Short Communication

Infection and the Risk of Spontaneous Cervical Artery Dissection
A Case-Control Study

Benoît Guillon, MD; Karine Berthet, MD; Lamia Benslamia, MD; Marion Bertrand, MSc; Marie-Germaine Bousser, MD; Christophe Tzourio, MD, PhD

Background and Purpose—Several constitutional and environmental risk factors may be involved in the occurrence of spontaneous cervical artery dissection (SCAD). This work explored the association between recent infection and SCAD in an hospital-based case-control study.

Methods—Forty-seven patients with SCAD and 52 with ischemic stroke from another cause were prospectively and consecutively recruited by 2 neurology departments. A specially designed questionnaire was used to assess the history of an acute infection that could have occurred within a month before the vascular event.

Results—Acute infection was more frequent in patients with SCAD (31.9%) than in control subjects (13.5%) (crude odds ratio, 3.0; 95% confidence interval, 1.1 to 8.2; \(P=0.032\)). This association was stronger in patients with multiple (odds ratio, 6.4) than single artery (odds ratio, 2.1) dissection.

Conclusions—Recent infection is a risk factor and could be a trigger for SCAD. (Stroke. 2003;34:e79-e81.)

Key Words: cerebral ischemia \(\square\) dissection \(\square\) infection \(\square\) risk factors

Spontaneous cervical artery dissection (SCAD) is a major cause of stroke in young adults. To date, its pathogenesis remains largely unknown but seems to involve both constitutional and environmental factors. Various constitutional abnormalities (eg, intracranial aneurysms, aortic root dilatation, ultrastructural abnormalities of dermal connective tissue components, increased distensibility of carotid arteries) have been found in SCAD, suggesting an underlying arteriopathy presumably related to a generalized extracellular matrix defect.\(^1\)\(^-\)\(^5\) Among environmental factors, recent infection was suggested as a potential trigger by Grau et al.\(^6\) The present report concerns the results of a hospital-based case-control study conducted to investigate the relationship between recent infection and risk of SCAD, with particular emphasis on the number of arteries involved.

Patients and Methods

Over a 20-month period, 47 patients between 18 and 65 years of age hospitalized for acute extracranial SCAD (21 women; mean±SD age, 44.8±7.4 years; range, 27 to 62 years) were recruited prospectively and consecutively from 2 centers. Diagnosis of SCAD was based on duplex scanning examination, MRI, and MR angiography (n=46) and/or conventional angiography (n=1). Patients with head or neck trauma were excluded.

SCAD patients were compared with 52 control patients of similar age (±5 years) and sex hospitalized during the same period and in the same centers for a cerebral ischemic event unrelated to a SCAD. The cause of cerebral ischemia was classified according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification. The study was approved by the local ethics committee, and all patients signed an informed consent.

Diagnosis of Infection

Diagnosis of infection was based on a face-to-face interview with the patient or, if necessary, with a close relative using a structured questionnaire and a standardized clinical examination performed as soon as possible after admission. Symptoms of infection had to be present within the 4 weeks preceding the vascular event. Infection was diagnosed when a patient had a positive history of fever (>38°C), a subfebrile state (37.5°C to 37.9°C), or chills, accompanied by 1 or more of the following: otalgia (otitis), cough with purulent sputum (upper respiratory tract infection such as tonsillitis, pharyngitis, laryngitis, sinusitis, bronchitis, or pneumonia if chest roentgenogram showed parenchymal consolidation), headache, myalgia (flu syndrome), nausea, vomiting and/or diarrhea (gastroenteritis), urinary frequency, dysuria and/or positive urine culture (lower urinary tract infection), and back pain with pyuria, bacteriuria, or positive urine culture (pyelonephritis). Infection was also considered present if physical examination and/or laboratory studies performed on admission revealed the presence of sepsis, otitis, upper respiratory tract infection, pneumonia, bacterial endocarditis, renal or urinary tract infection, skin or soft tissue infection, gingivitis or dental abscess, septic arthritis, or osteomyelitis. Patients were characterized as having infection on a clinical prospective basis without knowledge of biological and serological tests.

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TABLE 1. Clinical Features in SCAD and Control Patients

<table>
<thead>
<tr>
<th>SCAD Patients (n=47)</th>
<th>Control Patients (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dissected Arteries n (%)</td>
<td>Cause of Cerebral Ischemia n (%)</td>
</tr>
<tr>
<td>Single artery 33 (70)</td>
<td>Cardioembolism 8 (15)</td>
</tr>
<tr>
<td>ICA 24</td>
<td>Large-vessel atherosclerosis 10 (19)</td>
</tr>
<tr>
<td>VA 9</td>
<td>Small-vessel disease 8 (15)</td>
</tr>
<tr>
<td>Multiple arteries 14 (30)</td>
<td>Miscellaneous 3 (6)</td>
</tr>
<tr>
<td>Both ICA 9</td>
<td>Unknown 23 (44)</td>
</tr>
<tr>
<td>Both VA 3</td>
<td></td>
</tr>
<tr>
<td>&gt;2 2</td>
<td></td>
</tr>
</tbody>
</table>

Signs and symptoms* Signs and symptoms

| Ischemic event 33 (70) | Ischemic event 52 (100) |
| Cerebral infarction 24 (51) | Cerebral infarction 41 (79) |
| TIA 8 (17) | TIA 11 (21) |
| TMB 1 (2) | |
| Horner’s sign 15 (32) | |
| Pain 44 (96) | |
| Tinnitus 15 (32) | |
| Cranial nerve palsy 5 (11) | |

*More than one sign or symptom could be present in the same patient.

Statistical Analysis

Crude and adjusted odds ratios (ORs) with their 95% confidence intervals (CIs) were used to measure the association between SCAD and recent infection. Adjustment for potential confounders was done through multiple logistic regression models. Homogeneity of the association between SCAD and infection in subgroups based on age, sex, and center was tested by adding interaction terms to the relevant statistical models. All significance levels reported are 2 sided. Analyses were performed with the SAS package (release 8.0).

Results

Clinical features in SCAD and control patients are presented in Table 1, and the baseline characteristics of cases and controls are shown in Table 2. Both groups were comparable for age, sex, level of education, and main vascular risk factors, except for frequency of hypercholesterolemia and body mass index (higher in controls). We also observed a higher frequency of migraine in cases compared with controls.7

Recent infection was found in 31.9% of patients (15 of 47) with SCAD and 13.5% of controls (7 of 52), yielding a crude OR of 3.0 (95% CI, 1.1 to 8.2; P=0.032). In a logistic model adjusted for age, sex, center, educational level, and migraine, the OR for recent infection in cases was 3.1 (95% CI, 1.1 to 9.2; P=0.041).

The risk estimate did not differ significantly between the 2 centers, the 2 sexes, or carotid and vertebral artery dissection (data not shown). The infections diagnosed in cases and controls concerned mainly the respiratory tract (Table 3). The time lag between symptoms of infection and the first symptoms of the qualifying event was shorter for SCAD patients than for controls (11.9±7.8 versus 20.1±7.6 days, P=0.034). In patients with SCAD, there was no relationship between occurrence of a recent infection and type of clinical manifestation (with or without an ischemic event). A recent infection was diagnosed in 29.4% of cases with stroke or transient ischemic attacks and 38.5% of cases without ischemic complications (P=0.58).

The frequency of recent infection varied according to the number of arteries involved. An infection was present in 50% of patients with multiple dissections (OR, 6.4; 95% CI, 1.7 to 24.0) and in only 24.2% of those with single artery dissection (OR, 2.1; 95% CI, 0.7 to 6.3). The difference between both risk estimates, however, was not significant (P=0.19).

Discussion

In this case-control study, we found an association between recent infection and SCAD compared with other types of cerebral ischemic events (adjusted OR, 3.1; 95% CI, 1.1 to 9.2). This result is consistent with the hypothesis that infection may play a triggering role in the occurrence of SCAD. Several previous studies showed a relationship between recent infection and acute stroke,6,8,11 but only 1 study indicated that the role of this factor could be higher in SCAD compared with other causes of stroke.6 Our study also suggests that the association between recent infection and SCAD is stronger in patients with multiple dissections (OR, 6.4) than in those with single artery dissection (OR, 2.1), as suggested in 1 series of case reports.12

TABLE 3. Type of Infections Diagnosed in Cases and Controls

<table>
<thead>
<tr>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory tract</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory tract*</td>
<td>8</td>
</tr>
<tr>
<td>Bronchitis</td>
<td>3</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>...</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>2</td>
</tr>
<tr>
<td>Flu syndrome</td>
<td>2</td>
</tr>
</tbody>
</table>

*Including rhinopharyngitis (n=3), tonsillitis (n=5), sinusitis (n=2), and laryngitis (n=1).
Because SCAD is a relatively infrequent disease, our sample is rather small but comparable in size to that of the only other study dealing with the same subject. Controls were also hospitalized at the same period for a cerebral ischemic event, and both cases and controls were recruited prospectively and consecutively, which makes recruitment and selection biases unlikely. As a potential limitation of this study, practitioners who interviewed the patients were not blinded to the status (case or control) of the subjects and could involuntarily have overestimated the frequency of infection in cases. However, diagnosis of infection was based on a structured questionnaire, which was part of a large clinical assessment of vascular risk factors and signs of connective tissue disorders, and this may have limited such a bias. Systematic biochemical or serological analyses were not performed because infections were usually minor and frequently had resolved at the time of hospitalization. In previous studies on the same topic, the causes of infection remained serologically undefined in most patients despite an extensive workup. The mechanism underlying the association between recent infection and occurrence of SCAD remains speculative. A mechanical factor, induced by violent coughing, sneezing, or vomiting, in the context of upper respiratory tract infection does not seem to account for the association observed between infection and SCAD, as already demonstrated in a previous study, although it may play a role in some cases. Direct vessel wall injury by a microbial agent and cellular infiltration seem unlikely. The role of an indirect inflammatory and immunological host response, with activation of cytokines and proteases, could induce excessive extracellular matrix degradation and thus weaken the vessel wall. An inflammatory syndrome may induce multiple dissection, sometimes involving more than the cerebral arteries, and this has raised the possibility of an underlying connective tissue disease or fibromuscular dysplasia. Moreover, patients with multiple dissections are supposed to have a more severe underlying arterial wall disease or diffuse connective tissue disorder. Whether the stronger relationship between infection and dissection in multiple than single artery cases found in our study reflects a more severe underlying arterial wall disease or an increased susceptibility to environmental factors or both remains an unanswered question.

Finally, the understanding of the role of infections as a risk factor for SCAD could shed light on the overall pathophysiology of this condition.

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References
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