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Background and Purpose—Little is known about factors contributing to multiple rather than single cervical artery dissections (CeAD) and their associated prognosis.

Methods—We compared the baseline characteristics and short-term outcome of patients with multiple to single CeAD included in the multicenter Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) study.

Results—Among the 983 patients with CeAD, 149 (15.2%) presented with multiple CeAD. Multiple CeADs were more often associated with cervical pain at admission (odds ratio [OR], 1.59; 95% confidence interval [CI], 1.10–2.30), a remote history of head or neck surgery (OR, 1.87; 95% CI, 1.16–3.00), a recent infection (OR, 1.71; 95% CI, 1.12–2.61), and cervical manipulation (OR, 2.23; 95% CI, 1.26–3.95). On imaging, cervical fibromuscular dysplasia (OR, 3.97; 95% CI, 2.04–7.74) and the presence of a pseudoaneurysm (OR, 2.91; 95% CI, 1.86–4.57) were more often seen in patients with multiple CeAD. The presence of multiple rather than single CeAD had no effect on functional 3-month outcome (modified Rankin Scale score, ≥3; 12% in multiple CeAD versus 11.9% in single CeAD; OR, 1.20; 95% CI, 0.60–2.41).

Conclusions—In the largest published series of patients with CeAD, we highlighted significant differences between multiple and single artery involvement. Features suggestive of an underlying vasculopathy (fibromuscular dysplasia) and environmental triggers (recent infection, cervical manipulation, and a remote history of head or neck surgery) were preferentially associated with multiple CeAD. **(*Stroke*. 2014;45:37-41.)**

Key Words: outcome assessement ■ risk factors

Dissection of the cervical arteries is the major cause of ischemic stroke (IS) in young adults.[1] Cervical artery dissections (CeAD) involving multiple neck arteries are frequent, accounting for 13% to 28% of overall CeAD cases.[2–5] However, little is known about factors contributing to multiple CeAD, as well as its prognosis. The aim of this study was to compare the baseline characteristics and short-term outcome between patients with single CeAD and multiple CeAD in the Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) study.

Methods

Study Population

The objectives and methodology of the CADISP-clinical study have been described elsewhere.[6] Briefly, 983 patients with a diagnosis of CeAD were enrolled in centers from 8 countries (Argentina, Belgium, Finland, France, Germany, Italy, Switzerland, and Turkey). Patients were recruited either retrospectively (n=605) or prospectively (n=378). Retrospective patients had a qualifying event before the beginning of the study and were identified through local registries of CeAD. CeAD was defined by the presence of a mural hematoma, aneurysmal dilatation, long tapering stenosis, intimal flap, double

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lumen, or occlusion ≥2 cm above the carotid bifurcation revealing an aneurysmal dilatation or a long tapering stenosis after recanalization in a cervical artery (internal carotid or vertebral).[7] Purely intracranial or iatrogenic dissections were not included. The CADISP study was approved by local relevant authorities in each participating center.

Risk Factors and Baseline Characteristics

Demographics and the following putative risk factors were recorded: hypertension (previously known or patient under antihypertensive treatment or blood pressure ≥140/90 mm Hg during nonacute phase), hypercholesterolemia (total cholesterol ≥6.20 mmol/L or low-density lipoprotein-cholesterol ≥4.1 mmol/L, measured within 48 hours after admission to the hospital or diagnosed by the treating physician or patient under lipid-lowering treatment), diabetes mellitus (fasting glucose >7 mmol/L during nonacute phase or use of an antidiabetic therapy), smoking (current [within a month] or past), body mass index, and migraine (classified according the International Headache Society criteria).[8] We also recorded fibromuscular dysplasia (FMD), remote history of head or neck surgery, and an infection in the week preceding the dissection. FMD was defined at the discretion of the investigator based on data of magnetic resonance angiography or computed tomography angiography and did not necessarily require diagnosis by digital subtraction angiography. A trauma during the preceding month was also noted and was defined as physical effect on the head or neck (eg, extreme neck movements, cervical manipulation, lifting up heavy loads) <1 month before the CeAD.

The following clinical data were noted at admission: local symptoms/signs (cervical pain, headache, cranial nerve palsy, Horner syndrome, tinnitus); presence/absence of cerebral or retinal ischemia (IS, transient ischemic attack [TIA], or transient monocular blindness). In patients with stroke, clinical severity at admission was evaluated by means of the National Institutes of Health Stroke Scale score. Imaging data included single versus multiple dissections, arterial occlusion, stenosis, aneurysmal dilatation, and hemorrhages.

Outcome

Functional outcome was measured at 3 months using the modified Rankin Scale. A moderate-to-severe handicap was defined by a modified Rankin Scale ≥3. Major complications within the first 3 months were recorded: stroke or TIA, recurrent CeAD, intracranial hemorrhage, or major extracranial hemorrhage (ie, leading to death or requiring blood transfusion, surgery, or hospitalization).

Statistical Analyses

Baseline characteristics were compared between groups (single versus multiple CeAD) using χ^2 test or Fisher exact test for categorical variables and Student *t* test or a nonparametric test, such as Wilcoxon test, for continuous variables depending on normality assumption. Associations were then adjusted for age, sex, and country of inclusion using logistic regression analysis. Binary logistic regression models were used to estimate odds ratios (ORs) of moderate-to-severe handicap, recurrent CeAD, TIA, and stroke within 3 months and their 95% confidence intervals (CIs). Because the outcomes were clinically distinct entities with common and individual risk factors, we chose the statistical criteria to select potential confounding factors that would be relevant for each outcome. In multivariate models, we introduced multiple CeAD, age, sex, and baseline characteristics with a *P* value <0.20 in unadjusted models. Antiplatelet agents and anticoagulants were forced into the final models for recurrent TIA. None of the patients with major hemorrhage had taken anticoagulants or antiplatelet agents. Therefore, we did not control for both drugs in multivariate models for major hemorrhage because of empty cells that might have led to invalid estimates. SAS version 9.3 (SAS Institute Inc, Cary, NC) was used for the analyses. Multinomial logistic regression was performed with generalized logits to analyze major hemorrhage as a nominal 3-level outcome: extracranial, intracranial, and no hemorrhage. A 2-sided *P* value ≤0.05 was considered statistically significant.

Results

Characteristics of Patients

Among the 983 patients with CeAD, 149 (15.2%) presented with multiple artery involvement. Characteristic of patients are shown in Table 1. For retrospective patients, the qualifying event was an IS in 51.9%, a TIA in 10.4%, a transient monocular blindness in 0.8%, a combination of these events in 13.1%, and isolated local signs in 23.8%. A similar distribution of qualifying events was observed for prospective patients (57.1%, 9.0%, 1.3%, 11.1%, and 21.4%, respectively; *P*=0.54).

Multiple CeAD was more often associated with cervical pain at admission (OR, 1.59; 95% CI, 1.10–2.30), prior recent infection (OR, 1.71; 95% CI, 1.12–2.61), and cervical manipulation (OR, 2.23; 95% CI, 1.26–3.95), or a remote history of head or neck surgery (OR, 1.87; 95% CI, 1.16–3.00). Carotid location was more frequent in patients with single CeAD. The association between multiple CeAD and both cervical pain and cervical manipulation was still observed after adjustment for dissection site (ICAD/VAD [internal carotid arteriy dissection/vertebral arery dissection]; results not shown). Conversely, current smoking, transient monocular blindness, and TIA at admission were more frequent in patients with single CeAD. Patients with multiple CeAD had more often cervical FMD (OR, 3.97; 95% CI, 2.04–7.74) and pseudoaneurysm (OR, 2.91; 95% CI, 1.86–4.57) on imaging. Unadjusted analyses did not show any association between vascular risk factors and multiple CeAD but after adjustment for age, sex, and country of inclusion, hypertension become significantly associated with multiple CeAD.

Outcome

No death was observed during 3 months of follow-up. The proportion of patients with moderate-to-severe handicap at 3 months was similar between those with single CeAD and those with multiple CeAD (OR, 1.20; 95% CI, 0.60–2.41). No difference was observed between patients for stroke and CeAD recurrence during follow-up. In contrast, both TIA and intracranial hemorrhage tended to occur more frequently in patients with multiple CeAD. In multivariate analyses, only the association with intracranial hemorrhage was significant (OR, 5.43; 95% CI, 1.02–29.06; Table 2).

Discussion

Our findings about the prevalence of multiple CeAD (15.2%) are consistent with those from previous reports.[2–4] It was suggested that multiple CeAD could be more frequent in women,[3,4,9] but the present study shows only a nonsignificant trend toward an increased risk of multiple CeAD in women. As it was suggested by one other study, we demonstrated that multiple CeAD was more often preceded by an infection in the previous week.[9] We also confirmed the association of multiple CeAD with cervical manipulation[10] that could be explained by purely a mechanical trauma on the arterial wall resulting from overstretching the arteries during rotational manipulation, even though the causality of such an association remains controversial in the literature. Finally, the prevalence of a remote history of head and neck surgery seemed to be greater

Table 1. Baseline Characteristics of 983 Patients With Multiple vs Single Cervical Arteries Dissection

Characteristics	Unadjusted Analyses				Adjusted Analyses for Age, Sex, and Country of Inclusion		
	Total n=983 (%)*	Multiple CeAD n=149 (15.2)	Single CeAD n=834 (84.8)	*P* Value†	OR	95% CI	*P* Value‡
Age, years mean±SD	44.1±9.9	43.1±9.9	44.2±10.0	0.179	0.99	0.97–1.01	0.204
Female sex	426 (43.3)	74 (49.7)	352 (42.2)	0.091	1.22	0.85–1.77	0.284
Clinical features							
≥1 local sign (n=955)	834 (87.3)	128 (87.1)	706 (87.4)	0.920	0.89	0.52–1.52	0.658
Cervical pain (n=955)	469 (49.1)	89 (60.5)	380 (47.0)	0.003‖	1.59	1.10–2.30	0.013‖
Headache (n=955)	641 (67.1)	99 (67.3)	542 (67.1)	0.949	0.91	0.62–1.34	0.629
Cranial nerve palsy (n=955)	60 (6.3)	6 (4.1)	54 (6.7)	0.232	0.61	0.25–1.45	0.260
Horner syndrome (n=955)	272 (28.5)	35 (23.8)	237 (29.3)	0.172	0.84	0.55–1.27	0. 407
Tinnitus (n=955)	73 (7.6)	16 (10.9)	57 (7.1)	0.108	1.65	0.90–3.01	0.106
Cerebral infarct/TIA/TMB vs no ischemia	771 (78.4)	110 (73.8)	661 (79.3)	0.138	0.68	0.45–1.02	0.063
Cerebral infarct vs no ischemia (n=856)	644 (75.2)	96 (71.1)	548 (76.0)	0.227	0.71	0.46–1.08	0.107
TIA vs no ischemia (n=410)	198 (48.3)	23 (37.1)	175 (50.3)	0.056	0.53	0.29–0.95	0.033‖
Transient monocular blindness vs no ischemia (n=264)	52 (19.7)	3 (7.1)	49 (22.1)	0.026‖	0.20	0.06–0.68	0.010‖
NIHSS on admission							
Median (IQR; n=792)	1 (5-0)	1 (5-0)	1 (5-0)	0.336	0.98	0.95–1.02	0.316
0–1 (less or equal median)	420 (42.7)	65 (43.6)	355 (42.6)	0.666	Ref		
>1 (above median)	372 (37.8)	52 (34.9)	320 (38.4)		0.90	0.60–1.34	0.598
Undetermined	191 (19.4)	32 (21.5)	159 (19.1)		0.89	0.54–1.47	0. 654
CeAD imaging							
Cervical fibromuscular dysplasia (n=732)	41 (5.6)	18 (15.0)	23 (3.8)	<0.0001‖	3.97	2.04–7.74	<0.0001‖
Pseudoaneurysm	124 (12.6)	38 (25.5)	86 (10.3)	<0.0001‖	2.91	1.86–4.57	<0.0001‖
Wall hematoma (n=894)	719 (80.4)	115 (85.2)	604 (79.6)	0.130	1.46	0.86–2.48	0.165
Intracranial aneurysm (n=683)	21 (3.1)	6 (5.5)	15 (2.6)	0.114	2.04	0.74–5.64	0.169
Carotid vs vertebral location (n=946)§	619 (65.4)	62 (54.9)	557 (66.9)	<0.0001‖	0.62	0.41–0.94	0.023‖
Vascular risk factors							
Hypertension (n=973)	249 (25.6)	43 (29.1)	206 (25.0)	0.294	1.53	1.01–2.31	0.045‖
Hypercholesterolemia (n=963)	182 (18.9)	21 (14.6)	161 (19.7)	0.151	0.75	0.45–1.25	0.264
Diabetes mellitus (n=976)	21 (2.2)	5 (3.4)	16 (1.9)	0.264	1.87	0.66–5.32	0.243
Active smoking (n=971)	269 (27.7)	31 (20.9)	238 (28.9)	0.094	0.63	0.40–0.99	0.047‖
Obesity (BMI>30 kg/m^2; n=932)	68 (7.3)	11 (7.7)	57 (7.2)	0.843	1.13	0.58–2.24	0.716
Medical history							
Recent infection (previous week; n=960)	187 (19.5)	38 (26.0)	149 (18.3)	0.030‖	1.71	1.12–2.61	0.012‖
Recent traumatism (previous month; n=965)	391 (40.5)	66 (44.9)	325 (39.7)	0.240	1.12	0.77–1.64	0.540
Prior manipulation (n=965)	69 (7.2)	20 (13.6)	49 (6.0)	0.001‖	2.23	1.26–3.95	0.006‖
Remote history of head and neck surgery	165 (16.8)	40 (26.8)	125 (15.0)	0.0004‖	1.87	1.16–3.00	0.010‖

The number of patients with data available is indicated in parentheses. BMI indicates body mass index; CeAD, cervical artery dissection; CI, confidence interval; IQR, interquartile range (quartile 3–quartile 1); NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and TIA, transient ischemic attack.

*Expressed in percentages unless otherwise indicated.

†Characteristics were compared between groups using χ^2 test or Fisher exact test for categorical variables and ANOVA or nonparametric test, such as Wilcoxon test, for continuous variables.

‡Baseline characteristics were compared between groups using logistic regression to estimate adjusted associations for age, sex, and country of inclusion.

§One patient with CeAD located on the common carotid and subclavian arteries and 36 patients with CeAD located on both carotid and vertebral arteries were excluded from analyses.

‖Statistically significant.

in patients with multiple CeAD. It could be hypothesized that local trauma resulting from surgery could lead to permanent changes in the arterial wall increasing the susceptibility to CeAD. The present study shows also differences in clinical presentation, indeed multiple CeAD was more often associated with cervical pain at admission, whereas transient monocular blindnesses and TIA were more frequent in patients with single CeAD.

Table 2. Associations of Multiple CeAD With 3-Month Functional Outcome and Complications in 948 Patients

	Unadjusted Analyses					Age- and Sex-Adjusted Analyses			Multivariate Analyses		
Functional Outcome and Complications	Multiple CeAD n=145 (15.3%)	Single CeAD n=803 (84.7%)	OR	95% CI	*P* Value	OR	95% CI	*P* Value	OR	95% CI	*P* Value
Moderate-to-severe handicap (n=940)	17 (12.0)	95 (11.9)	1.01	0.58–1.75	0.982	1.06	0.61–1.84	0.844	1.20*	0.60–2.41	0.615
Stroke	5 (3.4)	14 (1.7)	2.01	0.71–5.68	0.186	2.01	0.71–5.71	0.191	2.25†	0.77–6.59	0.140
TIA	5 (3.4)	7 (0.9)	4.06	1.27–12.98	0.018¶	4.05	1.26–13.05	0.019¶	3.81‡	0.86–16.87	0.078
CeAD	6 (4.1)	18 (2.2)	1.88	0.73–4.83	0.188	1.83	0.71–4.70	0.212	1.61§	0.55–4.71	0.382
Major hemorrhage											
No	141 (97.2)	797 (99.2)	Ref	…	…	Ref	…	…	Ref	…	…
Extracranial	1 (0.7)	3 (0.4)	1.88	0.20–18.24	0.584	1.68	0.17–16.65	0.657	0.30‖	0.02–5.60	0.422
Intracranial (ICH)	3 (2.1)	3 (0.4)	5.66	1.13–28.29	0.035¶	6.00	1.19–30.36	0.030¶	5.43‖	1.02–29.06	0.048¶

Associations between multiple CeAD and outcomes were analysed using either binary or multinomial logistic regression models. CI indicates confidence interval; ICH, intracerebral hemorrhage; OR, odds ratio; Ref, reference; TIA, transient ischemic attack, and TMB, transient monocular blindness.

*Adjusted for age, sex, cervical pain, headache, cranial nerve palsy, Horner syndrome, tinnitus, cerebral infarct, TIA, pseudoaneurysm, carotid location, migraine, recent traumatism, and remote history of head or neck surgery.

†Adjusted for age, sex, cervical pain, Horner syndrome, TIA, and migraine with aura.

‡Adjusted for age, sex, cervical pain, TIA, TMB, carotid location, anticoagulants, and antiplatelet agents.

§Adjusted for age, sex, headache, cranial nerve palsy, cerebral infarct, hypertension, obesity, and recent infection.

‖Adjusted for age, sex, tinnitus, intracranial aneurysm, diabetes, and migraine with aura.

¶Statistically significant.

We found a higher prevalence of FMD in patients with multiple than in those with single CeAD (15% versus 3%). Cervical FMD has been associated with CeAD, with a prevalence ranging from 13% to 15 %.[11,12] The prevalence in our study was smaller (5.6%), which could be because of differences in the diagnostic criteria. Indeed, in some of the previous studies, digital subtraction angiography was performed in the majority of patients, which was not the case in our study because this invasive diagnostic tool is no longer recommended for the diagnosis of CeAD. This result could indicate that multiple CeAD is more common in patients with an underlying arteriopathy, such as FMD. Finally, we found a higher frequency of pseudoaneurysms in patients with multiple CeAD, as it was reported in other studies,[5,13] possibly reflecting that multiple dissections are more often subadventitial.

Among patients with overall CeAD, 12% had a moderate-to-severe handicap at 3 months and none had died. This proportion was similar between those with single and those with multiple CeAD. This favorable outcome is in agreement with previous studies.[11] However, it must be noticed that the possible noninclusion in this study of some patients with the best and worst prognosis may have contributed, in part, to this finding. Indeed, because patients were recruited through neurology departments, mostly in tertiary centers, it cannot be excluded that some patients with local signs only or with minor cerebral or retinal ischemia, as well as those with severe strokes requiring intensive care or leading to early death, may have been missed.

As demonstrated in previous studies, recurrence rates of CeAD were low.[14] Whereas multiple CeAD did not predict a poor outcome or CeAD recurrence, we noticed an increase in the risk of intracranial hemorrhage and only a trend in that of TIA at 3 months. Consistently with this finding, in a previous study with a mean follow-up of 31 months, the presence of multiple CeAD was associated with a higher risk of subsequent stroke or TIA.[15]

This study had several strengths, including the large sample size, given the low incidence of the disease in the general population and the standardized collection of extensive clinical information. However, we must acknowledge some limitations, including a partly retrospective recruitment of patients with CeAD that may have biased the assessment of risk factors. We cannot exclude a selection bias because patients with a severe short-term outcome may not have been included, both because of the partly retrospective design and to the fact that an extensive informed consent (required for genetic analyses) was required and sometimes difficult to obtain from critically ill patients or their families. If multiple dissections more often lead to a poor short-term outcome, we may have underestimated associations with outcome severity. Analyses of 3-month outcomes may have been entailed by a lack of sufficient statistical power to demonstrate significant associations with multiple CeAD. Future studies examining the association of multiple dissections with long-term recurrence rates will be of interest.

To conclude, our data suggest that multiple and single CeAD may differ in terms of pathogenesis, presentation, and outcome. Particularly, both features suggestive of an underlying vasculopathy (FMD) and environmental triggers (recent infection, cervical manipulation, and a remote history of head or neck surgery) were preferentially associated with multiple CeAD. Future research on the pathophysiology, risk profile, and outcome of CeAD should take into account the presence of multiple dissections. Furthermore, patients with multiple

CeAD should be more carefully investigated for FMD, and they require more careful monitoring.

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Disclosures

None.

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