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Differences in Demographic Characteristics and Risk factors in Patients with Spontaneous Vertebral Artery Dissections with and without Ischemic Events

Marcel Arnold, MD¹,², Rebekka Kurmann, MS², Aekaterini Galimanis, MD², Hakan Sarikaya, MD³, Christian Stapf, MD¹, Jan Gralla MD², Dimitrios Georgiadis, MD³, Urs Fischer, MD¹, Heinrich P. Mattle, MD³, Marie-Germaine Bousser, MD¹, Ralf W. Baumgartner, MD³

Department of Neurology, Hôpital Lariboisière, Assistance Publique-Hôpitaux de Paris, Paris Diderot University, Paris¹; Department of Neurology, Inselspital, Bern University Hospital, University of Bern, Switzerland²; Department of Neurology, University Hospital Zurich, Switzerland³; and Institute of Diagnostic and Interventional Neuroradiology, Inselspital, Bern University Hospital, University of Bern, Switzerland⁴

Address for correspondence:
Marcel Arnold
Department of Neurology
University Hospital Berne
Inselspital
Freiburgstrasse
3010 Bern
Phone: +41 31 632 33 32
Fax: +41 31 632 96 79
E-mail: marcel.arnold@insel.ch
ABSTRACT

Background: Spontaneous vertebral artery dissection (sVAD) mainly causes cerebral ischemia with or without associated local symptoms or signs (headache, neck pain, cervical radiculopathy) or local symptoms and signs only.

Patients and methods: We compared the presenting characteristics of patients with single sVAD and ischemic events and those with local symptoms and signs only.

Results: Of 186 included patients with unilateral first-ever sVAD, 165 (89%) presented with cerebral ischemia, and 21 (11%) local symptoms and signs only. Patients with sVAD and ischemia were more often of male gender (63% versus 29%; p=0.002), older (mean age 43.6 years ± 9.9 SD versus 38.6 years ± 9.0 SD; p=0.027), current smokers (14% versus 3%; p=0.010), and had less often a history of migraine without aura (17% versus 38%; p=0.025) than patients without ischemia.

After multivariate analysis there were independent associations between male sex (p=0.024), age (0.027) and current smoking (p=0.012) and patients with sVAD causing cerebral ischemia.

Conclusions: These results indicate that men, older patients and current smokers with sVAD may be at increased risk to suffer ischemic events.

Key words: vertebral artery dissection, risk factors, cerebral ischemia, gender
The clinical presentation of spontaneous vertebral artery dissection (sVAD) is broad and variable. Patients with sVAD may present with local symptoms and signs (headache, neck pain, cervical radiculopathy), signs of posterior circulation or spinal ischemia or subarachnoid hemorrhage, which can occur in isolation or in combination. SVAD may even remain clinically asymptomatic.

A case-control study of Pezzini et al suggested that hypertension might be associated with spontaneous cervical artery dissection (sCAD) causing ischemia. We found in an observational study that hypercholesterolemia was more frequent in spontaneous internal carotid artery dissections with ischemic events than in those without. Limited knowledge exists about presenting characteristics of sVAD associated with cerebral ischemia.

The aim of the present prospective observational study is to compare the prevalence of vascular risk factors and other presenting characteristics in patients with unilateral first-ever sVAD who suffered cerebral ischemia and those who experienced merely local symptoms and signs.

**Patients and methods**

We prospectively collected data on consecutive patients with first-ever sCAD at three university hospitals, between January 1991 and September 2008 (Zurich and Bern), and between January 1997 and September 2008 (Lariboisière Paris). Dissections were classified as spontaneous when occurring spontaneously or associated with an effort or minor trauma. Patients with dissection occurring after an obvious head or neck trauma were classified as traumatic and not entered in the database. All patients with single sVAD were included in the present study. Diagnosis of sVAD was established using cervical or cerebral magnetic resonance imaging (MRI) and MR angiography (MRA) or digital subtraction angiography (DSA), or both. Spontaneous vertebral artery dissection was considered proven if an intimal flap, a string sign, or a pseudoaneurysm at angiography, a wall hematoma at cervical or cerebral MRI, or both was present. Patients with
multiple sCAD (simultaneous occurrence of more than one sCAD) and patients with subarachnoid hemorrhage were excluded from this study. Clinical and imaging findings of some patients have been reported previously.\textsuperscript{10,11,12}

The following characteristics were assessed at baseline as reported previously.\textsuperscript{13} Current cigarette smoking that included by definition cigarette smoking within the last five years.\textsuperscript{14} Past smoking was defined by smoking cessation since more than five years. Hypertension was defined as a history of antihypertensive treatment or a history of hypertension (systolic blood pressure (BP) >160 mm Hg or diastolic BP >95 mm Hg, or both until September 2000.\textsuperscript{15} The new WHO criteria for diagnosis of hypertension (systolic BP >140 mm Hg or diastolic BP >80 mm Hg, or both) were used since October 2000.\textsuperscript{16}) Hypercholesterolemia was defined as total cholesterol value >5.2 mmol/l.\textsuperscript{17} Diabetes mellitus defined as a history of diabetes mellitus, fasting venous plasma glucose concentration on at least two separate occasions of \( \geq 7.8 \text{ mmol/L} \) or glucose concentration of \( \geq 11.1 \text{ mmol/L} \) at 2 hours after the oral ingestion of 75 g glucose. Diagnosis of migraine and migraine with aura was based on the criteria of the International Headache Society.\textsuperscript{18,19} A family history of sCAD was defined as a first degree relative with sCAD. A history of hereditary connective tissue disorder (CTD; Ehlers-Dahnlos syndrome, osteogenesis imperfecta, Marfan syndrome, polycystic kidney disease, pseudoxanthoma elasticum) and minor trauma were assessed by a standardized questionnaire.

All patients had a full neurological and general examination including the assessment of the National Institute of Health Stroke Scale (NIHSS) score in patients with stroke, routine blood examinations, an electrocardiogram, and an assessment of the cerebral arteries by MRI and MRA or DSA, or both as mentioned above. Patients with ischemic stroke had also cranial computed tomography (CT) or MRI, or both. Lumbar puncture was performed in patients with clinical suspicion of subarachnoid hemorrhage (SAH) or intracranial extension of sVAD on MRA or DSA.
Patients with sVAD were categorized according to the presenting symptoms and signs into two groups: (A) local symptoms or signs only: headache, neck pain, pulsatile tinnitus or cervical radiculopathy on the side of the dissection; (B) ischemic events (posterior circulation ischemic stroke (>24 hours) or transient ischemic attack (≤ 24 hours) or spinal ischemia. Patients with subarachnoid hemorrhage as the main presenting finding of sVAD were excluded from the study (n=6).

Statistical analysis was performed with the SPSS 10.0 program. For differences in categorical variables χ² test or Fisher’s exact test was used. Continuous variables were compared with the Mann-Whitney test. The following variables were analyzed: age, family history of dissection, hCTD, current 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, latency from symptom onset to diagnosis. Then logistic regression analysis with a forward stepwise method was performed including all variables with a p-value <0.2 in the univariate analysis.
Results

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

The presenting ischemic events included stroke in 141 patients (76.8%) and TIA in 24 patients (12.9%). 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%).

Possible risk factors for sVAD causing ischemia versus no ischemia are shown in Table 1. On univariate analysis, patients with sVAD and ischemic events were more often of male gender (63% versus 29%; p=0.002), older (mean age 43.6 years ± 9.9 SD versus 38.6 years ± 9.0 SD; p=0.027), more frequently current smokers (43% versus 14%; p=0.010), and had less often a history of migraine without aura (17% versus 38%; p=0.025) than patients without ischemia. The other presenting characteristics did not differ between the two groups (Table 1). After multivariate analysis, independent associations remained significant between male sex (p=0.024), age (p=0.027) and current smoking (p=0.012) and patients with sVAD causing ischemic events.
Discussion

We found that male gender, age and current smoking were independently associated with sVAD causing cerebral ischemia.

The association of male gender 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. However, in these studies ischemic stroke subtypes were not analyzed.

Genetic factors and the higher prevalence of migraine in women may explain gender differences in sVAD patients. However, in our study female sex remained independently associated with a lower risk of ischemia after multivariate analyses including confounding variables such as migraine. Another possible cause of the higher risk of ischemia in men with sVAD might be the protective effect of estrogens in women. Estrogens may contribute to a better endothelial function and more effective repair mechanisms in women after sVAD. However, protective effects on the vascular endothelium of estrogens in animal studies and experimental studies in post-menopausal women could not be confirmed by a clinical benefit on the frequency of vascular events in large controlled randomized trials. Hormone replacement therapy is even associated with an increased risk of stroke and of stroke severity.

Furthermore, oral contraceptives have been reported to be associated with an increased risk for ischemic stroke, and in the present study, oral contraceptive use in young women did not differ between sVAD patients with and without ischemia.

The association of increasing age and sVAD with ischemia is not surprising. Increasing age is one of the most important risk factors for ischemic stroke and the age-specific stroke incidence rates increase progressively with each decade of life in men and women.
There are several possible explanations of the present finding that current smoking may predispose to cerebral ischemia in patients with 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 lead to platelet activation and increase the susceptibility of platelets to activation by shear stress.\textsuperscript{31} Potential mechanisms of this activation include oxidative stress, and increase in fibrinogen, increase in thromboxane and increased platelet derived nitric oxide.\textsuperscript{32,33} Furthermore, an 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.\textsuperscript{34} Finally, an association between smoking and impaired endothelium dependent vasodilatation has been reported.\textsuperscript{35} In addition, several inflammatory markers including leucocyte count, C-reactive protein, fibrinogen, tumor necrosis factor and interleukin-6 have been shown to be elevated in smokers.\textsuperscript{36}

In this study, there was also a trend towards a higher frequency of hypertension in patients with sVAD causing ischemia. These results are in line with a previous case-control study reporting an association between hypertension and patients with sCAD causing ischemic stroke, particularly when the dissection involved the vertebral arteries.\textsuperscript{37}

In this study, we observed an association of migraine without aura with sVAD without ischemia only in univariate analysis. After regression analysis, migraine without aura was no longer related to sVAD without ischemia due to interaction with female sex.

This study has several limitations. This is a three-center university hospital based study with a potential selection bias. Another limitation is the small sample size of the sVAD group without ischemia. However, sVAD is a rare disease, and this is the largest reported series of patients with sVAD.
In conclusion, the present results suggest that male gender, 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.
Table 1. Presenting Characteristics in 186 Patients with Spontaneous Unilateral Vertebral Artery Dissection Causing Ischemia or Local Symptoms and Signs Only

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Ischemia (n=165)</th>
<th>Local symptoms and signs only (n=21)</th>
<th>P – value univariate</th>
<th>P – value multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>104 (63%)</td>
<td>6 (29%)</td>
<td>0.002</td>
<td>0.024</td>
</tr>
<tr>
<td>Mean age, years (SD)</td>
<td>43.6 (9.9)</td>
<td>38.6 (10.3)</td>
<td>0.027</td>
<td>0.027</td>
</tr>
<tr>
<td>Family history of cervical artery dissection</td>
<td>1 (0.5%)</td>
<td>0</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Connective tissue disorder</td>
<td>3 (1.8%)</td>
<td>0</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Current smoking</td>
<td>70 (43%)</td>
<td>3 (14%)</td>
<td>0.010</td>
<td>0.012</td>
</tr>
<tr>
<td>Past smoking</td>
<td>17 (11%)</td>
<td>0 (0%)</td>
<td>0.226</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>47 (29%)</td>
<td>3 (14%)</td>
<td>0.199</td>
<td>0.552</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>5 (3%)</td>
<td>0 (0%)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>90 (62%)</td>
<td>10 (60%)</td>
<td>0.937</td>
<td></td>
</tr>
<tr>
<td>Mean plasma cholesterol, mmol/l (SD)</td>
<td>5.5 (1.3)</td>
<td>5.3 (1.2)</td>
<td>0.624</td>
<td></td>
</tr>
<tr>
<td>Migraine with aura</td>
<td>11 (7%)</td>
<td>3 (14%)</td>
<td>0.232</td>
<td></td>
</tr>
<tr>
<td>Migraine without aura</td>
<td>28 (17%)</td>
<td>8 (38%)</td>
<td>0.025</td>
<td>0.127</td>
</tr>
<tr>
<td>Oral contraceptives in women &lt;50 years of age</td>
<td>12/40 (30%)</td>
<td>3/12 (25%)</td>
<td>0.737</td>
<td></td>
</tr>
<tr>
<td>Minor trauma</td>
<td>32 (19%)</td>
<td>2 (10%)</td>
<td>0.281</td>
<td></td>
</tr>
<tr>
<td>Mean latency to diagnosis, days (SD)</td>
<td>7(9)</td>
<td>8 (8)</td>
<td>0.549</td>
<td>z</td>
</tr>
</tbody>
</table>

P indicates difference between subgroups by χ² test, Fisher’s exact test or Mann–Whitney test.
References


