

Association of Vascular Risk Factors With Cervical Artery Dissection and Ischemic Stroke in Young Adults

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Background—Little is known about the risk factors for cervical artery dissection (CEAD), a major cause of ischemic stroke (IS) in young adults. Hypertension, diabetes mellitus, smoking, hypercholesterolemia, and obesity are important risk factors for IS. However, their specific role in CEAD is poorly investigated. Our aim was to compare the prevalence of vascular risk factors in CEAD patients versus referents and patients who suffered an IS of a cause other than CEAD (non-CEAD IS) in the multicenter Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) study.

Methods and Results—The study sample comprised 690 CEAD patients (mean age, 44.2 ± 9.9 years; 43.9% women), 556 patients with a non-CEAD IS (44.7 ± 10.5 years; 39.9% women), and 1170 referents (45.9 ± 8.1 years; 44.1% women). We compared the prevalence of hypertension, diabetes mellitus, hypercholesterolemia, smoking, and obesity (body mass index ≥ 30 kg/m²) or overweightness (body mass index ≥ 25 kg/m² and < 30 kg/m²) between the 3 groups using a multinomial logistic regression adjusted for country of inclusion, age, and gender. Compared with referents, CEAD patients had a lower prevalence of hypercholesterolemia (odds ratio 0.55; 95% confidence interval, 0.42 to 0.71; $P < 0.0001$), obesity (odds ratio 0.37; 95% confidence interval, 0.26 to 0.52; $P < 0.0001$), and overweightness (odds ratio 0.70; 95% confidence interval, 0.57 to 0.88; $P = 0.002$) but were more frequently hypertensive (odds ratio 1.67; 95% confidence interval, 1.32 to 2.1; $P < 0.0001$). All vascular risk factors were less frequent in CEAD patients compared with young patients with a non-CEAD IS. The latter were more frequently hypertensive, diabetic, and current smokers compared with referents.

Conclusion—These results, from the largest series to date, suggest that hypertension, although less prevalent than in patients with a non-CEAD IS, could be a risk factor of CEAD, whereas hypercholesterolemia, obesity, and overweightness are inversely associated with CEAD. (*Circulation*. 2011;123:1537-1544.)

Key Words: stroke ■ dissection ■ hypercholesterolemia ■ hypertension ■ obesity

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The online-only Data Supplement is available with this article at <http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.110.000125/DC1>. The Appendix lists the groups and individuals participating in CADISP.

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Little is known about the risk factors of cervical artery dissection (CEAD),^{1,2} one of the major causes of ischemic stroke (IS) in young adults.³ Hypertension, diabetes mellitus, smoking, hypercholesterolemia, and obesity are important risk factors for vascular disease, increasing the incidence of IS, myocardial infarction, and critical limb ischemia.^{4–7} However, their specific impact on the occurrence of CEAD is poorly understood. Indeed, although the relationship of CEAD with vascular risk factors has been investigated in the past, studies were performed in small cohorts,^{8–19} and only 2 studies were specifically designed to assess this relationship.^{16,19} A few studies reported a lower prevalence of vascular risk factors in CEAD patients compared with young patients with an IS of a cause other than CEAD (non-CEAD IS),^{8–10} whereas others did not observe any significant association.^{11–14} Studies including referents are scarce^{15–17,19} and yielded contradictory results: 1 study found no association¹⁷; another observed a lower body mass index (BMI)¹⁹; and 2 other studies found an increased prevalence of hypertension in CEAD patients compared with referents.^{15,16}

Clinical Perspective on p 1544

The aim of the present analysis was to compare the prevalence of vascular risk factors in CEAD patients and in both young patients with a non-CEAD IS and referents in the setting of the multicenter Cervical Artery Dissection and Ischemic Stroke Patients (CADISP) study, comprising the largest collection of CEAD patients to date.

Methods

Study Population

The structure and methods of the CADISP study have been described previously.²⁰ Between 2004 and 2009, across 20 centers in 9 countries, we included consecutive patients evaluated in a neurology department with a diagnosis of CEAD or non-CEAD IS and referents. The study protocol was approved by relevant local authorities in all participating centers and was conducted according to the national rules concerning ethics committee approval and informed consents.²⁰

Patients

Patients were recruited both prospectively and retrospectively. Retrospective patients had a qualifying event before the beginning of the study in each center and were identified through local registries of CEAD patients. The vast majority of patients had a qualifying event between 1999 and 2009 (<4% had a qualifying event before 1999). Patients in the CEAD and non-CEAD IS groups were recruited in the same centers; non-CEAD IS patients were frequency matched on age (by 5-year intervals) and gender with CEAD patients. The primary aim of the CADISP consortium was to perform a genetic association study to identify genetic susceptibility factors of CEAD.²⁰ All but 2 centers also participated in a clinical study including detailed screening of putative environmental risk factors and clinical and radiological characteristics using a standardized questionnaire. The CADISP clinical study comprises 983 CEAD and 658 non-CEAD IS patients recruited in 18 centers from 8 countries (Argentina, Belgium, Finland, France, Germany, Italy, Switzerland, and Turkey; Figure I in the online-only Data Supplement). Of these, 293 CEAD and 102 non-CEAD IS patients from Germany, Switzerland, Argentina, and Turkey were excluded because country-, gender-, and age-matched referents with detailed vascular risk factor data were not available (Figure II in the online-only Data Supplement). Thus, the present study comprises 690 CEAD and 556 non-CEAD IS patients from Belgium, Italy, Finland, and France. Detailed inclusion criteria are available online (Figure III in the online-only Data

Supplement). Briefly, CEAD patients 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 dilatation or a long tapering stenosis after recanalization in a cervical artery (internal carotid or vertebral); purely intracranial or iatrogenic dissections were not included. The non-CEAD IS group comprised patients with a recent IS confirmed on brain imaging in whom magnetic resonance or computed tomography angiography performed within 7 days after the IS ruled out CEAD; patients with iatrogenic IS, cardiopathies at very high embolic risk, arterial vasospasm after subarachnoid hemorrhage, or autoimmune or monogenic disease possibly explaining the IS were not included.

Referents

Referents were drawn randomly from existing population-based surveys for France, Belgium, and Italy (MONitoring NationaL du rISque Artériel [MONA-LISA]-Lille study for northern France and Belgium, n=383; MONA-LISA-Strasbourg study for central-eastern France, n=309; and Vobarno study for northern Italy, n=209). These studies had recruited participants from geographical regions similar to those of the cases and ascertained vascular risk factor exposure during a similar time period (2005 to 2007 for MONA-LISA and 2004 to 2006 for Vobarno). MONA-LISA study participants were randomly recruited from electoral rolls after stratification on gender, 10-year age group, and town size in the urban community of Lille and the district of Bas-Rhin (Strasbourg area).²¹ Vobarno study participants were randomly selected from the electoral rolls of Vobarno (Sabbia Valley, Brescia).²² Finnish referents (n=269) were recruited prospectively within the Helsinki area as part of the CADISP project; most of them (n=233) were recruited randomly with the help of the Finnish Population Register Center; the rest were spouses of CADISP patients (n=17) and unrelated friends or hospital staff (n=19). Referents were frequency matched on age (5-year intervals) and gender with CEAD patients. In Finland and Italy, only referents without a history of vascular disease (peripheral artery disease, stroke, or myocardial infarction) were included.

Variable Definitions

Hypertension was defined 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. Because blood pressure is modified at the acute phase of vascular events, blood pressure levels during the hospital stay were not taken into account. Hypercholesterolemia was defined as a fasting 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 use of a cholesterol-lowering therapy. Because cholesterol levels were not measured in Finnish referents, we did not include the Finnish sample in analyses involving hypercholesterolemia. Diabetes mellitus was defined as a history of diabetes mellitus diagnosed by the treating physician with a fasting glucose >7 mmol/L or use of an antidiabetic therapy. Smokers were categorized on the basis of current smoking status. Body mass index was calculated as the ratio of weight (kg) to the square of height (m^2). Weight and height were reported for CADISP patients (at the date of the qualifying event) and Finnish referents and measured for referents from the MONA-LISA and Vobarno studies. Overweight was defined as BMI ≥ 25 kg/ m^2 and <30 kg/ m^2 and obesity as BMI ≥ 30 kg/ m^2 . Patients with a non-CEAD IS were classified into IS subtypes according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.^{23,24}

Statistical Analyses

We compared the prevalence of hypertension, diabetes mellitus, hypercholesterolemia, past and current smoking, and obesity/overweightness and the mean BMI between the following groups: CEAD patients versus referents, non-CEAD IS patients versus referents, and CEAD versus non-CEAD IS patients. We used a multinomial logistic regression (generalized logit model) adjusting for country of inclusion, age, and gender to test the association between outcome variable (3

Table 1. Clinical Characteristics

	All	France/Belgium	Finland	Italy
CEAD patients				
n	690	353	175	162
Age (mean±SD), y	44.2±9.9	43.8±9.0	45.1±10.0	44.3±10.8
Women, n (%)	303 (43.9)	168 (47.6)	64 (36.6)	71 (43.8)
Carotid dissection, n (%)	446 (64.7)	240 (68.0)	96 (54.9)	110 (68.3)
Cerebral ischemia, n (%)	541 (78.4)	287 (81.3)	128 (73.1)	126 (77.8)
Cerebral infarct, n (%)	454 (65.8)	228 (64.6)	108 (61.7)	118 (72.8)
Non-CEAD IS patients				
n	556	254	168	134
Age, y	44.7±10.5	45.1±9.4	46.1±12.0	42.3±10.2
Women, n (%)	222 (39.9)	103 (40.5)	62 (36.9)	57 (42.5)
TOAST subtype, n (%)				
Large-artery atherosclerosis	75 (13.5)	27 (10.6)	20 (11.9)	28 (20.9)
Cardioembolic	205 (36.9)	115 (45.3)	55 (32.7)	35 (26.1)
Small-vessel disease	41 (7.4)	13 (5.1)	13 (7.8)	15 (11.2)
Other determined cause	9 (1.6)	3 (1.2)	1 (0.6)	5 (3.7)
Undetermined cause	226 (40.6)	96 (37.8)	79 (47.0)	51 (38.1)
Referents				
n	1170	692	269	209
Age, y	45.9±8.1	45.8±7.1	45.9±10.5	46.1±7.9
Women, n (%)	516 (44.1)	330 (47.8)	104 (38.7)	82 (39.1)

CEAD indicates cervical artery dissection; IS, ischemic stroke; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.²³

levels: CEAD, non-CEAD IS, and referent) and each vascular risk factor. We compared the association between CEAD and each vascular risk factor across countries by adding an interaction term with country and running analyses stratified on the country of inclusion.

In a secondary analysis, we included all vascular risk factors in the same multinomial logistic regression (except BMI, which is redundant with obesity/overweightness). We also ran a stepwise logistic regression with country of inclusion, age, and gender forced in and *P*=0.10 as a significance threshold for entering into and staying in the model. We tested whether associations with CEAD were maintained in the following CEAD subgroups: internal carotid or vertebral artery dissection (patients with both were excluded from this secondary analysis), presence or absence of cerebral ischemia, and retrospective or prospective recruitment. We used a multinomial logistic regression comparing CEAD subgroups with all referents; heterogeneity between odds ratios for different CEAD subgroups was assessed with logistic regression analysis restricted to CEAD patients (case-only analysis) with the CEAD characteristic as the outcome variable. Using a similar strategy, we also tested whether associations with non-CEAD IS were similar to those for IS resulting from classic causes (large-artery atherosclerosis, small-vessel disease, or cardioembolism) and IS resulting from other determined causes or of undetermined cause. Because few referents <35 years of age were available, resulting in a slight age imbalance between cases and referents, sensitivity analyses restricted to individuals >35 years of age were performed. Finally, the linearity of the inverse association between BMI and CEAD was assessed by comparing the log-likelihood of a model with BMI quintiles to the log-likelihood of a model in which BMI was replaced by the median value of the corresponding quintile using a 3-*df* χ^2 test. All analyses were performed with Statistical Analyses System software version 9.2 (SAS Institute, Cary, NC).

Results

Clinical characteristics of the study population are shown in Table 1. The majority of CEAD patients had suffered an internal carotid artery dissection, and more than three quarters

of CEAD patients sustained a cerebral ischemia as a consequence of the dissection. In the non-CEAD IS group, most ISs were cardioembolic or of undetermined origin.

Age, gender, and vascular risk factor distributions in each group, overall and by country, are given in Table 2. CEAD and non-CEAD IS patients were slightly younger than referents (*P*<0.0001 and *P*=0.02 respectively). Except for 2 CEAD patients who were siblings, all participants were unrelated. One CEAD patient had biologically confirmed vascular Ehlers-Danlos syndrome.

CEAD Patients Versus Referents

Hypertension was significantly more frequent in CEAD patients compared with referents (Table 3). Hypercholester-

Table 2. Prevalence of Vascular Risk Factors

	CEAD	Non-CEAD IS	Referent
n	690	556	1170
Age (mean±SD), y	44.2±9.9	44.7±10.5	45.9±8.1
Women, n (%)	303 (43.9)	222 (39.9)	516 (44.1)
Hypertension, n (%)	174 (25.3)	206 (37.0)	220 (18.8)
Diabetes mellitus, n (%)	13 (1.9)	49 (8.8)	44 (3.8)
Current smoking, n (%)	207 (30.0)	263 (47.3)	302 (25.8)
Hypercholesterolemia, n (%)	130 (19.0)	164 (29.5)	339 (29.0)
Obese, n (%)	49 (7.3)	84 (15.4)	192 (16.4)
Overweight, n (%)	209 (31.0)	208 (38.0)	408 (34.9)
BMI, kg/m ²	24.5±2.9	25.8±4.6	25.9±4.6
History of vascular disease, n (%)	275 (39.9)	93 (16.7)	12 (1.0)

CEAD indicates cervical artery dissection; IS, ischemic stroke; and BMI, body mass index.

Table 3. Comparison of Vascular Risk Factor Prevalence Between Cervical Artery Dissection Patients, Referents, and Non-Cervical Artery Dissection Ischemic Stroke Patients

	CEAD Patients vs Referents			Non-CEAD IS Patients vs Referents			CEAD Patients vs Non-CEAD IS Patients			Global P‡
	OR (95% CI)*	P	P†	OR (95% CI)*	P	P†	OR (95% CI)*	P	P†	
Hypertension§	1.67 (1.32–2.12)	<0.0001	0.0001	2.89 (2.27–3.68)	<0.0001	<0.0001	0.58 (0.45–0.75)	<0.0001	0.004	<0.0001
Diabetes mellitus	0.54 (0.29–1.02)	0.06	0.62	2.65 (1.72–4.08)	<0.0001	0.01	0.20 (0.11–0.38)	<0.0001	0.11	<0.0001
Current smoking	1.22 (0.99–1.50)	0.07	0.58	2.53 (2.04–3.14)	<0.0001	<0.0001	0.48 (0.38–0.61)	<0.0001	<0.0001	<0.0001
Hypercholesterolemia	0.55 (0.42–0.71)	<0.0001	<0.0001	1.12 (0.86–1.46)	0.40	0.42	0.49 (0.36–0.67)	<0.0001	0.0006	<0.0001
Obesity	0.37 (0.26–0.52)	<0.0001	<0.0001	1.03 (0.76–1.40)	0.84	0.10	0.36 (0.24–0.53)	<0.0001	0.005	<0.0001
Overweight	0.70 (0.57–0.88)	0.002	0.001	1.13 (0.89–1.43)	0.30	0.47	0.62 (0.48–0.81)	0.0003	0.04	<0.0001
BMI	0.92 (0.90–0.95)	<0.0001	...	0.99 (0.97–1.02)	0.65	...	0.93 (0.90–0.95)	<0.0001	...	<0.0001

CEAD indicates cervical artery dissection; IS, ischemic stroke; OR, odds ratio; CI, confidence interval; and BMI, body mass index.

*Multinomial logistic regression adjusted for age, gender, and country of inclusion.

†Adjusted for all risk factors (except BMI), age, gender, and country of inclusion.

‡P for difference between the 3 groups.

§In total, 13.1% of CEAD patients, 22.7% of non-CEAD IS patients and 11.4% of referents were on antihypertensive treatment ($P=0.02$ for CEAD versus referents, $P<0.0001$ for CEAD versus non-CEAD IS, and $P<0.0001$ for non-CEAD IS versus referents in multinomial logistic regression adjusted for country, age, and gender; global $P<0.0001$).

||Per 1-kg/m² increase.

olemia, obesity, and overweightness were significantly less frequent in CEAD patients, with a graded inverse effect of obesity and overweightness. Increasing BMI was associated with a reduced risk of CEAD, and this effect was linear ($P=0.89$ for test of nonlinearity). These results were similar across countries (Table 4), although the magnitude of associations with hypertension and hypercholesterolemia differed significantly between countries.

When all risk factors were included in the same model, there was still a significant positive association of hypertension with CEAD and an inverse association of hypercholesterolemia and obesity/overweightness with CEAD (Table 3). In a stepwise logistic regression with age, gender, and country of inclusion forced in, hypertension, hypercholesterolemia, and obesity/overweightness were the variables retained in the final model (Table I in the online-only Data Supplement). In a secondary analysis, we observed an inverse association with CEAD for both total cholesterol (odds ratio=0.51; 95% confidence interval, 0.44 to 0.59; $P<0.0001$ per 1-mmol/L increase) and low-density lipoprotein cholesterol levels (odds ratio 0.51; 95% confidence interval, 0.42 to 0.62; $P<0.0001$ per 1-mmol/L increase).

The associations of vascular risk factors with CEAD were substantially unchanged when stratifying on dissection site (carotid versus vertebral) and on the presence or absence of cerebral ischemia (Table 5). Results were similar for patients included retrospectively or prospectively and after exclusion of participants <35 years of age (Table II in the online-only Data Supplement).

CEAD Patients Versus Non-CEAD IS Patients

Compared with non-CEAD IS patients, CEAD patients had a significantly lower prevalence of hypertension, diabetes mellitus, current smoking, hypercholesterolemia, and obesity/overweightness and a significantly lower BMI (Table 3). Results were unchanged when all risk factors were included in the same regression (Table 3). Associations were similar across countries except for variability in effect size for hypertension, current smoking, and hypercholesterolemia (Table III in the online-only Data Supplement). Results were also unchanged when the comparison was restricted to CEAD patients with an IS ($n=454$) versus non-CEAD IS patients (Table IV in the online-only Data Supplement).

Table 4. Association of Vascular Risk Factors With Cervical Artery Dissection by Country of Inclusion

	France/Belgium		Finland		Italy		P for Interaction
	OR (95% CI)*	P	OR (95% CI)*	P	OR (95% CI)*	P	
Hypertension	1.18 (0.84–1.66)	0.34	2.06 (1.33–3.20)	0.001	3.21 (1.82–5.65)	<0.0001	0.003
Diabetes mellitus	0.76 (0.32–1.83)	0.54	0.08 (0.01–0.62)	0.01	1.45 (0.41–5.13)	0.57	0.08
Current smoking	0.91 (0.67–1.22)	0.51	1.92 (1.26–2.92)	0.002	1.34 (0.86–2.10)	0.20	0.01
Hypercholesterolemia	0.73 (0.53–1.01)	0.05	NA		0.29 (0.18–0.47)	<0.0001	0.002
Obesity	0.40 (0.25–0.63)	<0.0001	0.37 (0.19–0.70)	0.003	0.34 (0.15–0.81)	0.01	0.43
Overweight	0.69 (0.50–0.93)	0.01	0.94 (0.61–1.46)	0.80	0.58 (0.36–0.93)	0.02	
BMI†	0.92 (0.89–0.95)	<0.0001	0.95 (0.90–0.99)	0.02	0.91 (0.85–0.96)	0.002	0.33

OR indicates odds ratio; CI, confidence interval; BMI, body mass index.

*Multinomial logistic regression comparing cervical artery dissection (CEAD) patients with referents adjusted for age, gender, and country of inclusion (comparisons of CEAD versus non-CEAD ischemic stroke [IS] patients and of non-CEAD IS patients versus referents are shown in Tables III and V in the online-only Data Supplement).

†Per 1-kg/m² increase.

Table 5. Association of Vascular Risk Factors With Different Subgroups of Cervical Artery Dissection

	OR (95% CI)*	P		OR (95% CI)*	P	P for Heterogeneity†
Carotid artery dissection (n=416)			Vertebral artery dissection (n = 243)			
Hypertension	1.56 (1.19–2.05)	0.001	Hypertension	1.73 (1.21–2.46)	0.002	0.99
Diabetes mellitus	0.30 (0.12–0.75)	0.01	Diabetes mellitus	0.94 (0.39–2.28)	0.90	0.04
Current smoking	1.17 (0.91–1.51)	0.21	Current smoking	1.39 (1.02–1.89)	0.03	0.55
Hypercholesterolemia‡	0.57 (0.42–0.78)	0.0003	Hypercholesterolemia‡	0.48 (0.30–0.77)	0.002	0.64
Obesity	0.38 (0.25–0.57)	<0.0001	Obesity	0.33 (0.18–0.59)	0.0002	0.66
Overweight	0.69 (0.53–0.89)	0.004	Overweight	0.77 (0.55–1.07)	0.11	
BMI§	0.92 (0.89–0.94)	<0.0001	BMI§	0.93 (0.90–0.97)	0.0003	0.73
CEAD with cerebral ischemia (n = 541)			CEAD without cerebral ischemia (n=149)			
Hypertension	1.45 (1.12–1.88)	0.005	Hypertension	2.37 (1.61–3.48)	<0.0001	0.02
Diabetes mellitus	0.54 (0.27–1.10)	0.09	Diabetes mellitus	0.51 (0.15–1.67)	0.25	0.93
Current smoking	1.27 (1.01–1.59)	0.04	Current smoking	0.98 (0.66–1.45)	0.92	0.17
Hypercholesterolemia‡	0.53 (0.39–0.71)	<0.0001	Hypercholesterolemia‡	0.59 (0.35–0.97)	0.04	0.81
Obesity	0.33 (0.22–0.49)	<0.0001	Obesity	0.52 (0.28–0.94)	0.03	0.42
Overweight	0.69 (0.54–0.87)	0.002	Overweight	0.79 (0.53–1.18)	0.25	
BMI§	0.91 (0.89–0.94)	<0.0001	BMI§	0.95 (0.91–0.99)	0.03	0.11

OR indicates odds ratio; CI, confidence interval; BMI, body mass index; and CEAD, cervical artery dissection.

*Multinomial logistic regression comparing subgroups of CEAD patients with all referents adjusted for age, gender, and country of inclusion.

‡Assessed with logistic regression restricted to CEAD patients with the CEAD characteristic as the outcome variable.

‡n=323 for carotid artery dissection, n=164 for vertebral artery dissection, n=413 for CEAD with cerebral ischemia, and n=102 for CEAD without cerebral ischemia.

§Per 1-kg/m² increase.

Non-CEAD IS Patients Versus Referents

Hypertension, diabetes mellitus, and current smoking were significantly more frequent in non-CEAD IS patients compared with referents (Table 3). Similar results were observed when all risk factors were included in the same model (Table 3). The associations with hypertension, diabetes mellitus, and current smoking were homogeneous across countries (Table V in the online-only Data Supplement). Associations also did not differ between patients with an IS of classic origin (large-artery atherosclerosis, small-vessel disease, and cardioembolism) and patients with an IS of another determined cause or undetermined origin (Table VI in the online-only Data Supplement).

Discussion

Compared with country-, gender-, and age-matched referents, CEAD patients were more frequently hypertensive and had a lower prevalence of hypercholesterolemia, obesity, and overweightness. These associations were similar for internal carotid and vertebral artery dissections and in CEAD patients with or without cerebral ischemia. All vascular risk factors were less frequent in CEAD patients compared with country-, gender-, and age-matched patients with a non-CEAD IS. Young patients with a non-CEAD IS were more often hypertensive, diabetic, and current smokers compared with referents.

In the Context of the Current Literature

Although hypertension is usually considered one of the major risk factors for aortic dissection,^{25,26} its association with CEAD is controversial. Two studies described an increased prevalence of hypertension in CEAD patients^{15,16} (restricted to CEAD patients with cerebral ischemia in 1 study,¹⁶ which partly overlaps with our Italian subsample), whereas 2 other studies

reported no association.^{17,19} In the present sample, we found a significantly higher frequency of hypertension in CEAD patients compared with referents, regardless of the presence or absence of cerebral ischemia. Although a lower prevalence of hypercholesterolemia has been described in CEAD patients compared with non-CEAD IS patients,¹⁰ to the best of our knowledge, no such association has been reported in comparison with referents. The lower mean BMI and lower prevalence of obesity and overweightness in CEAD patients compared with referents are in agreement with recently published results from an independent French group for 239 patients and 516 referents.¹⁹ The lower prevalence of vascular risk factors in CEAD patients compared with young non-CEAD IS patients is in line with previous publications.^{8–10} Although the association of vascular risk factors with IS risk is well established in older individuals, few data are available in young adults.²⁷ We found that, as in older individuals, hypertension, diabetes mellitus, and current smoking were significantly more frequent in young non-CEAD IS patients compared with referents regardless of IS subtype.

Underlying Mechanisms

As for dissection in other arteries, CEAD probably results from multiple coexisting pathological processes, leading to a weakening of or increased stress on the arterial wall.²⁶ From earlier observations that structural and functional arterial anomalies are more frequent in CEAD patients than in referents,^{14,28–31} it has been postulated that CEAD patients could have a constitutional weakness of the vessel wall, on top of which acute events such as minor cervical trauma or infection could act as triggers.¹ Elevated blood pressure could contribute to CEAD risk by increasing carotid stiffness³²; alternatively, CEAD patients could have a constitutionally elevated arterial stiffness,³¹ leading to an

increase in systolic pressure. The inverse association of CEAD with hypercholesterolemia and BMI, as well as the young age of occurrence of CEAD, are in contrast to aortic dissection, which is most commonly associated with old age and atherosclerosis.²⁶ Although we did not screen specifically for atherosclerotic lesions, the vascular risk factor profile of CEAD patients suggests that atherosclerosis is probably not a predisposing condition to CEAD. Recently, an increase in wall material stiffness with a heterogeneous echostructure was described in CEAD patients.³¹ With aging and arteriosclerosis, the echostructure becomes more homogeneous, with an increase in collagen and elastin cross-links, making it less prone to dissection.³¹ This process could be accelerated in individuals with hypercholesterolemia and elevated BMI, analogous to diabetes mellitus, which is associated with an increased synthesis and reduced degradation of the extracellular matrix,³³ an increased number of covalent cross-links between proteins,³⁴ and a reduced incidence of abdominal aortic aneurysms.³⁵ One could also speculate that lean persons, with less adipose tissue protecting the arteries from minor cervical traumas, might be more prone to developing CEAD as a result of increased vulnerability to such traumas. Low cholesterol and BMI could also be mere confounders reflecting a common underlying genetic disorder or susceptibility factor. Patients with inherited connective tissue disorders such as Marfan syndrome tend to be taller and have a lower BMI than referents.³⁶ Although Marfan syndrome itself seems to be only marginally associated with CEAD, there is some evidence that other connective tissue disorders, and possibly other genetic susceptibility factors in connective tissue genes, may be important predisposing conditions to CEAD.^{37–40}

Strengths and Limitations

The main strengths of this study are the large sample size and the comparison to both referents and age-matched non-CEAD IS patients. Despite being one of the main causes of IS in young adults, CEAD is rare in the general population (incidence, 2.6/100 000 per year)⁴¹; thus, only an international multicenter effort could achieve a sufficiently large sample size for this analysis. The coherence of associations in different patient subgroups and countries strengthens our findings. CEAD and non-CEAD IS patients were recruited in the same centers according to a unique protocol, thus allowing optimal comparisons. We were limited by the heterogeneity in recruitment methods and risk factor evaluation for referents across countries; on the other hand, this heterogeneity enabled us to test the robustness of our findings. For Italy and Finland, the fact that referents were selected to be free of vascular disease may have inflated the association of CEAD and non-CEAD IS with vascular risk factors, but this is unlikely to have affected our results substantially because the prevalence of vascular disease is very low in this age category in the general population. In the Finnish sample, some of the associations, especially with BMI and obesity/overweightness, may have been weakened by assortative mating, but this effect should be marginal because only 6% of Finnish referents were spouses of patients. The imbalance in the proportion of participants <35 years of age between patients and referents in the French-Belgian and Italian samples could have artificially inflated the inverse associa-

tions of hypercholesterolemia and obesity/overweightness with CEAD. However, these associations were still significant after the exclusion of all individuals <35 years of age. Another limitation is that weight and height were measured in French-Belgian and Italian referents, whereas reported values were used for the other groups; reported weight tends to be an underestimation of the true measure, which could artificially inflate the inverse association of BMI with CEAD. We also cannot formally exclude nonrandom misclassification of hypertension history if the number of individuals with less prior access to care and therefore less opportunity for diagnosis of hypertension differed between groups. Our study sample is not perfectly representative of the general population. Patients in the CEAD and non-CEAD IS groups were recruited through neurology departments, often in tertiary centers, which are biased toward more complicated cases and rare causes. Persons with CEAD causing only local signs or minor strokes, which may be underdiagnosed, and CEAD patients with very severe strokes requiring intensive care were less likely to be included. Referents recruited through health surveys and epidemiological studies generally have fewer risk factors and less disease than persons who do not participate.⁴² Finally, we did not correct for multiple comparisons, but given the strength of the associations and the homogeneity of findings across countries and subgroups, false-positive associations seem unlikely.

Implications

Our findings, if confirmed in independent data sets, could improve the understanding of the mechanisms underlying CEAD, a major cause of IS in young adults, in whom the impact of stroke-related disability is particularly dramatic from a personal and socioeconomic point of view. Hypertension was associated with CEAD, but the relationship seems weaker than with IS resulting from other causes in young adults of the same age. Further studies testing whether hypertension is also associated with an increased risk of CEAD recurrence could be important for preventive purposes. These studies should include long-term follow-up of consecutive CEAD patients and ascertainment of hypertension on the basis both of history before the dissection and on blood pressure measurements at a distance of the vascular event. The inverse association of CEAD with hypercholesterolemia could have implications in terms of secondary stroke prevention, because statins are commonly prescribed after an IS, including in CEAD patients in some instances. In addition to validating these associations, future studies could include a simultaneous assessment of the carotid wall structure and genetic susceptibility factors of hypertension, obesity, and hypercholesterolemia to explore the underlying mechanisms.

Conclusions

The vascular risk factor profile of CEAD patients differs from referents and young adults with a non-CEAD IS. Hypertension was associated with an increased risk of CEAD, whereas an inverse association with hypercholesterolemia, obesity, and overweightness was observed.

Appendix

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CLINICAL PERSPECTIVE

Cervical artery dissection (CEAD), although rare in the general population, is a major cause of ischemic stroke (IS) in young adults. Little is known about its risk factors. Our aim was to compare the prevalence of vascular risk factors (hypertension, diabetes mellitus, hypercholesterolemia, current smoking, overweightness, and obesity) in CEAD patients versus referents and patients with IS of a cause other than CEAD (non-CEAD IS) in a multicenter setting. Compared with country-, gender-, and age-matched referents, CEAD patients were more frequently hypertensive and had a lower prevalence of hypercholesterolemia, obesity, and overweightness. All vascular risk factors were less frequent in CEAD patients compared with country-, gender-, and age-matched non-CEAD IS patients. These patients were more frequently hypertensive, diabetic, and current smokers compared with referents, as described in older cohorts of non-CEAD IS patients. Our findings, if confirmed in independent data sets, could improve the understanding of the mechanisms underlying CEAD, a major cause of IS in young adults, in whom the impact of stroke-related disability is particularly dramatic from a personal and socioeconomic point of view. They suggest that hypertension could be a risk factor of CEAD, although the relationship seems weaker than with non-CEAD IS. The inverse association of CEAD with hypercholesterolemia could have implications in terms of secondary stroke prevention because statins are commonly prescribed after an ischemic stroke, including in CEAD patients, in some instances.