European Journal of Neurology 2012, 19: 594–602 doi:10.1111/j.1468-1331.2011.03586.x

EUROPEAN JOURNAL OF NEUROLOGY
THE OFFICIAL JOURNAL OF THE EUROPEAN FEDERATION OF NEUROLOGICAL SOCIETIES

Gender and cervical artery dissection

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Keywords:
cervical artery dissection, gender, internal carotid artery, outcome, risk factors, stroke, vertebral artery

Received 31 August 2011
Accepted 30 September 2011

Background and purpose: To analyze previously established gender differences in cervical artery dissection (CeAD).

Methods: This case–control study is based on the CADISP (Cervical Artery Dissection and Ischemic Stroke Patients) population comprising 983 consecutive CeAD patients (mean age: 44.1 ± 9.9 years) and 658 control patients with a non-CeAD ischemic stroke (IS) (44.5 ± 10.5 years).

Results: Cervical artery dissection was more common in men (56.7% vs. 43.3%, $P < 0.001$) and men were older (46.4 vs. 41.0 years, $P < 0.001$). We assessed putative risk factors for CeAD including vascular risk factors, recent cervical trauma, pregnancies, and infections. All gender differences in the putative risk factors and outcome were similar in the CeAD and the non-CeAD IS groups.

Conclusion: Our analysis of the largest collection of CeAD patients to date confirms male predominance and differences in age at dissection between men and women. Gender differences in putative risk factors may explain the higher frequency of CeAD in men and their older age, but the putative risk factors are probably not specific for CeAD.

Introduction

Cervical artery dissection (CeAD) is one of the most frequent etiologies of ischemic stroke (IS) in young adults [1]. Clinical studies have identified several factors associated with CeAD [2,3]. We are aware of only one report in the literature focusing specifically on gender differences in CeAD [4]. That study suggested that risk factor profiles and clinical presentation of CeAD may differ in women and men, but lacked a control group.

Cervical Artery Dissections and Ischemic Stroke Patients (CADISP, http://www.CADISP.org) is the largest multicenter collection of CeAD patients published to date. CADISP included a group of age-, gender-, and country-matched non-CeAD ischemic stroke (non-CeAD IS) patients [5] allowing investigation of factors specific to CeAD *per se* distinct from IS more broadly. In this setting, we assessed gender-associated differences in CeAD patients in terms of (i) clinical presentation, (ii) vascular risk factors, (iii) other putative risk factors, and (iv) functional outcome and complication rates. We then studied their specificity by examining the same gender-associated differences in non-CeAD IS patients.

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Methods

Study population

Cervical Artery Dissection and Ischemic Stroke Patients is an international observational study focusing on risk factors and short-term outcome of CeAD and IS in young adults. The structure and methods of the CADISP study have been described in detail previously [3,5]. The aims of CADISP are to perform a genetic association

study and clinical studies on various debated topics including risk factors, clinical presentation, and outcome predictors of CeAD. In addition, a cohort of patients with an IS due to other causes than CeAD (non-CeAD IS), frequency-matched on age (by 5-year intervals), and gender, was recruited in the same centers, using the same questionnaire. All procedures were approved by ethics committees and other authorities at each participating center according to local rules.

Between 2004 and 2009, as part of a multicenter effort comprising 20 centers in nine countries, we included consecutive patients evaluated in departments of neurology with a diagnosis of CeAD or of non-CeAD IS. All but two centers also participated in the clinical part of the CADISP study, comprising altogether 983 CeAD patients and 658 patients with a non-CeAD IS, recruited in 18 centers in eight countries. Non-CeAD IS patients were classified into IS subtypes according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria [6].

Patients

Patients were recruited both retrospectively ($n = 891$) and prospectively ($n = 750$). Retrospective patients are participants who had a qualifying event before the beginning of the study or were interviewed after discharge, identified through local registries of CeAD or IS patients in each center. Over 96% of patients had a qualifying event between 1999 and 2009 (< 4% had a qualifying event before 1999). The detailed questionnaire included items related to symptoms of dissection and stroke: the National Institutes of Health Stroke Scale (NIHSS) score at admission and at discharge; imaging findings of dissection and stroke; medical history such as vascular risk factors, reported history of migraine, and traumas; ages of first-degree relatives; modified Rankin Scale (mRS) score before admission and at 3 months, complications [stroke, transient ischemic attack (TIA), CeAD, or major hemorrhage] by 3 months. For general descriptions of sites of dissections and details for multiple dissections, see Table S1. Etiologies of IS subtypes according to the TOAST criteria are shown in Table S2.

Variable definition

Definitions of the putative risk factors were standardized across sites and are displayed in Table S3.

Clinical and radiological characteristics of CeAD patients

The following radiological features at admission were recorded: arterial occlusion, stenosis, aneurysmal dilatation, and multiple dissections. Cervical pain and headache at the acute phase of CeAD, and the occurrence of tinnitus and Horner syndrome were recorded.

3-month outcome

Functional 3-month outcome was defined as good if mRS = 0–2. Major complications within 3 months included the following: stroke or TIA after admission, recurrent cervical artery dissection, intracranial hemorrhage, or major extracranial hemorrhage (i.e. leading to death, or requiring blood transfusion, surgery or hospitalization). Putative risk factors and 3-month outcome were defined identically in CeAD and non-CeAD IS patients.

Statistical analyses

The genders were first compared using chi-square or Fisher's exact for qualitative variables, and Student's *t*-test or Mann–Whitney *U* test for quantitative variables. Binary logistic regression with gender as the dependent variable, adjusted systematically for age, country of inclusion, and prospective vs. retrospective recruitment was used to assess differences within the patient groups regarding putative risk factors and clinical characteristics. Factors that displayed an association with gender with a significance level of $P < 0.10$ in univariate models were then analyzed in a multivariable logistic regression model with gender as the dependent variable and with a systematic adjustment for age, country of inclusion, and the potential effect of prospective vs. retrospective recruitment. These analyses were first performed separately in the CeAD group and the non-CeAD IS group. Then, to assess if the observed gender differences are specific for CeAD, the same analyses were run in the overall sample (CeAD + non-CeAD IS patients), adding an interaction term between the patient group and the tested variable.

To explore the association of gender with the dichotomized functional outcome (3-month mRS 0–2 vs. 3–5) and complication variables for CeAD patients, we ran the respective multivariable logistic regressions with outcome as the dependent variable, controlling systematically for the following factors: age, admission NIHSS score, occlusion, site of the dissection, country of inclusion, and prospective vs. retrospective recruitment. CeAD and non-CeAD IS groups were then compared regarding outcome and complication variables (gender*patient group – interaction), adjusting systematically for age, admission NIHSS score, country of inclusion, and prospective vs. retrospective recruitment. The latter analyses were repeated for the subgroup of CeAD patients with initial brain infarction. The analyses were performed using PASW 18.0 for

Windows software package (IBM Corporation, Armonk, NY, USA). A two-tailed value of $P < 0.05$ was considered statistically significant.

Results

Demographic features and distribution of the putative risk factors for CeAD are shown in Table 1. The majority (56.7%) of the 983 CeAD patients were men. There were no significant differences in the female:male ratios between the recruiting centers. Men with CeAD were older than women (Fig. 1).

Putative risk factors

Within the CeAD group, hypercholesterolemia and past smoking were more frequent, and BMI (body mass index) was higher in men, whereas the frequencies of current smoking and diabetes were not different between genders (Table 1). In the adjusted multivariable binary logistic regression, similar gender differences in the traditional vascular risk factors were observed for both CeAD and non-CeAD IS groups (Table S4). BMI and age were the only traditional vascular risk factors that displayed significant, but yet qualitatively similar gender differences in the groupwise comparison (Table 1). In CeAD patients, there was no gender difference in the pre-CeAD use of medical treatment for hypertension, hypercholesterolemia, and diabetes among patients having these risk factors (data not shown).

Men reported slightly more often of 'any cervical trauma within 1 month before CeAD', and this difference was more pronounced in the multivariable model (Table S4). In the CeAD group, women reported recent chiropractic manipulation of the neck more often than CeAD men, whereas lifting heavy loads was more common in CeAD men (Table 1). The same phenomena were also observed for the non-CeAD IS group, although the actual percentages were lower. Migraine was more frequent in women in both the CeAD and the non-CeAD IS groups. Numbers of preceding overall infections were similar. Non-CeAD IS women had slightly more children than CeAD women (1.6 vs. 1.4, $P = 0.022$ for T-test), but the groups did not differ in the rate of having children under 3 years of age (5.4% vs. 6.8%, $P = 0.478$).

Clinical characteristics

Headache was more common among CeAD women than CeAD men, whereas Horner syndrome, cervical pain, and tinnitus did not differ significantly between men and women in the multivariable logistic regression (Table 2). Men had internal carotid artery dissection (ICAD) more often than women, but after adjusting for age, this association was no longer significant (Table 2, Fig. 1). TIAs occurred more frequently in CeAD women than men when adjusted for possible confounders related to recruitment, but in the multivariable logistic regression, the difference was not independently associated with gender (Table 2). Ischemic strokes were equally common in both genders. Admission NIHSS score, patency of the dissected artery at diagnosis, occurrence of dissecting aneurysm, frequency of intramural hematoma, or multiple vessel dissection, did not differ by gender.

Gender and outcome

All were alive at 3 months and follow-up information was available in 940 (95.6%) patients. Table 3 presents the clinical outcome and complication rates by gender and patient group. Complications within 3 months were rare. Overall complication rates did not differ in the CeAD group, but women had more strokes within 3 months after admission than men. The frequency of TIA or hemorrhage within 3 months of admission for the qualifying event did not differ between CeAD men and women, nor did the functional outcome at 3 months in patients who sustained an IS (Table 3). In the model adjusted for age, country of inclusion, and prospective vs. retrospective recruitment, none of the outcome variables displayed a gender difference differing significantly between CeAD and non-CeAD IS patients (all P values for interaction term > 0.1) (Table 3). When the subgroup of CeAD patients with initial brain infarction were compared with non-CeAD IS patients, the gender difference in strokes during follow-up became statistically significant (CeAD men 2/352, 0.6% vs. women 11/262, 4.2%; P for CeAD vs. non-CeAD IS = 0.029). There were no significant gender differences in the frequencies of prescribed thrombolytic therapies, antiplatelet agents, or anticoagulation among CeAD patients (data not shown).

Discussion

We found that the majority of CeAD patients were men, in whom dissection occurred at an older age than in women. While gender differences in the putative risk factors may explain these findings, none of the gender differences in the putative risk factors or outcome were specific for CeAD, as similar differences were found in the non-CeAD IS group. We observed no gender differences in the frequency of multiple CeADs.

The male predominance and older age at onset are in keeping with most prior reports [4,7]. Interestingly, in a

Table 1 Characteristics of the study population

	CeAD				Non-CeAD IS		
	Men, n = 557	Women, n = 426	P-value[a]	OR (95% CI)[a]	Men, n = 401	Women, n = 257	CeAD vs. non-CeAD IS, P-value[b]
Age (years, mean ± SD)	46.4 ± 9.4	41.0 ± 9.8	< **0.001**	**1.06 (1.05–1.08)**	45.9 ± 10.2	42.3 ± 10.6	**0.014**
Hypertension	164/551 (29.8)	85/422 (20.1)	0.224	1.22 (0.89–1.68)	162/401 (40.4)	80/256 (31.3)	0.297
Hypercholesterolemia	125/546 (22.9)	57/417 (13.7)	**0.038**	**1.47 (1.02–2.12)**	128/400 (32.0)	58/253 (22.9)	0.758
Diabetes mellitus	16/551 (2.9)	5/425 (1.2)	0.153	2.18 (0.75–6.38)	43/401 (10.7)	12/256 (4.7)	0.570
Hormonal therapy in women	NA	166/422 (39.3)	NA	NA	NA	98/257 (38.1)	NA
BMI, mean ± SD	25.5 ± 3.5	23.2 ± 4.1	< **0.001**	**1.17 (1.12–1.22)**	26.5 ± 4.1	24.7 ± 5.2	**0.002**
BMI 25–30	211/521 (40.5)	59/411 (14.4)	< **0.001**	**3.99 (2.84–5.62)**	179/387 (46.3)	62/248 (25.0)	0.090
BMI > 30	43/521 (8.3)	25/411 (6.1)	**0.018**	**1.92 (1.12–3.28)**	62/387 (16.0)	33/248 (13.3)	0.548
Migraine	148/546 (27.1)	213/422 (50.5)	< **0.001**	**0.38 (0.28–0.50)**	73/398 (18.3)	106/255 (41.6)	0.429
Current smoker	157/548 (28.6)	112/423 (26.5)	0.304	1.17 (0.87–1.58)	192/400 (48.0)	115/255 (45.1)	0.965
Past smoker	150/548 (27.4)	77/423 (18.2)	**0.045**	**1.40 (1.01–1.95)**	83/400 (20.8)	40/255 (15.7)	0.326
Trauma within 1 month	226/542 (41.7)	165/423 (39.0)	0.066	1.31 (0.98–1.74)	40/398 (10.1)	30/253 (11.9)	0.336
Chiropractic maneuvers	20/542 (3.7)	49/429 (11.6)	< **0.001**	**0.36 (0.21–0.63)**	1/398 (0.3)	3/253 (1.2)	0.421
Lifting up heavy loads	66/542 (12.2)	21/423 (5.0)	< **0.001**	**2.70 (1.58–4.63)**	15/398 (3.8)	7/253 (2.8)	0.436
Previous infection	105/542 (19.4)	82/418 (19.6)	0.421	0.87 (0.62–1.22)	44/396 (11.1)	26/253 (10.3)	0.609

Values are n (%) unless otherwise indicated. All the data are not available for all of the patients; CeAD, cervical artery dissection group; non-CeAD IS, ischemic stroke without CeAD group; BMI, body mass index; SD, standard deviation; NA, not assessed; OR, odds ratio; CI, confidence interval; [a]CeAD men vs. CeAD women, univariate analysis adjusted for age, prospective vs. retrospective recruitment, and country of inclusion; [b]Logistic regression with gender as a dependent variable and age, prospective vs. retrospective recruitment country of inclusion, group and (group)*(each risk factor) as covariates. Bold font indicates statistically significant P values and ORs.

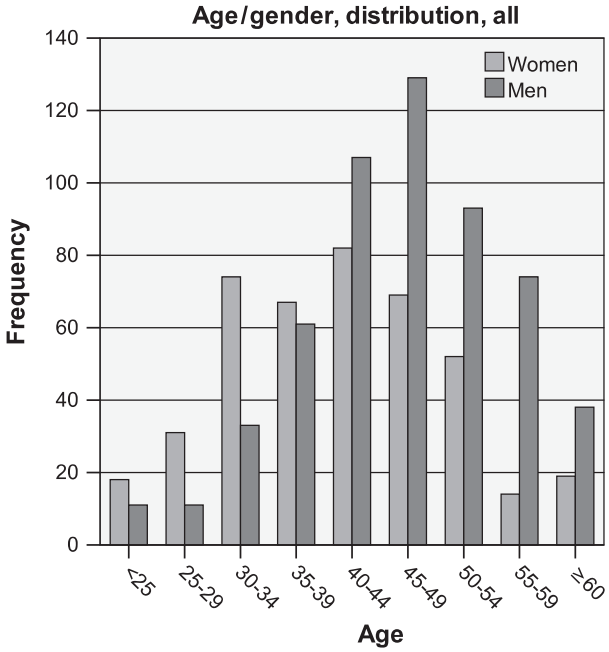

Figure 1 The frequency of cervical artery dissection as a function of gender.

Table 2 Clinical characteristics of CeAD patients

	Men, n = 557	Women, n = 426	P-value[a]	P for logistic regression[b]	OR (95% CI)[b]
ICA/VA dissection[c]	374/167 (69.1/30.9)	205/200 (60.5/39.5)	0.329	0.226	1.25 (0.87–1.81)
Occlusion	221/557 (36.1)	131/426 (30.8)	0.153	0.286	1.21 (0.85–1.72)
Dissecting aneurysm	72/557 (12.9)	52/426 (12.2)	0.763	NA	NA
Multiple dissection	77/557 (13.8)	74/426 (17.4)	0.275	NA	NA
Headache	330/538 (61.3)	310/416 (74.5)	**< 0.001**	**< 0.001**	**0.52 (0.36–0.73)**
Cervical pain	246/538 (45.7)	222/416 (53.4)	0.317	0.626	0.92 (0.66–1.29)
Horner syndrome	171/538 (31.8)	102/416 (24.5)	0.256	0.313	1.23 (0.83–1.82)
Tinnitus	28/538 (5.2)	45/416 (10.8)	**< 0.001**	0.118	0.61 (0.33–1.13)
Cerebral ischemia	425/557 (76.3)	346/426 (81.2)	0.338	NA	NA
Cerebral infarct	368/557 (66.1)	276/426 (64.8)	0.514	0.926	1.02 (0.69–1.51)
TIA	92/557 (16.5)	106/426 (24.9)	**0.006**	0.319	0.81 (0.54–1.22)
Mean (±SD) NIHSS on admission if infarction	6.44 (6.96)	5.44 (6.37)	0.089	NA	NA

Values are n (%) unless otherwise indicated. All the data are not available for all of the patients; CeAD, cervical artery dissection group; ICA, internal carotid artery; VA, vertebral artery; TIA, transient ischemic attack; NIHSS, the National Institutes of Health Stroke Scale; [a]CeAD men vs. CeAD women, adjusted for age, prospective vs. retrospective recruitment, and country of inclusion; [b]Men vs. women, all of the variables with $P < 0.1$ in univariate comparison as covariates, adjusted for age, prospective vs. retrospective recruitment and country of inclusion, and cerebral infarct for the CeAD group; [c]Both single and multiple dissections are included. Patients with CeAD in both ICA and VA are excluded. Bold font indicates statistically significant P values and ORs.

smaller population-based US cohort [8], this difference was absent. Prior studies have found gender differences in CeAD related to putative risk factors, clinical presentation, and outcome [4]. However, this is the first study to date to assess whether these differences are specific for CeAD.

We have previously shown that all traditional vascular risk factors are less frequent in CeAD patients compared with non-CeAD IS patients, whereas CeAD patients have more hypertension, less hypercholesterolemia, and less obesity/overweight than healthy controls [3]. The present data suggest that the gender differences in the risk factors for stroke in CeAD patients reflect differences between genders in general [9–11]. Arnold and co-workers [4] reported a slightly lower percentage of strokes (women 57%, men 60%) and TIAs (14% for both) for both genders. Similar to their study, we did not observe gender differences in the

Table 3 Outcome

	CeAD				Non-CeAD		
	Men, $n = 539$	Women, $n = 409$	P-value[a]	OR (95% CI)[a]	Men, $n = 355$	Women, $n = 238$	CeAD vs. non-CeAD, P-value[b]
mRS 0–2 at 3 months (%), if infarction	275/351 (78.1)	228/260 (87.0)	0.182	0.65 (0.34–1.23)	304/355 (85.6)	207/238 (87.0)	0.450
Complications[c]	27/539 (5.0)	31/409 (7.6)	0.239	0.68 (0.35–1.30)	17/354 (4.8)	11/237 (4.6)	0.471
Stroke	7/539 (1.3)	12/409 (2.9)	**0.020**	**0.23 (0.07–0.80)**	8/354 (2.3)	4/237 (1.7)	0.184
TIA	5/539 (0.9)	7/409 (1.7)	0.161	0.37 (0.09–1.49)	9/354 (2.5)	6/237 (2.5)	0.372
CeAD	13/539 (2.4)	11/409 (2.7)	0.244	1.93 (0.64–5.83)	0	0	NA
Hemorrhage	3/539 (0.6)	7/409 (1.7)	0.144	0.31 (0.07–1.49)	1/354 (0.3)	1/237 (0.4)	0.687

Values are *n* (%) unless otherwise indicated. All the data are not available for all of the patients; CeAD, cervical artery dissection group; non-CeAD IS, ischemic stroke without CeAD group; TIA, transient ischemic attack; mRS, modified Rankin Scale; NA, not assessed; [a]Logistic regression with dichotomized outcome (mRS 0–2 vs. 3–6) or each complication as a dependent variable, adjusted for age, gender, prospective vs. retrospective recruitment, the National Institutes of Health Stroke Scale score, occlusion, site of the dissection, and country of inclusion; [b]Logistic regression with dichotomized outcome (mRS 0–2 vs. 3–6) or each complication as a dependent variable and age, prospective vs. retrospective recruitment, the National Institutes of Health Stroke Scale score, country of inclusion, group, gender, and (group)*(sex) as covariates; [c]Any of the following by 3 months: stroke, TIA, recurrent CeAD, intracranial or major extracranial hemorrhage. Bold font indicates statistically significant *P* values and ORs.

number of strokes. In contrast to that study, our CeAD women had more TIAs and headache in the acute phase than CeAD men. Our observation regarding headache is in line with previous stroke studies reporting that women with ischemic stroke tend to have more 'non-traditional' symptoms than men [12]. In their series, tinnitus was similarly twice as frequent in CeAD women, but the percentages of patients suffering from it were higher (8% men, 16% women) than in our study, most probably due to their higher number of ICAD patients (men 74%, women 70%). Unlike in the study of Arnold *et al*., [4] tinnitus was not independently associated with gender in the CeAD group, and we could not confirm their previous result about multiple CeAD being more frequent in women.

A history of chiropractic manipulation of the neck was most common among CeAD women, probably reflecting the predominance of women among those seeking chiropractic care for cervical problems [13]. This finding is in keeping with chiropractic manipulation being a trigger for CeAD [14] or an epiphenomenon related to cervical pain induced by CeAD. However, our results suggest that women may not be more susceptible to CeAD by cervical manipulation than men, as the ratios of manipulated women vs. men did not differ between the CeAD and non-CeAD groups.

It is unclear whether migraine is a risk factor for CeAD or merely a bystander comorbidity. CeAD patients appear to have more migraine in both genders than healthy controls [15]. Our present results indicate that the relative frequency of women with migraine compared with men among CeAD patients is similar as that for the non-CeAD group. To our knowledge, there are no previous case–control studies about CeAD and childbirth. Our results suggest that pregnancy does not stand out as a marked risk factor for CeAD. However, this conclusion is limited by the fact that pregnancy is a predisposing factor for IS, and the non-CeAD IS group is thus not representative of the general population.

In general stroke populations, women are typically older than men and more often disabled, single and institutionalized at 3–6 months post stroke [10]. CeAD women in our study had more strokes during follow-up, but men had more ICAD which is associated with more severe strokes than vertebral artery dissection (VAD). These factors, together with the younger age and lesser overall comorbidity burden [10] of our patients, probably explain why the outcome did not differ between men and women.

There is no obvious explanation based on the risk factors for the male predominance and the later onset in men. Men had more ICAD than women, but ICAD was associated with age rather than with gender, which indicates a need for a more detailed analysis of factors

linked to age at onset. Age at onset is likely to be a surrogate marker for some predisposing factor(s) not targeted here, contributing to the observed gender pattern. The effects of hormones and pregnancies, and their interactions with genes also deserve more attention in future research. Structural and functional arterial anomalies have been reported to be more common in CeAD patients compared with controls [16–18]. For the present, CeAD can be considered a multifactorial disease, caused by weakening of or increased stress on the arterial wall [19], triggered by cervical trauma or infection [20]. Our present results support the view that the triggering factors may be partly different in men and women (e.g. heavy physical exercise vs. chiropractic manipulation).

The strengths of the CADISP-project are the large sample size and standardized collection of extensive clinical information in diverse populations. The existence of a control group is another major strength that allowed us to study whether the observed gender differences are specific for CeAD. The limitations of our study include the following [3]: Our patients were recruited primarily in tertiary academic centers, which may bias toward fewer CeAD patients with mild symptoms only. Patients with very severe strokes requiring intensive care were also less likely to be included, which may account for the surprisingly low case-fatality in the acute phase. The partly retrospective collection of patients could have biased the assessment of some risk factors. However, adjusting for retrospective vs. prospective recruitment did not modify our associations.

Clinicians should not think of CeAD patients as being different from other stroke patients in terms of gender-related precipitating factors and vascular risk factors. The trend toward more recurrent stroke among CeAD women compared with CeAD men during follow-up indicates that extra attention should be paid to their secondary prevention. Future studies could explore interactions of genetic susceptibility factors with gender, and assess whether genetic factors may contribute to some of the phenotypic differences we observed between men and women.

Our analysis of the largest collection of CeAD patients confirms male predominance and differences in age at dissection between men and women. Gender differences in putative risk factors may explain the higher frequency of CeAD in men and their older age, while the gender differences in the risk factor profiles appear to reflect differences between genders in general [9–11].

Acknowledgements

The authors thank the staff and participants of all CADISP centers for their contributions: Marja Metso, RN (collection of data and technical assistance), Department of Neurology, Helsinki University Central Hospital, Finland; Laurence Bellengier, MS (data monitoring and technical assistance), Sabrina Schilling, MS (data monitoring and technical assistance), Christian Libersa, MD, PhD (supervision of personnel), and Dominique Deplanque, MD, PhD (supervision of personnel), Centre d'Investigation Clinique, University Hospital of Lille, France; Nathalie Fievet, PhD (technical assistance), INSERM U744, Pasteur Institute, Lille, France; Jean-Christophe Corvol, MD, PhD (supervision of personnel), Sylvie Montel, MS (technical assistance), and Christine Rémy (technical assistance), Centre d'Investigation Clinique, Pitié-Salpêtrière University Hospital, Paris, France; Ana Lopes Da Cruz, PhD (technical assistance), Laboratory of Experimental Neurology, ULB, Brussels, Belgium; Annet Tiemessen, MS (technical assistance), Stroke Team, University Hospital Basel, Switzerland; Dr. Raffaele Palmirotta, MD, PhD (technical assistance), Department of Laboratory Medicine & Advanced Biotechnologies, IRCCS San Raffaele, Rome, Italy; Marie-Luise Arnold, PhD (collection of data and technical assistance), and Inge Werner, MS (technical assistance), Department of Neurology, Heidelberg University Hospital, Germany.

Disclosure of Conflict of Interest

S. Debette, A. Pezzini, C. Lichy, M. Kloss, T. Brandt, E. Touzé, A.M. Southerland, B.B. Worrall, S. Abboud, E. del Zotto, and C. Grond-Ginsbach: none. A.J. Metso has received research support from the Finnish Medical Foundation and the Alfred Kordelin Foundation. T.M. Metso has received research support from the Finnish Medical Foundation, Helsinki University Medical Foundation, Orion Farmos Research Foundation, Päivikki and Sakari Sohlberg's Foundation, Maire Taponen Foundation, the Lilly Foundation, Paavo Ilmari Ahvenainen Foundation, Aarne and Aili Turunen Foundation, Aarne Koskelo Foundation, Maud Kuistila Foundation, Emil Aaltonen Foundation, the Finnish Brain Foundation, and the Alfred Kordelin Foundation. J. Dallongeville serves on scientific advisory boards for AstraZeneca, Danone, Merck Sharp & Dohme, and sanofi-aventis; has received funding for travel and speaker honoraria from AstraZeneca and Novartis; and receives research support from AstraZeneca, Pfizer Inc, sanofi-aventis, INSERM, ANR, and CPER. P.A. Lyrer served on a scientific advisory board for Bayer Schering Pharma; serves as Co-Editor for *Neurologie und Psychiatrie*, and on the editorial board of *Swiss Archives of Neurology and Psychiatry*; and receives research support

from the Swiss National Foundation and the Swiss Heart Foundation. D. Leys serves on a scientific advisory board for Bayer Schering Pharma; served as an Associate Editor of the *Journal of Neurology, Neurosurgery and Psychiatry* and serves as an editorial board member of *Stroke and Cerebrovascular Diseases*; serves as a consultant for Allergan, Inc.; and receives research support from PHRC.S. Engelter has received funding for travel from Boehringer Ingelheim and Shire plc; serves on the editorial board of *Stroke*; and receives research support from the Käthe-Zingg-Schwichtenberg-Fonds of the Swiss Academy of Medical Sciences, the Swiss Heart Foundation, and Swiss National Funds. T. Tatlisumak serves on scientific advisory boards for Boehringer Ingelheim and Mitsubishi Tanabe Pharma Corporation; has received funding for travel from Boehringer Ingelheim; serves/has served on the editorial board of *Stroke*, *Current Vascular Pharmacology*, *The Open Pharmacology Journal*, *Clinics of Turkey*, *Clinics of Turkey/Neurology*, *The Open Cardiovascular Medicine Journal*, *Recent Patents on Biotechnology, Cerebrovascular Diseases, Recent Patents on CNS Drug Discovery*, *Experimental and Translational Stroke Medicine*, *Stroke Research and Treatment*, *BMC Journal of Experimental and Translational Stroke Medicine*, and *Frontiers in Stroke* and was founding Editor-in-chief of *Case Reports in Neurology*; has filed patents re: Stanniocalcin proteins and nucleic acids and methods based thereon, new therapeutic uses (method to prevent brain edema and reperfusion injury), and Thrombolytic compositions (method to prevent post-thrombolytic hemorrhage formation); serves as a consultant for Boehringer Ingelheim, PhotoThera, Mitsubishi Tanabe Pharma Corporation BrainsGate, Schering-Plough Corp., Lundbeck Inc., sanofi-aventis, Concentric Medical, Inc.; and receives/has received research support from Boehringer Ingelheim, the Finnish Academy of Sciences, the European Union, Biocentrum Finland, Biocentrum Helsinki, Sigrid Juselius Foundation, Liv och Hälsa, and Maire Taponen Foundation.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Sites of dissections.

Table S2. TOAST etiologies of non-CEAD IS.

Table S3. Definitions of the putative risk factors.

Table S4. Gender comparison in multivariate logistic regression.

Data S1. CADISP investigators.

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References

1. 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.
2. Debette S, Leys D. Cervical-artery dissections: predisposing factors, diagnosis, and outcome. *Lancet Neurology* 2009; **8:** 668–678.
3. Debette S, Metso TM, Pezzini A, *et al*. Do vascular risk factors matter in cervical artery dissection? *Circulation* 2011; **123:** 1537–1544.
4. Arnold M, Kappeler L, Georgiadis D, *et al*. Gender differences in spontaneous cervical artery dissection. *Neurology* 2006; **67:** 1050–1052.
5. 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.
6. Adams HJ, Bendixen B, Kappelle L, *et al*. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; **24:** 35–41.
7. 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.
8. 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.
9. Andersen KK, Andersen ZJ, Olsen TS. Age- and gender-specific prevalence of cardiovascular risk factors in 40 102 patients with first-ever ischemic stroke: a Nationwide Danish Study. *Stroke* 2010; **41:** 2768–2774.
10. Petrea RE, Beiser AS, Seshadri S, Kelly-Hayes M, Kase CS, Wolf PA. Gender Differences in Stroke Incidence and Poststroke Disability in the Framingham Heart Study. *Stroke* 2009; **40:** 1032–1037.
11. Fang MC, Singer DE, Chang Y, *et al*. Gender differences in the risk of ischemic stroke and peripheral embolism in atrial fibrillation: the AnTicoagulation and Risk factors In Atrial fibrillation (ATRIA) Study. *Circulation* 2005; **112:** 1687–1691.
12. Lisabeth LD, Brown DL, Hughes R, Majersik JJ, Morgenstern LB. Acute stroke symptoms. *Stroke* 2009; **40:** 2031–2036.
13. Waalen DP, Waale JK. Differences by gender in the incidence of cervical and lumbar complaints of chiropractic patients at the Canadian Memorial Chiropractic College. *J Can Chiropr Assoc* 1993; **37:** 145–150.
14. Lee KP, Carlini WG, McCormick GF, Albers GW. Neurologic complications following chiropractic manipulation: a survey of California neurologists. *Neurology* 1995; **45:** 1213–1215.
15. Artto V, Metso TM, Metso AJ, *et al*. Migraine with aura is a risk factor for cervical artery dissection: a case-control study. *Cerebrovasc Dis* 2010; **30:** 36–40.

16. Brandt T, Hausser I, Örberk E, *et al*. Ultrastructural connective tissue abnormalities in patients with spontaneous cervicocerebral artery dissections. *Ann Neurol* 1998; **44:** 281–285.
17. Brandt T, Orberk E, Weber R, *et al*. Pathogenesis of cervical artery dissections: association with connective tissue abnormalities. *Neurology* 2001; **57:** 24–30.
18. Schievink W, Michels V, Piepgras D. Neurovascular manifestations of heritable connective tissue disorders. A review. *Stroke* 1994; **25:** 889–903.
19. Brandt T, Grond-Ginsbach C. Spontaneous cervical artery dissection: from risk factors toward pathogenesis. *Stroke* 2002; **33:** 657–658.
20. Saver JL, Easton JD. Dissections and trauma of cervicocerebral arteries. In: Barnett HJM, Mohr JP, Stein BM, Yatsu FM, eds. *Stroke: Pathophysiology, Diagnosis, and Management*. Churchill Livingstone: New York, 1998: 769–786.