD are sparse, the present multicentre study was undertaken.

The objective of the present analysis was to evaluate time of onset of post-dissection ECAA, and to identify independent risk factors associated with presence of these aneurysms.

METHODS

Participants

The article was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[9] Eligible patients were selected from four European stroke centres (Supplementary Table 1). These study centres were members of the Cervical Artery Dissection and Ischaemic Stroke Patients (CADISP) consortium and the standard data collection has been published before.[2] Owing to varying local ethics legislation, four of 20 centres were able to participate in the present study. Briefly, consecutive patients aged 18 years or older admitted to the neurology department with suspect CeAD (both carotid and/or vertebral) were included between 1987 and 2019 and registered both prospectively and retrospectively following a standardised protocol. Retrospective patients had the qualifying event before the beginning of the study in each centre and were identified through local registries of patients with CeAD. The diagnosis of CeAD was defined as the presence of a typical radiological finding (intramural haematoma, aneurysmal dilatation, long tapering stenosis, intima flap, double lumen, or occlusion $>$ 2 cm above the carotid bifurcation revealing a dilatation or a long tapering stenosis after recanalisation) within the vascular wall of the internal carotid or vertebral artery.[10] Iatrogenic and purely intracranial artery dissections were excluded. For the present *post hoc* cohort study, only patients with a spontaneous CaAD were included. Exclusion criteria were a traumatic[11] and or purely vertebral artery dissection. All study procedures were approved by ethics committees at each participating hospital according to local legislation.

Clinical data

Patient demographics and the following putative risk factors were recorded: hypertension (previously known, any antihypertensive treatment, or blood pressure $\geq$ 140/90 mmHg on repeated measurement); diabetes mellitus (fasting glucose $>$ 7 mmol/L or antidiabetic medication); any statin treatment; smoking (current, within three months, or former smoker); and migraine (classified according to International Headache Society criteria).[12] In addition, any reported trauma in the patient interview within three months prior to symptom onset and known connective tissue disease were recorded. Presenting symptom (Horner's syndrome or cerebral ischaemia) and estimated time of CaAD symptom onset were recorded. Lastly, endovascular thrombosuction as treatment for ischaemic stroke following CaAD was recorded.

Imaging data

All available carotid imaging and reports were reviewed up to two years after the diagnosis of dissection. Follow up imaging more than two years after baseline was considered to be for an indication other than the CaAD. The indication for imaging was not available and therefore not included in the analysis. Imaging follow up was carried out every three to six months in the first year after diagnosis, and thereafter, depending on the individual case, monitored every six or 12 months. The following imaging characteristics were retrieved from the radiology charts reported by experienced local (neuro)radiologists: time and type of imaging; arterial stenosis or occlusion; cerebral infarct on magnetic resonance imaging; cervical arterial tortuosity in terms of coiling or kinking;[13] additional intracranial or multiple cervical artery dissections; and the presence of aneurysmal dilatation. Tortuosity of the carotid arteries was defined as any degree of abnormality in the dynamics of the vessel in relation to their normal morphology, which was underlying the structural injury of the carotid vessel.[13] The imaging modalities used varied from computed tomography angiography (CTA; 64 slice), magnetic resonance angiography (MRA; 1.5 and 3.0 T), digital subtraction angiography, and duplex ultrasonography of the carotid arteries, or a combination. An aneurysmal dilatation or post-dissection ECAA was defined as $\geq$ 150% fusiform dilatation of the carotid artery *vs.* the non-affected contralateral side, or saccular aneurysms of any size.[14,15]

Outcome and statistical analysis

The primary endpoint measure was the time between the estimated dissection and aneurysm formation (diagnosis) of post-dissection ECAAs in the CaAD cohort. In addition, independent risk factors associated with post-dissection ECAA were analysed. Time of diagnosis of the post-dissection ECAA was assessed by calculating the time between the reported onset of CaAD and the first radiology report in which the post-dissection aneurysm was described. The baseline characteristics of patients with or without post-dissection ECAAs were compared with the chi square test and an independent *t* test. The probability of diagnosis of a post-dissection ECAA following CaAD was estimated using the Kaplan—Meier method; time to event curves were compared using the log rank test. Cox proportional hazard

regression analysis was used to identify predictors for the development of a post-dissection ECAA and scaled Schoenfeld residuals were used to confirm the assumption of proportionality. Next to the observed differences in baseline characteristics, sex and age were included in the model. A p value $< .050$ was considered to be statistically significant throughout. Ties were corrected with use of the exact method. All statistical analyses were conducted using SPSS version 25.0 (IBM, Armonk, NY, USA) and Rstudio version 3.4.1 (RStudio Team, Boston, MA, USA).

RESULTS

Four hundred and sixteen patients with CeAD were analysed from four stroke centres. After the exclusion of patients with a purely traumatic dissection ($n = 30$) and those without any available imaging information ($n = 26$), 360 patients with CaAD remained (Fig. 1; Supplementary Table 1). Approximately 59.4% ($n = 214$) of patients were men and mean ± standard deviation (SD) age was 45.2 ± 9.8 years. The patients' baseline characteristics are summarised in Table 1 and Supplementary Table 2. The median duration of follow up was 6.1 months (interquartile range [IQR] 2.9 — 10.2) with a median of two follow up scans (IQR 2 — 3; Supplementary Table 3).

Time of onset of post-dissection extracranial carotid artery aneurysms

Seventy-five post-dissection ECAAs were diagnosed in 70 patients (19.4%; 95% confidence interval [CI] 15.7 — 23.8) of whom five had a bilateral ECAA. The majority ($n = 61/78$; 78%) of post-dissection aneurysms were located in the distal internal carotid artery (zone 3),[16] and were saccular ($n = 51/78$; 65%). In 52/70 (74%) patients, the ECAA was diagnosed at the initial CaAD diagnosis work up. The time between estimated CaAD symptom onset and first imaging scan was a median of six days (IQR 0 — 25). In the remaining 18 patients (26%) with multiple imaging on detection of an ECAA, the time to diagnosis was a median of 6.2 months (189 days; IQR 128 — 198 [see Fig. 2]).

Putative features for post-dissection extracranial carotid artery aneurysms

In patients with CaAD with multiple cervical artery dissections and tortuosity of the carotid arteries (Table 1), the presence of a post-dissection ECAA was more frequent. Patients with CaAD who were current smokers and who had an additional intracranial artery dissection less frequently developed a post-dissection ECAA . The probability of diagnosis of a post-dissection ECAA at the one year follow up after CaAD in patients with and without multiple artery dissections was 41% (95% CI 25.4 — 67.3) *vs.* 79.1% (95% CI 72.5 — 86.4; log rank test $p < .001$ [Fig. 3]). Stratification according to age ≥ 55 years or sex (Supplementary Fig. 1) did not result in a statistically significant difference. After adjustment, the presence of an additional intracranial artery dissection (hazard ratio [HR] 0.31, 95% CI 0.13 — 0.73) and composite smoking history (HR 0.40, 95% CI 0.22 — 0.74) were negatively associated with presence of a post-dissection ECAA (Table 2). The presence of multiple cervical artery dissections was strongly associated with post-dissection ECAAs (HR 2.58, 95% CI 1.54 — 4.33), as was tortuosity of the cervical arteries (HR 1.79, 95% CI 1.08 — 2.95).

DISCUSSION

The present multicentre study of patients with CaAD showed that, overall, approximately one in five patients with CaAD developed an ipsilateral ECAA. One quarter of these post-dissection ECAAs was detected after the initial clinical work up. In this subset of patients ($n = 18/70$), the time to aneurysm diagnosis was a median of six months after the onset of dissection symptoms, although the estimated time of ECAA diagnosis was highly subjective to the follow up scheme applied, as illustrated in Figure 2. Cox proportional hazard regression showed that multiple artery dissections and arterial tortuosity were associated with the presence of a post-dissection ECAA at any time point. In contrast, an additional intracranial artery dissection and composite smoking history (former and current combined) seemed preventive for the development of an ECAA.

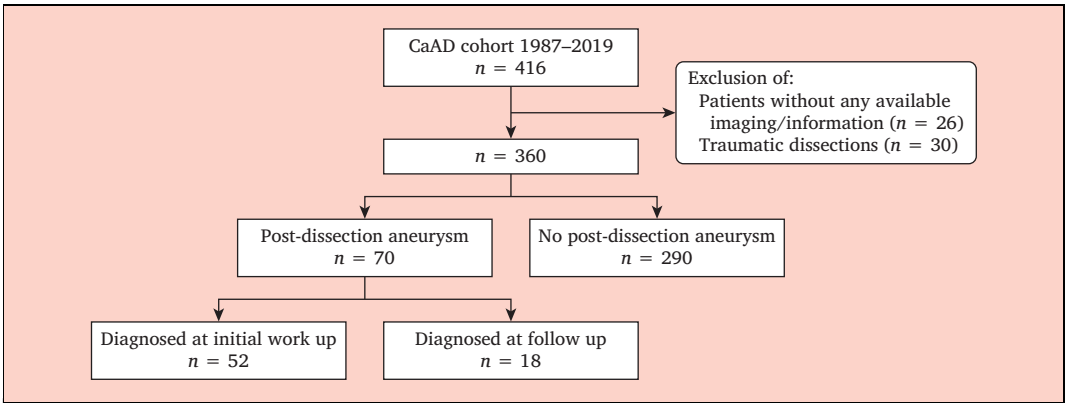

Figure 1. Flow chart of included patients with carotid artery dissection (CaAD) from four European stroke centres to study development of post-dissection extracranial carotid artery aneurysms.

Table 1. Baseline characteristics of 360 included patients with carotid artery dissection (CaAD)

Characteristics	CaAD without aneurysm (n = 290)	Post-dissection ECAA aneurysm (n = 70)	p value
Female sex	120 (41.4)	26 (37)	.61
Age on admission − y	45.0 ± 9.6	46.0 ± 10.7	.47
Hypertension	100 (34.5)	27 (39)	.64
Diabetes mellitus	3 (1.0)	0 (0)	.90
Migraine	80 (27.6)	23 (33)	.57
Connective tissue disease	3 (1.0)	0 (0)	.91
Any reported trauma in previous 3 mo before symptom onset	58 (20.0)	11 (16)	.46
Statin use	21 (7.2)	4 (6)	.86
Smoking history	122 (45.9)	15 (23)	.001
Current	88 (33.1)	11 (17)	.014
Former	34 (12.8)	4 (6)	.19
Multiple cervical artery dissections	39 (13.4)	27 (39)	<.001
Bilateral carotid	16 (5.5)	19 (27)	
Both carotid and vertebral	23 (7.9)	8 (11)	
Additional intracranial artery dissection	80 (27.6)	6 (9)	.001
Arterial tortuosity	79 (27.4)	34 (49)	.001
Coiling	62 (21.5)	24 (34)	.037
Kinking	70 (24.3)	33 (47)	<.001
Horner's syndrome	98 (34.0)	30 (43)	.21
Cerebral ischaemia	47 (16.9)	6 (9)	.14
Endovascular thrombosuction following CaAD	18 (6.6)	2 (3)	.43

Data are presented as n (%) or mean ± standard deviation. ECAA = extracranial carotid artery aneurysm, y = years, mo - months.

Several studies have discussed the characteristics and clinical outcomes of post-dissection aneurysms following CeAD.[4–7] Multicentre data indicated that time of onset could vary among patients with post-dissection aneurysms.[4] The results of the present study, in CaAD patients alone, also showed that the identification of a post-dissection ECAA is highly dependent on the follow up interval applied. Although accurate estimation is not possible owing to data heterogeneity, presumably one quarter of post-dissection ECAAs developed at a later stage and would have been missed without follow up imaging of the carotid arteries. Prolonged dynamic wall changes were also observed in a prospective MRA study of 10 patients with CaAD[17] in which the mural haematoma in all participants had resolved six months after symptom onset. Overall, this indicates that CaAD is a dynamic process with both stenotic and aneurysmal arterial wall changes in the days and months after dissection and may require follow up cerebrovascular imaging to detect potential subclinical ischaemic events. Defining an exact estimate of the time of onset of post-dissection ECAA was not feasible owing to both patient and centre burden of many imaging intervals in a short period of time. Future studies with standardised follow up intervals including imaging of the cerebrovascular tree in any participant are warranted, in order to define a more accurate time frame in which the post-dissection aneurysm will develop. The results show that these dynamic wall changes occur in the first six months after dissection, and in a few cases even after six months (Fig. 2). In future larger studies subgroup analyses could be performed in patients with short and late onset post-dissection aneurysms, but, owing to the small sample size in the present study and varying durations of follow up, this analysis was not feasible. Once developing time intervals of post-dissection ECAAs are identified, well considered follow up and treatment algorithms can be established. Taken together, baseline imaging

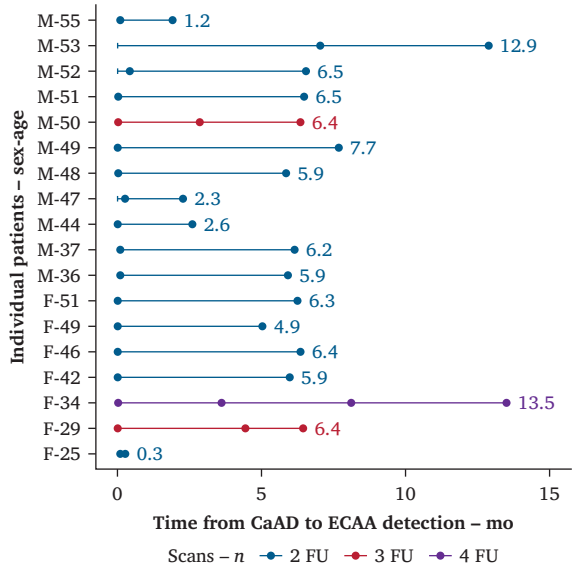

Figure 2. Reported time of late detection of the extracranial carotid artery aneurysm (ECAA) after initial follow up (FU) of 18 patients with carotid artery dissection (CaAD) in four European stroke centres. Dots represent imaging follow up interval; final dot and value represents time of ECAA diagnosis in months (mo). M = male; F = female.

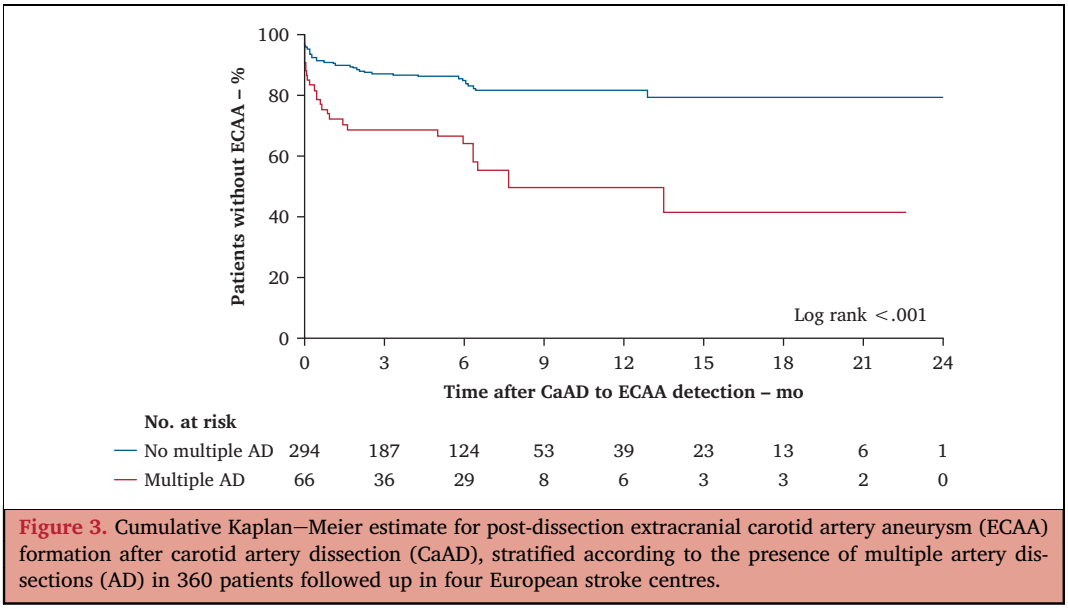

Figure 3. Cumulative Kaplan–Meier estimate for post-dissection extracranial carotid artery aneurysm (ECAA) formation after carotid artery dissection (CaAD), stratified according to the presence of multiple artery dissections (AD) in 360 patients followed up in four European stroke centres.

Table 2. Cox proportional hazard regression analysis for post-dissection aneurysms in 66 of 331 patients with carotid artery dissection

Characteristics	HR (95% CI)	*p* value
Female sex	0.69 (0.41–1.16)	.16
Age ≥ 55 years	1.16 (0.60–2.26)	.65
Composite smoking history	0.40 (0.22–0.74)	.003
Multiple cervical artery dissection	2.58 (1.54–4.33)	<.001
Additional intracranial artery dissection	0.31 (0.13–0.73)	.007
Arterial tortuosity	1.79 (1.08–2.95)	.023

Data are presented as hazard ratio (HR) with 95% confidence interval (CI). Ties in survival data were corrected with the exact method.

and at least one follow up at 3– 6 months is advised. If carotid and cerebral alterations are detected with respect to previous imaging, follow up should be considered until a stable cerebrovascular tree has been imaged.

The clinical prognosis and outcome of post-dissection ECAA has been studied previously,[4–7,18] and was beyond the scope of the current study. Despite the distinct characteristics per artery type, both carotid and vertebral[4,6,7,18] or intracranial[5] post-dissection aneurysms were conjointly analysed in these studies without an indication of the time to diagnosis of the post-dissection aneurysm. Although the maximum duration of follow up differed among the included patients (range 3.5 – 109 months), it was estimated that ± 50% of developed aneurysms were relatively stable during follow up and that the other half decreased in size or gradually resolved.[4–7] A histopathological study conducted in symptomatic patients with ECAAs showed that the presumed aetiology was, in some cases, CaAD, despite a lack of radiological dissection signs such as intima flap at the time of symptom presentation.[19] The authors of that study pointed out that time dependent vascular remodelling could have affected the exact number of these CaAD derived cases of ECAA. This study also indicated that even though most post-dissection ECAA seem to have a benign course, some may cause symptoms during long term follow up. As local follow up imaging schemes vary, or patients with mild CaAD symptoms refrain from further follow up visits, it is imaginable that additional ECAAs are missed and diagnosed several years later. Putative features associated with ECAA growth and symptoms at any time point remain to be identified. It is remarkable that only three patients were diagnosed with a connective tissue disease, and none developed an ECAA. Available follow up of these patients varied from nine days to six and 19 months. Perhaps the length of follow up, as well as the lack of genetic testing in regular clinical practice, may explain the observed difference. The finding that multiple artery dissections[6,18,20] and arterial tortuosity[6] are associated with post-dissection ECAAs is in line with previous research. It seems reasonable that, in the case of multiple artery dissections, the vessel wall is locally weakened at different vascular sites and thus more prone to aneurysm formation. Multiple artery dissections tend to cluster on the same artery type, as was also seen in the present cohort,[2] rather than involving both carotid and vertebral arteries (Table 1). In a previous large CADISP analysis (n = 1 958), multiple artery dissections were associated with an increased risk of a cerebral ischaemic event at three to six months, and were suggested to be indicative of a transient vasculopathy.[21] As 39% of all post-dissection ECAA had multiple artery dissections (Table 1), these patients may also harbour an increased risk of cerebral ischaemic events, especially in the first six months after CaAD. The long term cerebral outcome of relatively young patients with ECAA should be investigated in future longitudinal research. Additionally, arterial tortuosity has been described to be associated with CeAD,[22–25] and could reflect a separate vascular subtype

that may be prone to exaggerated vascular remodelling. Moreover, arterial tortuosity reflects the weakness of the tunica media, allowing the intramural haematoma to spread towards the adventitial layer, which may facilitate aneurysm development.[3] At this point, the preventive role of an additional intracranial dissection remains unknown. A recent study suggested carotid siphon tortuosity as an independent marker for the development of spontaneous cervicocerebral artery dissection in patients with both intracranial and extracranial carotid and vertebral artery dissections.[25] It would be of interest to add this parameter to future studies and investigate its potential role in additional intracranial artery dissections. Smoking history, both current and former, has been related to the rupture of intracranial and abdominal aortic aneurysms.[26,27] In contrast, few cases of ECAA rupture have been reported in the literature.[28,29] Smoking, therefore, seems to have a limited role in the development of a post-dissection ECAA.

Some limitations need to be addressed while interpreting the results of the present study. This observational study was subject to locally applied follow up practices. As a consequence, accurate determination of the onset of dissection is unclear and imaging follow up was not done as frequently as would have been needed to estimate the time of onset more accurately. In addition, potential cases of ECAA may not have been identified as the included patients may have had a relatively short follow up period. However, the present study is the largest to date to analyse post-dissection ECAAs following CaAD.[4] Future standardised follow up imaging studies at fixed time intervals to assess both vessel wall and brain outcome imaging are warranted. Also, the indication for imaging was not systematically registered and was therefore unknown. This was anticipated and only patients with imaging up to two years after the onset of dissection were included; however, an indication bias cannot be completely ruled out. In addition, reliable quantitative measures and user friendly CTA or MRA software are available to assess arterial tortuosity.[30] A quantitative tortuosity value incorporating future prediction models could minimise observer bias. Additionally, purely traumatic CaAD is seen as a different entity and was excluded. As the magnitude of a mechanical trigger and CaAD is unknown, and may be patient specific, obtaining a clearly defined patient group is challenging. Therefore, it was decided that patients with any reported trauma three months prior to symptom onset were included, which may have introduced additional bias in patient selection. Lastly, but importantly, the clinical relevance of these extracranial post-dissection aneurysms needs to be fully established.[28] The identification of patients with post-dissection ECAA and a high and low risk of adverse cerebral outcome was beyond the scope of the present study, but will be addressed by future analyses within the ongoing international registry (www.carotidaneurysmregistry.com).[31]

Conclusions

One in every five patients with CaAD developed an ipsilateral ECAA. In a quarter of these patients with an ECAA, the post-dissection aneurysm developed months after baseline. Multiple artery dissections and arterial tortuosity were identified as putative factors in the development of a post-dissection ECAA. These novel indicators can be used in future prediction models of ECAA development in patients with CaAD.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2022.08.010.

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