

Cervical Artery Dissections with and without stroke, risk factors and prognosis: a Chilean prospective cohort

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We aimed to characterize spontaneous cervical artery dissection (CeAD) patients with and without stroke and describe risk factors for cerebrovascular complications in a Chilean prospective cohort.

Methods: Consecutive CeAD patients admitted to a Chilean center confirmed by neuroimaging. Logistic regression was used.

Results: 168 patients were included, median follow-up time was 157 days. Stroke occurred in 49 (29.2%) cases, 4 (2%) patients died, all of whom had a stroke, and 10 (6%) presented CeAD recurrence. In univariate analyses, men (odds ratio [OR] 3.97, 95% confidence interval [CI] 1.97–8.00, $P < 0.001$), internal carotid artery CeAD (OR 2.82, 95% CI 1.38–5.78, $P = 0.005$) and vessel occlusion (OR 4.45, 95% CI 1.38–14.38, $P = 0.035$) increased stroke risk. Conversely, vertebral artery dissection (OR 0.35, 95% CI 0.16–0.74, $P = 0.006$) and longer symptom onset to admission (O–A) time (OR 0.79, 95% CI 0.70–0.90, $P < 0.001$) were associated to decreased stroke risk. After multivariate analysis, men (OR 2.88, 95% CI 1.32–6.27, $P = 0.008$) and O–A time (OR 0.80, 95% CI 0.69–0.92, $P = 0.002$) remained independently associated with stroke.

Conclusion: CeAD presented commonly as a non-stroke entity, with favorable prognosis. Albeit to a higher frequency of CeAD in women, stroke occurred predominantly in men, who were admitted earlier.

Keywords: Carotid artery dissection—Vertebral artery dissection—Cervical artery dissection—Stroke—Risk factors—Cohort

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Introduction

Spontaneous cervical artery dissection (CeAD) is a frequent cause of cerebrovascular disease in young adults.^{1,2} Clinical manifestations vary from local minor symptoms to stroke leading to disability or death.³ Published series

describe predominantly CeAD patients presenting with stroke, whereas patients with minor symptoms have been usually underrepresented.^{4–6} In addition, most literature regarding CeAD comes from North-American and European populations, with only few available data including

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Latin American patients.^{5,7} Hence, we aimed to characterize a cohort of Chilean CeAD patients and determine risk factors for stroke in a single center prospective cohort.

Methods

Study Population

All consecutive adult patients diagnosed with CeAD from two time periods - June 2011 to September 2015 and May 2016 to July 2018 - admitted to Clínica Alemana de Santiago, a teaching non-for-profit private hospital in Chile, were prospectively included. Patients presenting exclusively with intracranial dissections were excluded.

CeAD was either suspected by the emergency department neurologist because of local symptoms and signs (such as unusual headache or neck pain, Horner's syndrome or cranial nerve palsy) or in young patients with stroke. Subsequently, CeAD was confirmed by cervicocranial Computed Tomography Angiography (CTA); Magnetic Resonance Angiography (MRA) or Digital Subtraction Angiography (DSA) were performed only if deemed necessary by the neurology team. Standard imaging criteria were followed:

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.⁵ Additionally, two neuroradiologists (CDLB, PZ) independently adjudicated 22 cases on which the radiological diagnosis was in doubt. Multiple CeAD was defined as the simultaneous presence of >1 CeAD at the initial diagnosis. Recurrent dissection was defined as a new, radiologically confirmed diagnosis of CeAD at follow-up after the first CeAD symptoms (the delay between symptom onset and follow-up was variable given the observational setting).⁵ Stroke was defined as a sudden neurological deficit presumed to be caused by ischemia or hemorrhage, lasting for at least 24 h. Stroke etiology was attributed to the CeAD only after a comprehensive assessment including electrocardiogram monitoring and echocardiography. In most patients, a Transcranial Doppler with Microembolic Signals monitoring was performed. Patients were followed after discharge during outpatient visits, and in case of not attending to these appointments, were contacted by telephone. The Ethics Committee approved the study protocol and informed consent was obtained from participants.

Statistical Analysis

Logistic regression was used to compare CeAD patients with simultaneous or posterior diagnosis of stroke, classified as CeAD-S, and CeAD patients without stroke (CeAD-nonS). Multivariable analyses were adjusted for all putative risk factors with $p < 0.25$ in univariable

analyses following Hosmer-Lemeshow criteria. The data were processed with STATA version 14.0.

Results

Demographic and clinical characteristics

During the study period, 168 patients with CeAD were included. Median follow-up time was 157 days (interquartile range [IQR] 173). Four patients died and 14 were lost to follow-up (8.3%). Mean age was 41 (SD 9.2) years, 67 (39.9%) were men and 130 (77.4%) had cervical vertebral artery involvement (table 1). Most patients were diagnosed during cold seasons: autumn and winter (101, 60.1%). There were 6 patients with fibromuscular dysplasia, mostly diagnosed during acute workup, all of them presenting without stroke. One patient had previous diagnosis of Ehlers-Danlos disease, two with previous diagnosis of other connective tissue disease and one patient with family history of CeAD. Only one patient had a previous CeAD. Clinical presentation included headache (72.0%), neck pain (61.3%), vertigo/dizziness (19.0%) and Horner syndrome (8.9%). During the acute phase, all patients were prescribed antiplatelets (aspirin 87.2%, clopidogrel 6.7% and dual antiplatelets (aspirin+clopidogrel) 7.1%) except for 1 who was treated with anticoagulants (unfractionated heparin). Five patients with internal carotid cervical dissection were treated with angioplasty and stenting.

Patient prognosis

Regarding prognosis, 49/154 (31.8%) patients had a stroke at the time of presentation or during follow-up. Four patients died in the CeAD-S group and none in the CeAD-nonS group – in all cases stroke was the primary cause of death - with a median time from CeAD admission to death of 1.5 (IQR 4) days. Most strokes were ischemic (45/49, 91.8%). CeAD-S patients presented with a mean NIH stroke scale (NIHSS) score of 7 points (SD 9) during the acute phase. Among these CeAD-S patients, 78% had an excellent functional prognosis at follow up (modified Rankin score (mRS) 0 or 1).(figure 1) CeAD recurrence occurred in 10/154 (6.5%) patients, with a median time from first admission to recurrence of 63 (IQR 625) days. Recurrence occurred mostly in CeAD-S patients (8.1%) compared to 2.3% in CeAD-nonS group. Of note, other neurological events were also seen during follow-up: intracranial hypertension syndrome (2), subarachnoid hemorrhage (1) and reversible cerebral vasoconstriction syndrome (1).

In univariable analyses, male gender, carotid artery involvement and vessel occlusion in neuroimaging were associated to higher stroke risk, whereas vertebral artery compromise and longer symptoms onset to admission time related to reduced stroke risk (table 1). After multivariable analysis, only male gender (OR 2.88, 95% CI 1.32–6.27, $P = 0.008$) and time from symptom onset to

Table 1. Association between presumable risk factors and stroke in CeAD patients

Variable	Total N = 168	CeAD with stroke N = 49	CeAD without stroke N = 119	OR (95% CI)	P-value
Patient characteristics					
Age, mean (SD)	41 (9.2)	41 (9.1)	41 (9.3)	1.02 (0.99–1.05)	0.266
Male, n (%)	67 (39.9)	31 (63.3)	36 (30.3)	3.97 (1.97–8.00)	<0.001
Hypertension, n (%)	24 (14.3)	11 (22.4)	13 (10.9)	2.36 (0.97–5.72)	0.057
Hypercholesterolemia, n (%)	20 (11.9)	8 (16.3)	12 (10.1)	1.74 (0.66–4.56)	0.260
Current smoker, n (%)	40 (23.8)	10 (20.4)	30 (25.2)	0.75 (0.33–1.69)	0.490
Migraine, n (%)	40 (23.8)	12 (24.5)	28 (23.5)	1.05 (0.48–2.29)	0.894
Triggers, n (%)					
Minor trauma (includes unusual physical activity and Valsalva)	60 (35.7)	16 (32.7)	44 (37)	0.42 (0.09–1.96)	0.268
Respiratory tract infection	21 (12.5)	3 (6.1)	18 (15.1)	0.37 (0.10–1.30)	0.121
Clinical presentation					
ICAD	46 (27.4)	21 (42.9)	25 (21.0)	2.82 (1.38–5.78)	0.005
VAD	130 (77.4)	31 (63.3)	99 (83.2)	0.35 (0.16–0.74)	0.006
Multiple arteries dissection	35 (20.8)	9 (18.4)	26 (21.8)	0.80 (0.35–1.87)	0.614
Transient ischemic attack	17 (10.1)	5 (10.2)	12 (10.1)	1.01 (0.34–3.05)	0.981
Time from symptom onset to admission in days, median (IQR)	3 (6)	1 (3)	4 (5.5)	0.79 (0.70–0.90)	<0.001
Neuroimaging, n (%)					
Mural hematoma	113 (67.3)	28 (57.1)	85 (71.4)	0.53 (0.27–1.07)	0.075
Vessel occlusion	13 (7.7)	8 (16.3)	5 (4.2)	4.45 (1.38–14.38)	0.035
Dissection flap	15 (8.9)	5 (10.2)	10 (8.4)	1.24 (0.40–3.83)	0.710
Pseudoaneurysm	67 (39.9)	17 (34.7)	50 (42.0)	0.73 (0.37–1.46)	0.379
TCD MES (n = 158)	11 (6.6)	5 (11.6)	6 (5.2)	2.45 (0.71–8.52)	0.157

CeAD: Cervical artery dissection, OR: Odds ratio, ICAD: internal carotid artery dissection, VAD: vertebral artery dissection, TCD: transcranial doppler ultrasound, MES: microembolic signals

admission, per each day of delay (OR 0.80, 95% CI 0.69–0.92, $P = 0.002$) remained associated with stroke.

Discussion

The main findings of this report are: i) CeAD presented predominantly as a non-stroke entity; ii) affected women more frequently; and iii) men were associated to more than a 2-fold increase in stroke risk. Overall, CeAD was associated to a good functional outcome at follow-up, and mortality was restricted exclusively to those patients suffering a stroke.

Previous cohorts reported more than two-thirds CeAD patients presenting with stroke.^{1,3} In contrast, in our cohort stroke occurred in 32% of cases. This may be

explained by a high suspicious index from emergency attending physicians, which included 24/7 ED neurologist, and broad availability of vascular imaging at our center. It is possible that CeAD patients presenting with mild symptoms were underrepresented in other epidemiological studies (3), and this could explain the different gender distribution and stroke rates seen in our cohort. In addition, shorter time between symptoms onset to admission was associated to stroke. Milder symptoms in patients without stroke could have translated into delays in admission times (either by lack of patient awareness or diagnostic challenges) and thus might explain the protective effect seen in multivariable analysis of longer awaiting periods.

Although the predominance of cervical vertebral artery involvement seen in this cohort has been previously

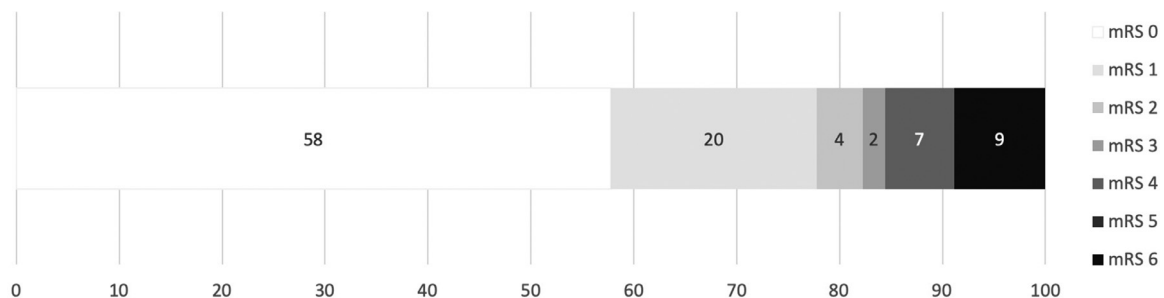


Figure 1. Functional status of patients with CeAD-S at follow-up according to the modified Rankin Scale (mRS), in percentages.

described,^{8,9} it differs from other reports, where internal carotid artery dissections was more prevalent.^{1,9} A high index of suspicion and adequate imaging interpretation is required for proper diagnosis.¹⁰ To overcome radiological diagnosis challenge, we used prespecified imaging criteria and an independent radiology team review of all discrepant results.

Most patients with CeAD were acutely treated with antiplatelets according to the local practice in our center. However, there is lack of evidence regarding the best treatment approach for this disease.⁹ As shown in our results, only one patient received acute full dose anticoagulation treatment. There is neither local or global consensus about this preference and underpins the areas of uncertainty still present on this topic.^{11,12}

Regarding prognosis, only male gender was independently associated with stroke in this cohort. Previous studies have recognized a larger number of risk factors, including male gender, older age, smoking, high-grade vessel stenosis or occlusion and detection of microembolic signals in Transcranial Doppler.^{5,7,13,14} Of interest, most CeAD-S patients presented with stroke of mild to moderate severity. This is in line with previous reports, where severe stroke and related disability in CeAD patients were rare.¹⁵ CeAD recurrence is low.⁹ We described a 6% recurrence rate and previous reports have shown even lower numbers,⁹ yet follow-up time was longer in our series.

This study has several limitations, namely its observational nature and lack of pairing. Although an effort was made to assess for most known features that can impact the risk of stroke, there still may be unknown variables which can affect the outcomes in CeAD patients and could have not been included in our analyses.

CeAD presented commonly as a non-stroke entity, with favorable prognosis. Albeit to a higher frequency of CeAD in women, stroke occurred predominantly in men, early after symptom onset. The stroke predominance in men warrants further research.

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Declaration of Interest (Disclosures)

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