# Differential features of carotid and vertebral artery dissections

## The CADISP Study

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**Supplemental data at www.neurology.org**

Supplemental Data

## ABSTRACT

**Objective:** To examine whether risk factor profile, baseline features, and outcome of cervical artery dissection (CEAD) differ according to the dissection site.

**Methods:** We analyzed 982 consecutive patients with CEAD included in the Cervical Artery Dissection and Ischemic Stroke Patients observational study (n = 619 with internal carotid artery dissection [ICAD], n = 327 with vertebral artery dissection [VAD], n = 36 with ICAD and VAD).

**Results:** Patients with ICAD were older ($p < 0.0001$), more often men ($p = 0.006$), more frequently had a recent infection (odds ratio [OR] = 1.59 [95% confidence interval (CI) 1.09–2.31]), and tended to report less often a minor neck trauma in the previous month (OR = 0.75 [0.56–1.007]) compared to patients with VAD. Clinically, patients with ICAD more often presented with headache at admission (OR = 1.36 [1.01–1.84]) but less frequently complained of cervical pain (OR = 0.36 [0.27–0.48]) or had cerebral ischemia (OR = 0.32 [0.21–0.49]) than patients with VAD. Among patients with CEAD who sustained an ischemic stroke, the NIH Stroke Scale (NIHSS) score at admission was higher in patients with ICAD than patients with VAD (OR = 1.17 [1.12–1.22]). Aneurysmal dilatation was more common (OR = 1.80 [1.13–2.87]) and bilateral dissection less frequent (OR = 0.63 [0.42–0.95]) in patients with ICAD. Multiple concomitant dissections tended to cluster on the same artery type rather than involving both a vertebral and carotid artery. Patients with ICAD had a less favorable 3-month functional outcome (modified Rankin Scale score >2, OR = 3.99 [2.32–6.88]), but this was no longer significant after adjusting for baseline NIHSS score.

**Conclusion:** In the largest published series of patients with CEAD, we observed significant differences between VAD and ICAD in terms of risk factors, baseline features, and functional outcome.

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## GLOSSARY

**BMI** = body mass index; **CADISP** = Cervical Artery Dissection and Ischemic Stroke Patients; **CEAD** = cervical artery dissection; **CI** = confidence interval; **ICAD** = internal carotid artery dissection; **IS** = ischemic stroke; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **OR** = odds ratio; **VAD** = vertebral artery dissection.

Cervical artery dissection (CEAD) is one of the major causes of ischemic stroke (IS) in young adults.[1,2] CEAD can affect the cervical portion of the internal carotid artery (ICAD), the vertebral artery (VAD), or both. The incidence of ICAD is estimated to be slightly higher than the incidence of VAD (1.7/100,000 per year vs 1.0/100,000).[3] Commonly, when assessing risk factors, natural course, and outcome of CEAD, ICAD and VAD are studied jointly.[4] However, in analogy with aortic dissection where the pathogenesis and clinical presentation differ according

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to the aortic segment concerned,[5] ICAD and VAD may have distinct underlying mechanisms and characteristics.

Our aim was to compare the distribution of putative risk factors, clinical and radiologic presentation, and short-term outcome in patients with ICAD and patients with VAD in the Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) study, a large multicenter cohort of consecutive patients with CEAD.

## METHODS

**Study population.** Structure and methods of the CADISP study have been described in detail previously.[6] Between 2004 and 2009, as part of a multicenter effort comprising 20 centers in 9 countries, we have included consecutive patients evaluated in a department of neurology with a diagnosis of CEAD or a diagnosis of IS of another cause than CEAD (non-CEAD IS). Patients were recruited both prospectively and retrospectively. Retrospective patients are participants who had a qualifying event before the beginning of the study in each center and were identified through local registries of patients with CEAD. The vast majority of patients had a qualifying event between 1999 and 2009 (<4% before 1999). The primary aim of the CADISP consortium was to perform a genetic association study, currently underway, to identify genetic susceptibility factors of CEAD.[6] All but 2 centers also participated in an observational clinical study including detailed screening of putative environmental risk factors, clinical and radiologic characteristics, and 3-month outcome (assessed as part of the standard outpatient follow-up of young patients in each center), using a standardized questionnaire. The CADISP clinical study comprises a total of 983 patients with a diagnosis of CEAD and 658 patients with a diagnosis of non-CEAD IS frequency matched on age (by 5-year intervals) and gender, included in 8 countries (Argentina, Belgium, Finland, France, Germany, Italy, Switzerland, Turkey) and 18 centers (figure e-1 on the *Neurology*® Web site at www.neurology.org). Only patients with a diagnosis of CEAD were included in the present analysis. Detailed inclusion criteria are available online (figure e-2). Briefly, patients with CEAD had to present a mural hematoma, aneurysmal dilatation, long tapering stenosis, intimal flap, double lumen or occlusion >2 cm above the carotid bifurcation revealing an aneurysmal dilation, or a long tapering stenosis after recanalization, in a cervical artery (internal carotid or vertebral); purely intracranial or iatrogenic dissections were not included. Of the 983 patients with a diagnosis of CEAD we excluded one patient who sustained a dissection of the common carotid and subclavian artery (neither ICAD nor VAD); for most analyses, except secondary analyses on multisite dissections, we also excluded 36 patients who had sustained both an ICAD and a VAD. Hence the sample size for the main analyses was 946 patients, 619 with 1 or 2 ICAD and 327 with 1 or 2 VAD (figure e-3).

**Variable definition.** ***Putative risk factors.*** We examined the prevalence (at the time of the qualifying event) of clinical parameters that were previously shown to be associated with an increased risk (hypertension,[7–9] cervical trauma,[10,11] recent infection,[12–14] migraine[15,16]) or a reduced risk (elevated body mass index [BMI],[9,17] hypercholesterolemia[9]) of CEAD. We defined vascular risk factors as follows: hypertension, by a history of elevated blood pressure (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg) diagnosed by the treating physician, or use of a blood pressure–lowering therapy; hypercholesterolemia, by a fasting total cholesterol ≥6.20 mmol/L or fasting low-density lipoprotein cholesterol ≥4.1 mmol/L, measured within 48 hours after admission or diagnosed by the treating physician, or use of a cholesterol-lowering therapy; and BMI as the ratio of weight (kg) to the square of height ($m^2$). Migraine was defined according to the International Classification of Headache Disorders.[18] An infection in the week preceding the dissection corresponded to the presence of at least one typical symptom of infection, in combination with fever (temperature ≥38 °C) or the presence of at least one typical symptom of infection with corresponding serologic, culture, or radiologic findings indicating an acute infection or the combination of at least 2 typical corresponding symptoms.[19] We categorized cervical trauma in the month preceding the dissection as severe if leading to a medical visit or hospitalization, and as minor otherwise. We also recorded the presence or absence of a history of CEAD.

***Clinical presentation.*** Presence or absence of cerebral or retinal ischemia (ischemic stroke, TIA, or transient monocular blindness) and of cervical pain or headache at admission were recorded. For patients who sustained an ischemic stroke, we computed the NIH Stroke Scale (NIHSS) score at admission, as a marker of initial stroke severity.

***Radiologic presentation.*** We recorded the following radiologic features on the dissected arteries at admission: arterial occlusion, defined by the absence of blood flow; stenosis, defined by a narrowing of the arterial lumen, regardless of the presence or absence of hemodynamic blood flow modifications; aneurysmal dilatation, defined by a focal enlargement of the arterial lumen and external diameter; mural hematoma, defined by eccentric thickening of the arterial wall with imaging characteristics compatible with acute or subacute bleeding within the thickened wall; multiple dissections, defined by the simultaneous presence of a recent dissection on more than one cervical artery.

***Short-term outcome.*** We rated the 3-month functional outcome according to the modified Rankin Scale (mRS),[20] and recorded recurrent CEAD and stroke or TIA within 3 months after admission.

**Statistical analyses.** We compared risk factors and clinical and radiologic characteristics between patients with ICAD and patients with VAD, using Student *t* test for continuous variables and a $\chi^2$ test for categorical variables (or Fisher exact test when appropriate). In addition, we ran a multivariable logistic regression adjusted for age, gender, and country of inclusion. For clinical and radiologic characteristics, we also adjusted for risk factors that we found to be associated with dissection site (ICAD vs VAD), in a secondary analysis.

To explore the association of dissection site with 3-month functional outcome in patients who had sustained an IS at admission, we dichotomized the mRS score into 0–2 vs 3–5, and ran a multivariable logistic regression, where the dissection site was the main predictor variable. The primary model was adjusted for age, gender, and country of inclusion. In a secondary model, we additionally adjusted for the NIHSS score at admission. We also examined the relation of dissection site with recurrent CEAD and stroke or TIA at 3 months, using a multivariable logistic regression adjusted for age, gender, and country of inclusion.

As a sensitivity analysis, all models were adjusted for the delay between the qualifying event (first clinical signs) and inclu-

**Table 1** Association of demographic characteristics and putative risk factors with dissection site (ICAD vs VAD)

| | ICAD | VAD | p[a] | OR (95% CI)[b] | p[b] |
|---|---|---|---|---|---|
| No. | 619 | 327 | | | |
| Age, y, mean ± SD | 45.7 ± 9.6 | 41.1 ± 9.9 | <0.0001 | 1.05 (1.03-1.06) | <0.0001 |
| Women, n (%) | 245 (39.6) | 160 (48.9) | 0.006 | 0.68 (0.52-0.90) | 0.006 |
| Non-European origin,[c] n (%) | 4 (0.7) | 8 (2.5) | 0.04 | 0.31 (0.09-1.08) | 0.07 |
| Hypertension, n (%) | 165 (27.0) | 74 (22.8) | 0.16 | 0.95 (0.68-1.33) | 0.77 |
| Hypercholesterolemia, n (%) | 125 (20.7) | 52 (16.2) | 0.10 | 1.01 (0.70-1.47) | 0.94 |
| BMI, mean ± SD | 24.5 ± 3.9 | 24.4 ± 4.0 | 0.86 | 0.97 (0.94-1.01) | 0.18 |
| Infection in previous week, n (%) | 131 (21.7) | 47 (14.6) | 0.009 | 1.59 (1.09-2.31) | 0.01 |
| Minor cervical trauma in previous month, n (%) | 177 (29.2) | 118 (36.5) | 0.02 | 0.75 (0.56-1.007) | 0.05 |
| Severe cervical trauma in previous month, n (%) | 28 (4.6) | 18 (5.6) | 0.52 | 0.94 (0.50-1.77) | 0.84 |
| Migraine, n (%) | 221 (36.3) | 123 (38.1) | 0.60 | 1.09 (0.81-1.47) | 0.57 |
| History of CEAD, n (%) | 13 (2.1) | 4 (1.2) | 0.32 | 1.56 (0.49-4.94) | 0.45 |

Abbreviations: BMI = body mass index; CEAD = cervical artery dissection; CI = confidence interval; ICAD = internal carotid artery dissection; OR = odds ratio; VAD = vertebral artery dissection.
[a] Univariate.
[b] Adjusted for age and gender, except the first 2 lines, and inclusion country (the probability modeled is ICAD vs VAD).
[c] For patients with ICAD, non-European origin was Hispanic (n = 1), North African (n = 1), or unknown (n = 2); for patients with VAD, non-European origin was mixed Caribbean and Mauritian (n = 3), North African (n = 2), South African (n = 1), South Asian (n = 1), and Middle Eastern (n = 1).

sion to account for a potential recall bias in patients included several weeks or months after the dissection occurred.

Analyses were performed using Statistical Analyses System® software version 9.2 (SAS Institute, Cary, NC).

## RESULTS

**Putative risk factor distribution.** Patients with ICAD were significantly older compared to patients with VAD (table 1). While VAD occurred at a similar frequency in men and women, patients with ICAD were more often men (table 1). An infection in the week preceding the dissection was more often reported in patients with ICAD; a minor cervical trauma in the previous month was more common in patients with VAD, although this result reached only borderline significance in the multivariable model (table 1). The results were unchanged when additionally adjusting for the delay of inclusion (data not shown).

**Clinical presentation and radiologic features.** Cervical pain was about twice as common in patients with VAD, while headache at admission was slightly more frequent in patients with ICAD (table 2). Cerebral ischemia, and specifically IS, was significantly more frequent at admission in VAD than in ICAD. Among patients with an IS, the NIHSS score at admission was higher in patients with ICAD than in patients with VAD. Aneurysmal dilatation was more

**Table 2** Clinical presentation at admission according to dissection site (ICAD vs VAD)

| | ICAD | VAD | p[a] | OR (95% CI)[b] | p[b] |
|---|---|---|---|---|---|
| No. | 619 | 327 | | | |
| Cervical pain, n (%) | 231 (38.7) | 212 (66.0) | <0.0001 | 0.36 (0.27-0.48) | <0.0001 |
| Headache, n (%) | 405 (67.8) | 207 (64.5) | 0.30 | 1.36 (1.01-1.84) | 0.04 |
| Cerebral ischemia, n (%) | 453 (73.2) | 295 (90.2) | <0.0001 | 0.32 (0.21-0.49) | <0.0001 |
| Ischemic stroke | 374 (60.4) | 252 (77.1) | <0.0001 | 0.45 (0.33-0.61) | <0.0001 |
| TIA | 123 (19.9) | 70 (21.4) | 0.58 | 1.02 (0.72-1.43) | 0.92 |
| TMB | 51 (8.2) | 0 (0) | — | — | — |
| Subarachnoid hemorrhage, n (%) | 6 (1.0) | 1 (0.3) | 0.43 | 2.96 (0.34-25.69) | 0.32 |
| Mean ± SD NIHSS score[c] | 8.1 ± 7.5 | 3.0 ± 4.1 | <0.0001 | 1.17 (1.12-1.22) | <0.0001 |

Abbreviations: CI = confidence interval; ICAD = internal carotid artery dissection; NIHSS = NIH Stroke Scale; OR = odds ratio; TMB = transient monocular blindness; VAD = vertebral artery dissection.
[a] Univariate.
[b] Adjusted for age, gender, and inclusion country (the probability modeled is ICAD vs VAD).
[c] Among patients with an ischemic stroke at admission in whom the NIHSS score was available (n = 208 VAD [82.5% of VAD cases with ischemic stroke] and n = 291 ICAD [78.0% of ICAD cases with ischemic stroke]).

Table 3 Radiologic features at admission according to dissection site (ICAD vs VAD)

| | ICAD | VAD | p[a] | OR (95% CI)[b] | p[b] |
|---|---|---|---|---|---|
| No. | 619 | 327 | | | |
| Bilateral dissection[c] | 62 (10.0) | 51 (15.6) | 0.01 | 0.63 (0.42–0.95) | 0.03 |
| Arterial occlusion[d] | 208 (33.6) | 109 (33.3) | 0.93 | 0.94 (0.70–1.26) | 0.68 |
| Stenosis[d] | 407 (65.7) | 221 (67.6) | 0.57 | 1.02 (0.76–1.36) | 0.89 |
| Aneurysmal dilatation[d] | 86 (13.9) | 27 (8.3) | 0.01 | 1.80 (1.13–2.87) | 0.01 |
| Mural hematoma[d,e] | 453 (81.6) | 239 (78.4) | 0.25 | 1.18 (0.82–1.69) | 0.36 |

Abbreviations: CI = confidence interval; ICAD = internal carotid artery dissection; OR = odds ratio; VAD = vertebral artery dissection.
[a] Univariate.
[b] Adjusted for age, gender, and inclusion country (the probability modeled is ICAD vs VAD).
[c] Patients with both a vertebral and an internal carotid artery dissection were excluded (see Methods).
[d] Two or more of these features could be present simultaneously in the same patient.
[e] In 86 patients (n = 22 VAD, n = 64 ICAD) the presence of a mural hematoma could not be assessed at admission.

often seen in patients with ICAD, while the distribution of arterial occlusion, stenosis, and mural hematoma did not differ significantly (table 3). Bilateral VAD among patients with VAD only was more common than bilateral ICAD among patients with ICAD only (table 3). When considering as well the 36 patients who had sustained both an ICAD and a VAD, 98/655 patients (15.0% [95% confidence interval (CI) 12.2%–17.7%]) with at least one ICAD had multiple concomitant dissections, 62 (9.5% [7.2%–11.7%]) of both internal carotid arteries and 36 (5.5% [3.8%–7.2%]) of at least one internal carotid and one vertebral artery; 87/363 patients (24.0% [19.6%–28.4%]) with at least one VAD had multiple concomitant dissections, 51 (14.0% [10.5%–17.6%]) of both vertebral arteries and 36 (9.9% [6.8%–13.0%]) of at least one vertebral and one internal carotid artery. The results were unchanged when additionally adjusting for the delay of inclusion, for infection in the previous week or minor cervical trauma in the previous month (data not shown), except for the association of ICAD with headache, which was no longer significant ($p$ = 0.07) after adjusting for recent infection.

**Short-term outcome.** Three-month follow-up information was available in 900 (95.1%) patients. All survived at 3 months. Among patients who sustained an IS, the 3-month functional outcome was favorable in 74.7% of patients with ICAD and 92.5% of patients with VAD. In a multivariable analysis patients with ICAD were at increased risk of poor functional outcome (mRS >2) compared to patients with VAD (OR = 3.99 [95% CI 2.32–6.88], $p < 0.0001$). This association was no longer significant after adjusting for the NIHSS score at admission (OR = 1.10 [0.54–2.25], $p = 0.80$). Results were unchanged after adjusting for the delay of inclusion and after adjusting for or excluding patients who received thrombolysis at the acute phase (data not shown).

Nineteen patients (2.1%) had a recurrent CEAD at 3 months. There was a nonsignificant trend toward a higher frequency of CEAD recurrences in patients with ICAD vs patients with VAD (OR = 2.96 [0.84–10.46], $p = 0.09$). Twenty-six patients (2.9%) had a stroke or TIA within 3 months after admission (16 had a stroke, 8 a TIA, and 2 both), which was associated with concomitant CEAD recurrence in 2 patients (both of whom had a TIA). In 23 patients this was a recurrent ischemic event, and in 3 a first ischemic event. There was no significant difference in the rate of stroke or TIA within 3 months after admission between patients with ICAD and patients with VAD (OR = 1.82 [0.71–4.67], $p = 0.21$). Adjusting for the delay of inclusion did not modify these associations (data not shown).

**DISCUSSION** In a large multicenter sample of almost 1,000 patients with CEAD, we found that patients with ICAD were older than patients with VAD and more often men; they more frequently experienced an infection in the week preceding the dissection, while patients with VAD more often reported a minor cervical trauma in the previous month. Patients with VAD more commonly complained of cervical pain and had a higher prevalence of bilateral dissection and cerebral ischemia at admission, while patients with ICAD more often showed aneurysmal dilatation on arterial imaging. Among patients who sustained an IS, patients with ICAD were more severely affected at admission and more likely to have an unfavorable functional 3-month outcome. Recurrent CEAD events at 3 months were rare and tended to be more common in ICAD.

Few studies have compared risk factors, baseline characteristics, and outcome between patients with

ICAD and patients with VAD, in single-center series of limited sample size.[3,21–23] Recent cervical manipulation was significantly more common in patients with VAD than patients with ICAD in a single-center series of 126 patients with CEAD.[21] While cerebral infarction on neuroimaging was significantly more common in patients with VAD than patients with ICAD in a small community-based cohort,[3] only trends toward a higher frequency of clinical stroke in VAD were reported.[3,21,23] One previous report suggested that VADs are more often bilateral.[21] The significantly higher prevalence of aneurysmal dilatation that we observed in patients with ICAD compared to patients with VAD has not been reported previously to our knowledge, although a similar trend was suggested before.[23,24] A better functional outcome in patients with VAD compared to patients with ICAD had been reported in an earlier series.[25] The fact that this association disappeared here after adjusting for initial stroke severity is in line with previous data showing that baseline NIHSS score is the main independent predictor of poor functional outcome in patients with IS.[26] The low rate of ischemic events after admission and of recurrent dissections at 3 months both in patients with VAD and patients with ICAD is in agreement with previous observations reporting low recurrence rates in the first months following the index event.[27]

If confirmed in independent datasets, some of the differences we observed between VAD and ICAD characteristics could suggest that the mechanisms might partly differ according to the dissection site, although these are hypotheses. The younger age of patients with VAD could suggest that age-related risk factors differentially affect the risk of VAD and ICAD, while the overrepresentation of men among patients with ICAD could perhaps be related to gender-specific hormonal or genetic risk factors of ICAD.[28] The slightly higher prevalence of minor cervical traumas preceding VAD compared to ICAD could be partly accounted for by anatomic features. Indeed, the carotid artery is essentially mobile in its cervical trajectory and protected by muscular and adipose tissue layers, while the vertebral artery is anchored to the cervical spine which could render it more vulnerable to mechanical solicitations. The higher prevalence of recent infection in patients with ICAD compared to patients with VAD could reflect that endothelial damage, prothrombotic state, and protease activation, which are thought to underlie the association between infection and CEAD,[29–32] might be more likely to occur in close proximity of the infection, as carotid arteries are anatomically closer to the upper respiratory tract.[33] Future studies could examine the association of recent infection with ICAD and VAD stratified on the infection type (e.g., upper respiratory tract vs other). As patients with ICAD more frequently had cerebral ischemia and more often had an aneurysmal dilatation, one could speculate that dissections in the internal carotid artery could more often be subadventitial, expanding externally, while dissections in the vertebral artery could more often be subintimal, expanding toward the arterial lumen, thus leading to a higher frequency of ischemic events.[34] Interestingly, a high intrafamilial correlation between the affected vessel (internal carotid or vertebral) was observed in familial forms of CEAD.[35] Furthermore, pericytes and smooth muscle cells in carotid arteries are derived from the neural crest, whereas vertebral arteries emerge exclusively from the mesoderm.[36] This could suggest that distinct genetic and developmental factors may be involved in the occurrence of ICAD and VAD, in analogy with aortic dissection where pathogenesis differs between the proximal or distal aortic segment, which also have distinct embryonic origins and inheritance patterns.[5,37]

The main strengths of this project are the large sample size and the standardized collection of extensive clinical information. The partly retrospective recruitment may have biased the assessment of risk factors present prior to the qualifying event; however, adjusting for the delay between qualifying event and inclusion in the study did not modify the associations. The frequency of infection in the previous week may be an overestimation given the broad definition we have used, but both groups were subject to the same bias. Our patients were recruited through neurology departments, mostly in tertiary centers, thus patients with CEAD with local signs only or with minor cerebral or retinal ischemia, as well as patients with very severe strokes requiring intensive care, were less likely to be included. Since the clinical presentation of single VAD can be mild and unspecific, ascertainment of patients with VAD could be biased toward individuals with bilateral VAD, who have more conspicuous symptoms. In addition, patients experiencing VAD without cerebral ischemia usually have unspecific symptoms that are more likely to be misdiagnosed, which could have inflated the proportion of patients with VAD with cerebral ischemia in our sample. Cervical pain or other symptoms whose detection relies on the patient's report may have been underestimated in patients with ICAD, as aphasia is more frequent in patients with cerebral ischemia in the carotid territory. Finally, we did not perform any correction for multiple testing as we considered our study as exploratory. Our findings, some of which were only moderate in terms

both of strength of association and effect size, require confirmation in independent cohorts.

Our observations suggest that, in analogy with the aorta where there is heterogeneity in the characteristics and mechanisms of aortic disease according to the segment involved, cervical artery dissections have distinct features according to the type of artery affected. Research on the pathophysiology, risk factors (including genetic susceptibility factors), and outcome of CEAD should take into account the dissection site, as pooled analyses could fail to identify important site-specific determinants.

In the largest multicenter series of patients with CEAD, we describe significant differences between VAD and ICAD in terms of putative risk factors, baseline characteristics, and short-term functional outcome.

## AUTHOR CONTRIBUTIONS

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## REFERENCES

1. Leys D, Bandu L, Henon H, et al. Clinical outcome in 287 consecutive young adults (15 to 45 years) with ischemic stroke. Neurology 2002;59:26–33.
2. Putaala J, Metso AJ, Metso TM, et al. Analysis of 1008 consecutive patients aged 15 to 49 with first-ever ischemic stroke: the Helsinki young stroke registry. Stroke 2009;40:1195–1203.
3. Lee VH, Brown RD Jr, Mandrekar JN, Mokri B. Incidence and outcome of cervical artery dissection: a population-based study. Neurology 2006;67:1809–1812.
4. Engelter ST, Brandt T, Debette S, et al. Antiplatelets versus anticoagulation in cervical artery dissection. Stroke 2007;38:2605–2611.
5. Allaire E, Schneider F, Saucy F, et al. New insight in aetiopathogenesis of aortic diseases. Eur J Vasc Endovasc Surg 2009;37:531–537.
6. Debette S, Metso TM, Pezzini A, et al. CADISP-genetics: an International project searching for genetic risk factors of cervical artery dissections. Int J Stroke 2009;4:224–230.
7. Longoni M, Grond-Ginsbach C, Grau AJ, et al. The ICAM-1 E469K gene polymorphism is a risk factor for spontaneous cervical artery dissection. Neurology 2006;66:1273–1275.
8. Pezzini A, Caso V, Zanferrari C, et al. Arterial hypertension as risk factor for spontaneous cervical artery dissection: a case-control study. J Neurol Neurosurg Psychiatry 2006;77:95–97.
9. Debette S, Metso T, Pezzini A, et al, for the CADISP Group. Do vascular risk factors increase the risk of cervical artery dissection? Circulation 2011;123:1537–1544.
10. Dittrich R, Rohsbach D, Heidbreder A, et al. Mild mechanical traumas are possible risk factors for cervical artery dissection. Cerebrovasc Dis 2007;23:275–281.
11. Haldeman S, Kohlbeck FJ, McGregor M. Risk factors and precipitating neck movements causing vertebrobasilar artery dissection after cervical trauma and spinal manipulation. Spine 1999;24:785–794.
12. Grau AJ, Buggle F, Ziegler C, et al. Association between acute cerebrovascular ischemia and chronic and recurrent infection. Stroke 1997;28:1724–1729.
13. Guillon B, Berthet K, Benslamia L, Bertrand M, Bousser MG, Tzourio C. Infection and the risk of spontaneous cervical artery dissection: a case-control study. Stroke 2003;34:e79–e81.
14. Genius J, Dong-Si T, Grau AP, Lichy C. Postacute C-reactive protein levels are elevated in cervical artery dissection. Stroke 2005;36:e42–e44.
15. Tzourio C, Benslamia L, Guillon B, et al. Migraine and the risk of cervical artery dissection: a case-control study. Neurology 2002;59:435–437.
16. Pezzini A, Granella F, Grassi M, et al. History of migraine and the risk of spontaneous cervical artery dissection. Cephalalgia 2005;25:575–580.
17. Arnold M, Pannier B, Chabriat H, et al. Vascular risk factors and morphometric data in cervical artery dissection: a case-control study. J Neurol Neurosurg Psychiatry 2009;80:232–234.

18. The International Classification of Headache Disorders: 2nd edition. Cephalalgia 2004;24(suppl 1):9–160.
19. Grau AJ, Buggle F, Heindl S, et al. Recent infection as a risk factor for cerebrovascular ischemia. Stroke 1995;26:373–379.
20. Bonita R, Beaglehole R. Recovery of motor function after stroke. Stroke 1988;19:1497–1500.
21. Dziewas R, Konrad C, Drager B, et al. Cervical artery dissection: clinical features, risk factors, therapy and outcome in 126 patients. J Neurol 2003;250:1179–1184.
22. Schievink WI, Mokri B, O'Fallon WM. Recurrent spontaneous cervical-artery dissection. N Engl J Med 1994;330:393–397.
23. Metso TM, Metso AJ, Salonen O, et al. Adult cervicocerebral artery dissection: a single-center study of 301 Finnish patients. Eur J Neurol 2009;16:656–661.
24. Touze E, Randoux B, Meary E, Arquizan C, Meder JF, Mas JL. Aneurysmal forms of cervical artery dissection: associated factors and outcome. Stroke 2001;32:418–423.
25. Arauz A, Hoyos L, Espinoza C, Cantu C, Barinagarrementeria F, Roman G. Dissection of cervical arteries: long-term follow-up study of 130 consecutive cases. Cerebrovasc Dis 2006;22:150–154.
26. De Marchis GM, Kohler A, Renz N, et al. Posterior versus anterior circulation strokes: comparison of clinical, radiological and outcome characteristics. J Neurol Neurosurg Psychiatry 2011;82:33–37.
27. Debette S, Leys D. Cervical-artery dissections: predisposing factors, diagnosis, and outcome. Lancet Neurol 2009;8:668–678.
28. Arnold M, Kappeler L, Georgiadis D, et al. Gender differences in spontaneous cervical artery dissection. Neurology 2006;67:1050–1052.
29. Smedly LA, Tonnesen MG, Sandhaus RA, et al. Neutrophil-mediated injury to endothelial cells. Enhancement by endotoxin and essential role of neutrophil elastase. J Clin Invest 1986;77:1233–1243.
30. Bhagat K, Moss R, Collier J, Vallance P. Endothelial "stunning" following a brief exposure to endotoxin: a mechanism to link infection and infarction? Cardiovasc Res 1996;32:822–829.
31. Smeeth L, Cook C, Thomas S, Hall AJ, Hubbard R, Vallance P. Risk of deep vein thrombosis and pulmonary embolism after acute infection in a community setting. Lancet 2006;367:1075–1079.
32. Guillon B, Peynet J, Bertrand M, Benslamia L, Bousser MG, Tzourio C. Do extracellular-matrix-regulating enzymes play a role in cervical artery dissection? Cerebrovasc Dis 2007;23:299–303.
33. Mootz W, Bleif H. [Internal carotid artery aneurism following peritonsillar abscess (author's transl)]. Hno 1980;28:197–200.
34. Bostrom K, Liliequist B. Primary dissecting aneurysm of the extracranial part of the internal carotid and vertebral arteries: a report of three cases. Neurology 1967;17:179–186.
35. Martin JJ, Hausser I, Lyrer P, et al. Familial cervical artery dissections: clinical, morphologic, and genetic studies. Stroke 2006;37:2924–2929.
36. Etchevers HC, Vincent C, Le Douarin NM, Couly GF. The cephalic neural crest provides pericytes and smooth muscle cells to all blood vessels of the face and forebrain. Development 2001;128:1059–1068.
37. Topouzis S, Majesky MW. Smooth muscle lineage diversity in the chick embryo. Two types of aortic smooth muscle cell differ in growth and receptor-mediated transcriptional responses to transforming growth factor-beta. Dev Biol 1996;178:430–445.

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