Differences in Demographic Characteristics and Risk Factors in Patients With Spontaneous Vertebral Artery Dissections With and Without Ischemic Events

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Background and Purpose—Spontaneous vertebral artery dissection (sVADs) mainly cause cerebral ischemia, with or without associated local symptoms and signs (headache, neck pain, or cervical radiculopathy), or with local symptoms and signs only.

Methods—We compared the presenting characteristics of consecutive patients with single sVADs and ischemic events and those with local symptoms and signs only.

Results—Of the 186 patients with first-ever unilateral sVAD, 165 (89%) presented with cerebral ischemia, and 21 (11%) presented with local symptoms and signs only. Patients with sVAD and ischemia were more often male (63% vs 29%; $P=0.002$), older (mean±SD age, 43.6±9.9 vs 38.6±9.0 years; $P=0.027$), and smokers (14% vs 3%; $P=0.010$), but less often, they had a history of migraine without aura (17% vs 38%; $P=0.025$) than did patients without ischemia. The multivariate analysis confirmed independent associations between male sex ($P=0.024$), increasing age (0.027), and smoking ($P=0.012$) and sVADs causing cerebral ischemia.

Conclusions—These results suggest that men, older patients, and smokers with sVADs may be at increased risk for ischemic events. **(*Stroke*. 2010;41:802-804.)**

Key Words: vertebral artery dissection ■ risk factors ■ cerebral infarct ■ sex

The clinical presentation of spontaneous vertebral artery dissection (sVAD) is highly variable.[1] Patients with sVAD may present with local symptoms, ischemia, or both. A case-control study suggested that hypertension might be associated with spontaneous cervical artery dissection (sCAD) causing ischemia.[2] In an observational study, we found that hypercholesterolemia was more frequent in subjects with spontaneous internal carotid artery dissections with ischemic events than in those without.[3]

The aim of the present prospective, observational study was to compare the prevalence of presenting characteristics in patients with unilateral first-ever sVADs and cerebral ischemia with those who experienced merely local symptoms and signs.

Patients and Methods

We prospectively collected data on consecutive patients with first-ever sCAD. All patients with single sVADs were included in the present study. The diagnosis of sVAD was established according to previously published criteria.[1] Patients with multiple sCADs (simultaneous occurrence of >1 sCAD) and patients with subarachnoid hemorrhage were excluded from this study. Clinical and imaging findings of some patients have been reported previously.[1,4,5]

The following characteristics were assessed at baseline, as reported previously[3]: smoking, past smoking, hypertension, migraine, family history of sCAD, connective-tissue disorders, minor trauma, and hypercholesterolemia. Cholesterol levels were determined either within 48 hours after admission or at the 3-month follow-up. Diabetes mellitus was defined as a history of diabetes mellitus, a fasting venous plasma glucose concentration on at least 2 separate occasions of ≥7.0 mmol/L, or a glucose concentration ≥11.1 mmol/L 2 hours after oral ingestion of 75 g glucose. Patients with sVAD were categorized, according to their presenting symptoms and signs, into 2 groups: (1) local symptoms or signs only: headache, neck pain, pulsatile tinnitus, or cervical radiculopathy on the side of the dissection; and (2) ischemic events (posterior circulation ischemic stroke (>24 hours), transient ischemic attack (≤24 hours), or spinal ischemia. Patients with subarachnoid hemorrhage were excluded from the study (n=6).

Statistical analysis was performed with the SPSS 10.0 program. For differences in categorical variables, a χ^2 or Fisher exact test was used. Continuous variables were compared with the Mann-Whitney test. The following variables were analyzed: age, family history of

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Table. Presenting Characteristics in 186 Patients With Unilateral sVAD Causing Ischemia, or Local Symptoms and Signs Only

Characteristics	Ischemia (n=165)	Local Symptoms and Signs Only (n=21)	*P* Value, Univariate	*P* Value, Multivariate
Men	104 (63%)	6 (29%)	0.002	0.024
Mean age (SD), y	43.6 (9.9)	38.6 (10.3)	0.027	0.027
Family history of cervical artery dissection	1 (0.5%)	0	1.000	
Connective-tissue disorder	3 (1.8%)	0	1.000	
Smoking	70 (43%)	3 (14%)	0.010	0.012
Past smoking	17 (11%)	0 (0%)	0.226	
Hypertension	47 (29%)	3 (14%)	0.199	0.552
Diabetes mellitus	5 (3%)	0 (0%)	1.000	
Hypercholesterolemia	90 (62%)	10 (60%)	0.937	
Mean plasma cholesterol (SD), mmol/L	5.5 (1.3)	5.3 (1.2)	0.624	
Migraine with aura	11 (7%)	3 (14%)	0.232	
Migraine without aura	28 (17%)	8 (38%)	0.025	0.127
Oral contraceptive use in women <50 years of age	12/40 (30%)	3/12 (25%)	0.737	
Minor trauma	32 (19%)	2 (10%)	0.281	
Mean interval to diagnosis (SD), d	7 (9)	8 (8)	0.549	

P indicates difference between subgroups by χ^2 test, Fisher exact test, or Mann-Whitney test.

dissection, connective-tissue disorders, smoking, past smoking, hypertension, diabetes mellitus, hypercholesterolemia, mean plasma cholesterol level, history of migraine with aura, history of migraine without aura, current use of oral contraceptives in women ≤50 years of age, minor trauma, and interval from symptom onset to diagnosis. Then, logistic multivariable regression analysis with a forward stepwise method was performed including all variables with a probability value <0.2 in the univariate analysis.

Results

Of the 867 consecutive patients with sCAD, 186 (110 men, 59%) were diagnosed with a single sVAD. Among the 186 single-sVAD patients, 165 had an ischemic event (89%), and 21 had local symptoms or signs only (11%).

The presenting ischemic events included stroke in 141 (76.8%) and transient ischemic attack in 24 (12.9%) patients. The presenting clinical manifestation in the group without ischemia was isolated pain in 20 patients (10.8%) and cervical radiculopathy in 1 patient (0.5%). Presenting characteristics for sVADs causing ischemia versus no ischemia are shown in the Table. On univariate analysis, patients with sVAD and ischemic events were more often male (63% vs 29%; $P=0.002$), older (mean±SD age, 43.6±9.9 vs 38.6±9.0 years; $P=0.027$), and more frequently smokers (43% vs 14%; $P=0.010$), but less often, they had a history of migraine without aura (17% vs 38%; $P=0.025$) compared with patients without ischemia. The other presenting characteristics did not differ between the 2 groups (Table). After multivariable regression analysis, independent associations between male sex ($P=0.024$), age ($P=0.027$), and smoking ($P=0.012$) and patients with sVAD causing ischemic events remained significant.

Discussion

We found that male sex, increasing age, and smoking were independently associated with sVAD causing ischemia. The association of male sex with ischemia in this study is in agreement with recent epidemiological data from several European countries showing higher age-adjusted incidence rates for men than women for ischemic stroke. Moreover, a recent systemic review reported a 33% higher incidence rate of stroke in men than in women.[6] However, in those studies, ischemic stroke subtypes were not analyzed. A possible cause of the higher risk of ischemia in men with sVADs might be the protective effect of estrogens in women. Estrogens may contribute to better endothelial function and more effective repair mechanisms in women after sVAD. However, protective effects of estrogens on the vascular endothelium in animal studies and experimental studies in postmenopausal women could not be confirmed by a clinical benefit on the frequency of vascular events in large randomized, controlled trials. Hormone replacement therapy is even associated with an increased risk of stroke.[7] Furthermore, oral contraceptives have been reported to be associated with an increased risk for ischemic stroke,[8] and in the present study, oral contraceptive use in young women did not differ between sVAD patients with and without ischemia. It might also be possible that selection bias is responsible for this sex effect because women may more readily seek medical advice in case of isolated local symptoms.

The association of increasing age and sVAD with ischemia has not been reported so far. One could hypothesize that increasing inflammation and increasing susceptibility to thrombosis with increasing age may explain this result. Increasing age is known to be 1 of the most important risk factors for ischemic stroke, and the age-specific stroke incidence rates increase progressively with each decade of life in both men and women.[9]

There are several possible explanations for the present finding that smoking may predispose to cerebral ischemia in

acute sVAD. In smokers, endothelial function is impaired, and the coagulation cascade is activated. This might enhance thrombus formation in the dissected artery and increase the risk of cerebral embolization leading to cerebral ischemia. Cigarette smoke extracts enhance platelet activation and increase the susceptibility of platelets to activation by shear stress.[10] Potential mechanisms of this activation include oxidative stress and increased levels of fibrinogen, thromboxane, and platelet-derived nitric oxide.[11,12] Furthermore, inhibition of substance P–induced tissue plasminogen activator release has been observed in smokers. Thus, impaired endogenous fibrinolysis might predispose smokers with sVAD to thrombus formation.[13] Finally, an association between smoking and impaired endothelium-dependent vasodilatation has been reported.[14] In addition, several inflammatory markers, including leukocyte count, C-reactive protein, fibrinogen, tumor necrosis factor, and interleukin-6, have been shown to be elevated in smokers.[15]

This study has several methodological limitations. This was a 3-center, university hospital–based study, with a potential referral bias. Moreover, it is possible that patients with isolated local symptoms do not seek medical attention. Another limitation is the small sample size of the sVAD group without ischemia. However, sVAD is a relatively rare disease, and our sample constitutes the largest reported series of patients with single sVAD to date. Nevertheless, our results have to be confirmed by an independent cohort.

In conclusion, the present results suggest that male sex, increasing age, and cigarette smoking predispose to ischemic events in patients with sVAD. This indicates that stroke risk factors may also play a role in the development of cerebral ischemia in sVAD.

Disclosures

None.

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