Gender differences in spontaneous cervical artery dissection

Abstract—We analyzed sex differences in 696 patients with spontaneous cervical artery dissection. There were more men (n = 399; $p < 0.0001$), and men showed a higher frequency of hypertension (31% vs 15%; $p < 0.0001$). Women were younger (42.5 ± 9.9 vs 47.5 ± 9.3 years; $p < 0.0001$), had more often multiple dissections (18 vs 10%; $p = 0.001$), migraine (47 vs 20%; $p < 0.0001$), and tinnitus (16 vs 8%; $p = 0.001$). Outcome and mortality were similar in both sexes.

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Little is known about sex differences in patients with spontaneous cervical artery dissection (sCAD).

We aimed to determine sex differences in demographic characteristics, vascular risk factors, clinical manifestations, clinical outcome, and mortality in patients with sCAD.

Methods. We prospectively collected data on consecutive patients presenting with first-ever sCAD at three academic centers between January 1991 and June 2005 (Zurich and Berne), and between January 1997 and June 2005 (Lariboisière Paris).

Risk factors for sCAD were assessed as reported previously.[1] SCAD was diagnosed using cervical MRI and magnetic resonance angiography or digital subtraction angiography (DSA), or both. SCAD was considered proven if the investigated artery showed a string sign, an intimal flap or a pseudoaneurysm at angiography, a wall hematoma at cervical or cerebral MRI, or both. Multiple sCAD were defined as spontaneous dissections of more than one internal carotid (sICAD) or vertebral (sVAD) artery. Fibromuscular dysplasia was assessed only in patients who underwent DSA. Clinical and imaging findings of some patients have been reported previously.[1-3]

Patients were categorized according to the presenting signs and symptoms into the following five groups: (A) stroke (ischemic deficit > 24 hours); (B) TIA (ischemic deficit ≤ 24 hours); (C) subarachnoid hemorrhage (SAH); (D) retinal ischemia; (E) one or several of the following local symptoms: head or neck pain in patients with sCAD; pulsatile tinnitus, Horner syndrome, or cranial nerve palsy on the side of the dissection in patients with sICAD; cervical radiculopathy on the side of the dissection in patients with sVAD.

Twenty-three patients with stroke (13 women, 10 men; $p = 0.17$) were treated with IV thrombolysis, and another 14 (9 women, 5 men; $p = 0.1$) with intra-arterial thrombolysis. Antithrombotic therapy included full dose heparin (n = 470; 209 women, 261 men; $p = 0.17$) followed by warfarin for 3 to 6 months. Patients with large infarcts or hemorrhagic transformation or intracranial sVAD without SAH were treated with aspirin during the first 1 to 3 weeks (n = 219; 84 women, 135 men; $p = 0.12$). Subsequently, the treating physician decided whether aspirin was replaced by warfarin. Four patients with SAH and three with both ischemic stroke and SAH due to intracranial sVAD (four women, three men) had no antithrombotic treatment.

Three months clinical follow-up information of patients with stroke (n = 408) was obtained through neurologic examination (n = 341) or a structured telephone interview (n = 42) including recording of the modified Rankin scale score (mRS).

Statistical analysis was performed with the SPSS 10.0 program. For sex differences in categorical variables $\chi 2$ test was performed, and for comparisons in mean age Student t test. Other continuous variables were compared with Mann-Whitney test. Then logistic regression analysis with a forward stepwise method was performed. The variables included were age, family history of stroke, family history of connective tissue disorders or dissection, diabetes, hypertension, history of migraine, dissected vessel, presence of multiple dissections, minor trauma, presenting symptom, National Institutes of Health Stroke Scale score on admission, time to diagnosis.

For comparison of outcome we divided patients with ischemic stroke into two groups with favorable (mRS score 0 to 1) and nonfavorable outcome or death (mRS score 2 to 6).

Results. We included 696 patients with SCAD, 399 (57%) men and 297 (43%) women ($p < 0.0001$).

Mean age was 45.3 ± 9.8 years. Women were younger than men when comparing patients with sCAD (42.5 ± 9.9 years vs 47.5 ± 9.3 years; $p < 0.0001$; table 1), sICAD (43.0 ± 10.0 years vs 48.5 ± 9.3 years; $p < 0.0001$), and sVAD (40.8 ± 9.6 years vs 44.4 ± 8.6 years; $p = 0.012$). Men more often had a history of hypertension (31% vs 15%; $p < 0.0001$), whereas women were more likely to have migraine (47% vs 20%; $p < 0.0001$). These sex differences were observed for migraine without aura (35% vs 16%; $p < 0.0001$) and migraine with aura (12% vs 4%; $p < 0.0001$). There were no sex differences for other presenting charac-

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Table 1 *Presenting characteristics and vascular risk factors*

Characteristic	Men	Women	*p* Value univariate	*p* Value multivariate
No. of patients	399 (57)	297 (43)		
Mean age (SD), y	47.5 (9.3)	42.5 (9.9)	<0.0001	<0.0001
Family history of stroke				
Yes	52 (13)	51 (18)	NS	NS
No	337 (87)	217 (82)		
Family history of CTD				
Yes	3 (1)	3 (1)	NS	NS
No	384 (99)	265 (99)		
Diabetes				
Yes	4 (1)	5 (2)	NS	NS
No	391 (99)	285 (98)		
Current smoking				
Yes	122 (31)	89 (30)	NS	NS
No	273 (69)	204 (70)		
Past smoking				
Yes	54 (14)	26 (9)	NS	NS
No	341 (86)	267 (91)		
Hypercholesterolemia				
Yes	186 (56)	115 (49)	NS	NS
No	148 (44)	121 (51)		
Hypertension				
Yes	121 (31)	44 (15)	<0.0001	<0.0001
No	272 (69)	247 (85)		
Migraine without aura				
Yes	60 (16)	98 (35)	<0.0001	<0.0001
No	326 (84)	186 (65)		
Migraine with aura				
Yes	17 (4)	35 (12)	<0.0001	<0.0001
No	369 (96)	249 (88)		
Minor trauma				
Yes	76 (19)	42 (13)	NS	
No	322 (81)	252 (87)		

Values represent n (%) or mean (SD); *p* indicates difference between subgroups by χ^2 test or Mann-Whitney test (univariate) or forward stepwise regression analysis (multivariate).

CTD = connective tissue disorders; NS = nonsignificant.

Table 2 *Presenting clinical and vascular findings*

Characteristic	Men, n = 399	Women, n = 297	*p* Value univariate	*p* Value multivariate
Dissected vessels				
Carotid artery	295 (74)	206 (70)	NS	
Vertebral artery	91 (23)	72 (24)	NS	
Both	13 (3)	19 (6)	NS	
Multiple dissections				
Yes	39 (10)	54 (18)	0.001	0.001
No	360 (90)	243 (82)		
Fibromuscular dysplasia				
Yes	4 (4)	10 (11)	NS	
No	97 (96)	82 (89)		
Presenting symptom				
Stroke	239 (60)	171 (57)	NS	
TIA	55 (14)	42 (14)	NS	
Retinal ischemia	8 (2)	6 (2)	NS	
Local symptoms only	97 (24)	76 (25)	NS	
SAH	2 (1)	2 (1)	NS	
Headache				
Yes	276 (69)	221 (75)	NS	
No	122 (31)	73 (25)		
Neck pain				
Yes	135 (34)	112 (38)	NS	
No	263 (66)	182 (72)		
Pulsatile tinnitus				
Yes	31 (8)	46 (16)	0.001	0.001
No	267 (92)	249 (84)		
Cranial nerve palsies				
Yes	25 (8)	10 (4)	NS	
No	283 (92)	215 (96)		
Horner syndrome				
Yes	146 (47)	88 (39)	NS	
No	162 (53)	137 (61)		
NIHSS score on admission				
Median (range)	6 (1–38)	7 (1–35)	NS	
Time to presentation, mean (SD), d	9 (17)	10 (25)	NS	

Values represent n (%), median (range), or mean (SD). Prevalence of Horner syndrome and cranial nerve palsies were analyzed only in patients with internal carotid artery dissection. *p* Indicates difference between subgroups by χ^2 test.

SAH = subarachnoid hemorrhage; NIHSS = National Institutes of Health Stroke Scale; NS = nonsignificant.

teristics and risk factors (table 1 and table E-1 on the *Neurology* Web site at www.neurology.org).

Presenting clinical and vascular findings are summarized in table 2. Multiple dissections occurred more often in women (18% vs 10%; $p = 0.001$). Triple dissections tended to be more frequent in women (seven women vs three men; $p = 0.078$). Women more often reported a pulsatile tinnitus (16% vs 8%; $p = 0.001$), whereas the other clinical and vascular findings were similar in both sexes.

Three-month follow-up was obtained in 383 of 408 (94%) patients with stroke. There were no sex differences for favorable outcome (women, 58%; men, 55%; $p = 0.57$) and mortality (women, 2%; men, 5%; $p = 0.11$; table 3).

Discussion. In this study the percentage of men was higher compared to women than previous sCAD studies reporting 48 to 55% male patients.[4] This higher prevalence of men is unlikely due to a sex-based selection bias, because patients with sCAD are mainly young and middle-aged adults who are usually referred to an academic center independent of their sex.

Other important findings of this study are the later onset of sCAD and the higher frequency of hypertension in men. In contrast, women had more often migraine and presented more frequently with multiple dissections and tinnitus.

Similar differences of age between both sexes were found in a study reporting a mean age of 41.9 years in women and 48.1 years in men.[4] The higher age of men with sCAD is in contrast to atherosclerotic diseases, which occur earlier in men. The reasons for this result are difficult to explain. A selection bias is an unlikely cause, because of the large sample size of this study. Genetic factors, hormones, and pregnancies may play a role and oral contraceptive use may

Table 3 *Three-month clinical outcome in 383 patients with ischemic stroke due to spontaneous cervical artery dissection*

Modified Rankin Scale score	Men, n = 221	Women, n = 162
0	46 (21)	42 (26)
1	75 (34)	52 (32)
2	37 (17)	30 (18)
3	34 (15)	22 (14)
4	18 (8)	10 (6)
5	0 (0)	3 (2)
6	11 (5)	3 (2)

Values represent n (%).

be a risk factor for sCAD in young women. However, there is no clear evidence that oral contraceptive use is a risk factor for sCAD,[5] and in our series only 21% of premenopausal women used oral contraceptives. The frequency of minor trauma was similar in men and women and thus cannot explain the abovementioned sex differences. Another possible contributing factor might be the difference in strength of neck muscles and dynamic stabilization during head acceleration between both sexes.[6]

Although hypertension is the most important vascular risk factor for ischemic stroke, it is not clear whether individuals with hypertension are at increased risk for sCAD although a higher prevalence of hypertension in sCAD patients compared with matched controls was recently reported.[7] However, further prospective studies of younger individuals using 24-hour blood pressure measurement are needed to prove an association between sCAD and hypertension. In the present study, hypertension was twice as frequent among men. This reflects in part the slightly higher prevalence of hypertension among men in the middle-aged general population, but the highly significant sex differences in the present study may also indicate that hypertension is a more important risk factor for sCAD in men compared to women.

Migraine has been found to be an independent risk factor for sCAD in three case-control studies.[5] The higher prevalence of migraine in our female patients reflects the female predominance in the general population.

The higher frequency of multiple dissections in women is in agreement with the results of a previous study reporting 11 of 13 patients with both vertebral and carotid artery dissection to be women.[4]

In this study we found no sex differences in clinical outcome or mortality. The favorable outcome and low mortality are in agreement with previous studies.[8]

Our study is limited by its long observation period with different examination techniques. However, only patients with sCAD diagnosed by MRI or arteriography were included.

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