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# Stroke in first-degree relatives of patients with cervical artery dissection

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**Background and purpose:** Patients with ischaemic stroke (IS) caused by a spontaneous cervical artery dissection (CeAD) worry about an increased risk for stroke in their families. The occurrence of stroke in relatives of patients with CeAD and in those with ischaemic stroke attributable to other (non-CeAD) causes were compared.

**Methods:** The frequency of stroke in first-degree relatives (family history of stroke, FHS) was studied in IS patients (CeAD patients and age- and sex-matched non-CeAD patients) from the Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) database. FHS ≤ 50 and FHS > 50 were defined as having relatives who suffered stroke at the age of ≤50 or >50 years. FHS ≤ 50 and FHS > 50 were studied in CeAD and non-CeAD IS patients and related to age, sex, number of siblings, hypertension, hypercholesterolemia, smoking and body mass index (BMI).

**Results:** In all, 1225 patients were analyzed. FHS ≤ 50 was less frequent in CeAD patients (15/598 = 2.5%) than in non-CeAD IS patients (38/627 = 6.1%) ($P = 0.003$; odds ratio 0.40, 95% confidence interval 0.22–0.73), also after adjustment for age, sex and number of siblings ($P = 0.005$; odds ratio 0.42, 95% confidence interval 0.23–0.77). The frequency of FHS > 50 was similar in both study groups. Vascular risk factors did not differ between patients with positive or negative FHS ≤ 50. However, patients with FHS > 50 were more likely to have hypertension and higher BMI.

**Conclusion:** Relatives of CeAD patients had fewer strokes at a young age than relatives of non-CeAD IS stroke patients.

## Introduction

Cervical artery dissection (CeAD) is a major cause of stroke in young patients. Most CeAD events occur spontaneously in healthy subjects without known vascular risk factors [1]. Whereas dyslipidemia, smoking, arterial hypertension and obesity are frequent in

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young patients with ischaemic stroke (IS) [2,3], the prevalence of these modifiable risk factors in CeAD patients is low [4]. In CeAD patients, however, minor mechanical events (sudden movements, minor trauma or physical strain) are common [5]. The association with mild connective tissue alterations [6,7] and with rare mutations in genes associated with connective tissue disorders [8,9] points to the existence of a constitutional susceptibility for CeAD.

Outcome after CeAD is usually favorable and recurrent events are rare [10,11]. After recovery from the acute event, many CeAD patients are concerned about the risk for stroke in their families and ask for genetic counseling. However, systematic studies of stroke in families of CeAD patients are missing. In the current study of the Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) database registered stroke (ischaemic as well as hemorrhagic) in first-degree relatives of CeAD patients and in first-degree relatives of patients with IS of other (non-CeAD) etiologies were analyzed retrospectively. The aim was to test the hypothesis that stroke was more common in young relatives of CeAD patients than in those of non-CeAD patients.

## Methods

In the CADISP clinical study, consecutive patients diagnosed with CeAD, and age- and sex matched IS patients without CeAD (non-CeAD IS), were enrolled at neurology departments across 18 centers in eight countries [12]. The diagnosis of CeAD was based on widely accepted diagnostic criteria, in particular on magnetic resonance imaging findings. CeAD was defined by the presence of a mural hematoma, aneurysmal dilatation, long tapering stenosis, intimal flap, double 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). Patients with purely intracranial or iatrogenic dissections were not included. Patients with CeAD events triggered by trauma or by other mechanical trigger events were also included in the study. The non-CeAD group comprised patients with IS confirmed on brain imaging in whom CeAD had been ruled out by imaging findings. Patients were recruited both prospectively and retrospectively. Patients recruited retrospectively had their qualifying event (CeAD or non-CeAD IS) before the enrolling center joined the CADISP clinical study [12]. Their clinical data had been ascertained systematically in local databases or registries.

All CeAD and non-CeAD IS patients were interviewed using a standardized questionnaire; prospective patients had their interview soon after the event, mostly during their hospital stay, whereas for retrospective patients the same questionnaire was filled in during a separate visit. For the current study, all patients with information on the occurrence of stroke in first-degree relatives [familial history of stroke (FHS) in parents, children or siblings] were eligible. Information about FHS was retrieved during the interview. Strokes in relatives and their ages at stroke occurrence were reported by the index patients. Patients who had no contact with their first-degree relatives or were unable to give information about stroke in first-degree relatives were excluded from the analysis due to missing value of FHS. Strokes in relatives were not classified into hemorrhagic or ischaemic strokes. However, family history of CeAD was specifically documented. Relatives with stroke were dichotomized with regard to age. Positive FHS ≤ 50 was defined as having one or several first-degree relatives who suffered first-ever stroke at an age ≤50 years. FHS > 50 was defined as having one or several first-degree relatives who suffered first-ever stroke at an age >50 years.

For the index patients, the following standardized variables were used from the CADISP database [4]: age, sex, history of arterial hypertension, history of hypercholesterolemia, body mass index (BMI) and smoking (any regular current and past smoking). Hypertension was defined by a history of elevated blood pressure (systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg) diagnosed by the treating physician or use of a blood-pressure-lowering therapy. Hypercholesterolemia was defined as a fasting total cholesterol ≥6.20 mM or low-density lipoprotein cholesterol ≥4.1 mM, measured within 48 h after admission to the hospital or diagnosed by the treating physician, or use of a cholesterol-lowering therapy. BMI was calculated as the ratio of weight (kg) to the square of height ($m^2$).

For the first-degree relatives, information was available on sex and relatedness (sister, brother, mother, father, daughter, son), age at onset of stroke (reported by the index patient) and age of death of first-degree relative.

### Statistical analyses

FHS ≤ 50, FHS > 50 and the occurrence of stroke in parents with onset before or after the age of 50 (parent stroke ≤50, parent stroke >50) were compared between CeAD patients and non-CeAD patients with the chi-squared test, and for each test the odds ratio (OR) and the 95% confidence interval (CI) were calculated in a univariate logistic regression model.

In the whole study population (CeAD and non-CeAD patients) patients with a positive FHS ≤ 50, with regard to age, sex, number of siblings, arterial hypertension, hypercholesterolemia, smoking, BMI and stroke etiology (CeAD versus non-CeAD), with patients without FHS were compared. Similar comparisons were made between patients with FHS > 50 and those without any FHS. The chi-squared test was used to calculate crude *P* values. In a multivariate logistic regression model *P* values, OR and 95% CI after adjustment for sex, age and number of siblings were calculated. The SPSS version 19 (IBM Corporation, Somers, NY, USA) was used for all statistical analyses.

### Ethics

The CADISP study protocol (http://clinicaltrials.gov/ct2/show/NCT00657969) was approved by relevant local authorities in all participating centers and was conducted according to the national rules concerning ethics committee approval and informed consent.

## Results

The CADISP study sample comprised 644 CeAD IS patients and 658 patients with IS of other (non-CeAD) etiology. Two hundred and twenty-nine (38.3%) of the CeAD patients and 348 (55.5%) of the non-CeAD patients were prospectively recruited. Data about stroke in first-degree relatives was missing in 46 CeAD patients and in 31 non-CeAD patients, which includes patients without contact with their first-degree relatives or those unable to provide such information. The study population was composed of 1225 patients including 598 CeAD patients (42.8% women, 43.8 ± 10.0 years) and 627 non-CeAD patients (39.6% women, 44.3 ± 10.5 years).

Fifty-three (4.3%) patients had first-degree relatives who suffered stroke with onset at age ≤50 years (FHS ≤ 50), whereas 171 (14.0%) patients had first-degree relatives who suffered a stroke at an older age (FHS > 50). Four CeAD and five non-CeAD patients had both FHS ≤ 50 and FHS > 50. A positive FHS ≤ 50 was documented in 28 (4.3%) retrospective and 25 (4.3%) prospective patients (*P* = 1.000), a positive FHS > 50 in 97 (15.0%) retrospective and 74 (12.8%) prospective patients (*P* = 0.284). The prevalence of FHS > 50 was similar in CeAD and non-CeAD patients (Table 1; *P* = 0.218), but FHS ≤ 50 was less frequent in CeAD patients (Table 1; *P* = 0.003). The analysis of stroke in parents, separately for strokes with onset before the age of 50 years and for those that occurred in parents older than 50 years, yielded similar results: a history of stroke with onset before the age of 50 was significantly more likely in parents of non-CeAD stroke patients (*P* = 0.001), whereas stroke at an older age occurred at similar frequencies in parents of stroke patients attributable to CeAD or to other causes (*P* = 0.900).

**Table 1** Family history of stroke in young patients with stroke of different causes

| | Non-CeAD (627) | CeAD (598) | *P* (crude) | OR (95% CI) |
|---|---|---|---|---|
| FHS | 128 (20.4) | 87 (14.5) | 0.007 | 0.664 (0.49–0.90) |
| FHS ≤ 50 | 38 (6.1) | 15 (2.5)[b] | 0.003 | 0.399 (0.22–0.73) |
| FHS > 50 | 95 (15.2)[a] | 76 (12.7) | 0.218 | 0.815 (0.59–1.13) |
| Parent stroke ≤ 50 | 26 (4.2) | 4 (0.7) | 0.001 | 0.155 (0.05–0.49) |
| Parent stroke > 50 | 86 (13.7) | 75 (12.5) | 0.536 | 0.900 (0.65–1.26) |

FHS, family history of stroke, having one or more first-degree relatives with cerebral stroke of any cause; FHS ≤ 50, having one or more first-degree relatives with cerebral stroke of any cause before or at the age of 50; parent stroke ≤50, having one or both parents with cerebral stroke of any cause before or at the age of 50.
[a]Including one first-degree relative with stroke caused by CeAD.
[b]Including two first-degree relatives with stroke caused by CeAD.

Factors related to a positive FHS are analyzed in Table 2. A positive FHS ≤ 50 was less likely in CeAD patients, also after adjustment for age, sex and number of siblings (*P* = 0.004; OR 0.41, 95% CI 0.22–0.75). FHS ≤ 50 was not associated with hypercholesterolemia, smoking or BMI but showed a trend towards association with arterial hypertension (1.75, 95% CI 0.96–3.21). After adjustment for age, sex, number of siblings, arterial hypertension, hypercholesterolemia and BMI, the association between stroke etiology (CeAD versus non-CeAD) and FHS ≤ 50 remained strong (*P* = 0.006; OR 0.41, 95% CI 0.22–0.77).

In contrast, a positive FHS > 50 was independent from stroke etiology (CeAD versus non-CeAD) but more likely for patients with hypertension (*P* = 0.002) and with higher BMI (*P* = 0.005). In a logistic regression model with age, sex, number of siblings, arterial hypertension, hypercholesterolemia, BMI and stroke etiology (CeAD versus non-CeAD) as determinants, FHS > 50 was independently associated with arterial hypertension (*P* = 0.024; OR 1.57, 95% CI 1.07–2.30) and BMI (*P* = 0.034; OR 1.05, 95% CI 1.00–1.09) and showed a trend towards an inverse association with smoking (*P* = 0.056; OR 0.70, 95% CI 0.48–1.01).

## Discussion

This analysis of stroke in first-degree relatives of IS patients from the CADISP database revealed that

**Table 2** Determinants of FHS ≤ 50 and FHS > 50. Both patient groups (those with positive FHS ≤ 50 and those with positive FHS > 50) were compared with patients with negative FHS

| | Negative FHS ($n$ = 1010) | Positive FHS ≤ 50 ($n$ = 53) | $P_{crude}$ | $P_{adj}$[a] | OR[a] (95% CI)[a] | Positive FHS > 50 ($n$ = 171) | $P_{crude}$ | $P_{adj}$[a] | OR[a] (95% CI)[a] |
|---|---|---|---|---|---|---|---|---|---|
| Age (mean ± SD) | 43.1 ± 10.2 | 44.8 ± 11.3 | 0.239 | – | – | 49.7 ± 8.4 | <0.001 | – | – |
| Female sex (%) | 426 (42.2) | 26 (49.1) | 0.323 | – | – | 56 (32.7) | 0.023 | – | – |
| Siblings (mean [range]) | 2.3 [0–13] | 3.3 [0–13] | 0.003 | – | – | 2.8 (0–11) | 0.001 | – | – |
| Hypertension (%) | 273 (27.1) | 21 (39.6) | 0.058 | 0.069 | 1.75 (0.96–3.21) | 81 (47.4) | <0.001 | 0.002 | 1.78 (1.24–2.55) |
| Hypercholesterolemia | 221 (22.1) | 12 (22.6) | 1.000 | 0.775 | 0.90 (0.46–1.80) | 53 (31.4) | 0.010 | 0.212 | 1.27 (0.87–1.86) |
| Smoking (%) | 589 (58.7) | 33 (62.3) | 0.669 | 0.840 | 0.94 (0.52–1.70) | 103 (60.2) | 0.737 | 0.189 | 0.78 (0.55–1.13) |
| BMI (mean ± SD) | 24.9 ± 4.3 | 25.4 ± 4.1 | 0.420 | 0.440 | 1.03 (0.96–1.09) | 26.5 ± 4.1 | <0.001 | 0.005 | 1.06 (1.02–1.10) |
| CeAD (%) | 511 (50.6) | 15 (28.3) | 0.002 | 0.004 | 0.41 (0.22–0.75) | 76 (44.4) | 0.160 | 0.216 | 0.81 (0.57–1.14) |

BMI, body mass index; CeAD, cervical artery dissection; FHS, family history of stroke.
[a]$P$ values, odd ratios (ORs) and 95% confidence intervals (CI) adjusted for age, sex and number of siblings in a logistic regression model.

relatives of CeAD patients had fewer strokes at a young age than those of non-CeAD patients. The frequency of stroke in relatives at an older age was similar for index patients of both groups. Stroke in older relatives (FHS > 50) was associated with the vascular risk profile of the index patient (hypertension and high BMI).

These findings suggest that young family members of CeAD patients have a lower stroke risk than young family members of non-CeAD IS patients. Hypertension was reported to explain a significant part of the heritability of stroke [13–15]. In the CADISP population of young stroke patients, hypertensive patients had more relatives with stroke at an older age. Patients with a positive FHS ≤ 50 more often had hypertension than those without an FHS, but the difference was not significant.

Because of the young age of the index patients in the CADISP study, many of their siblings or children were younger than 50 years. As a consequence, both FHS ≤ 50 and FHS > 50 are underestimated. A separate analysis of stroke in parents of the index patients was therefore performed, since the vast majority of the parents were older than 50. Indeed, this analysis demonstrated the difference in FHS ≤ 50 between both study groups more clearly ($P$ = 0.001; OR 0.16, 95% CI 0.05–0.49). Again, the risk for stroke with onset at older age was similar in both groups.

Our study has several limitations.

**1** Data on presence of stroke in first-degree relatives were reported by the index patients but no direct contact was made with the affected relatives or their physicians to confirm the relatives' diagnoses. Stroke in relatives was not classified in subtypes (hemorrhagic, ischaemic). However, family history of CeAD was also reported by the index patients. Our data (Table 1) suggested that two of 15 (13%) strokes that occurred in young first-degree relatives of CeAD patients were caused by CeAD. However, CeAD as a cause of stroke in first-degree relatives may have been under-reported, in particular by index patients from the non-CeAD group.

**2** FHS was not studied in a control group of healthy relatives. It was therefore not possible to determine a baseline FHS ≤ 50, nor to test whether FHS ≤ 50 in CeAD patients is significantly increased compared with FHS ≤ 50 of age- and sex-matched healthy control subjects.

**3** Due to the young age of the index patients in this study, many siblings and almost all children were younger than 50 years, leading to an underestimation of FHS ≤ 50. In the current study an additional analysis of stroke in the parents of index patients was therefore performed, which might yield a more reliable estimate of the heritability of stroke in the CADISP study population of young patients.

**4** Although the CADISP study sample was large, the number of index patients with familial stroke was small, due to the restriction to first-degree relatives of young age (FHS ≤ 50). As a consequence, the power of our analyses was modest. Confirmation of our findings in other study samples is warranted.

**5** FHS was classified into FHS ≤ 50 and FHS > 50. The cut-off at the age of 50 years was arbitrary but in line with several other studies of 'young' stroke [16–20]. In the CADISP sample the number of relatives with onset of stroke at an even younger age (a cut-off at an age of 45 years was proposed in other studies [21,22]) was too small for a powerful analysis.

**6** To study the risk for stroke in families of CeAD patients was the main intention of this study. In our sample of non-CeAD IS patients, FHS did not differ between stroke subtypes (data not shown). Unfortunately, however, our non-CeAD sample was not large enough to analyze FHS for separate

stroke subtypes in detail. Moreover, no information was available on the subtype of the strokes in first-degree relatives.

7 Our analysis was based on the non-prospective CADISP database. Stroke in relatives of the patients was reported by the index patients. Presence or absence of stroke in relatives of the patients relied solely on the information given by the index patient. Verification of these data was not possible. There is a possibility of recall bias. However, there is no reason to assume that the extent of the recall bias would differ between CeAD and non-CeAD groups.

## Conclusion

The background of this study was mainly clinical: CeAD often occurs unexpectedly and spontaneously in healthy individuals without obvious vascular risk factors, whereas many young patients with stroke of other causes have distinct vascular risk profiles [4]. Many CeAD patients therefore believe that genetic factors play an important role in the etiology of their disease and worry about the stroke risk of their relatives. However, the findings of the current study suggest that stroke is less common in young first-degree relatives of CeAD patients than in young first-degree relatives of patients with stroke of other causes, independently from the prevalence of modifiable risk factors. Our data suggest that the familial stroke risk of CeAD patients is low compared with the familial stroke risk of patients with other stroke etiologies. Prospective and verified information studies are warranted to gain further knowledge on the risk for stroke in young relatives of CeAD patients.

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## Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

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## Appendix

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