Recent Respiratory Infection Predicts Atherothrombotic Stroke
Case–Control Study in a Buenos Aires Healthcare System

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Background and Purpose—Increasing evidence links infections to atherosclerosis. Case–control and cohort studies have found that infections, especially respiratory and dental, are associated with coronary heart disease. However, data on the association of infections with cerebrovascular disease are limited, especially beyond Europe and the United States. We assessed the relationship between recent infections and atherothrombotic disease in a South American cohort.

Methods—We conducted a case–control study of 105 cases and 354 control subjects in a Buenos Aires healthcare system matched by age (mean age, 73.2±12.3 and 72.9±12.8 years), sex, and major cardiovascular risk factors. Cases were patients hospitalized with atherothrombotic ischemic stroke from December 2006 to October 2007. Control subjects were randomly assigned from an electronic outpatient database. Data from the preceding year on inpatient and ambulatory respiratory, urinary and abdominal infections as well as peripheral white blood cell count were collected.

Results—Infections were more frequent in cases than control subjects (29% versus 13%; OR, 2.6; 95% CI, 1.4 to 4.5; P=0.0004); however, this was driven by community-acquired respiratory tract infections (19% versus 6%; OR, 3.9; 95% CI, 1.9 to 8; P<0.001) because there were no differences between cases and control subjects for other types of infection. Respiratory tract infections were the most prevalent type of infection during the 3 months before an atherothrombotic ischemic event, occurring more in cases compared with control subjects (17% versus 4%; OR, 5; 95% CI, 2.2 to 11.3; P<0.001). In multivariable analysis adjusting for major vascular risk factors, history of respiratory infection in the prior year was associated more with cases than control subjects (OR, 4.9; 95% CI, 2.3 to 10.2; P<0.001). White blood cell count was slightly higher in cases versus control subjects (7602±2058 versus 7121.6±1947, P=0.01).

Conclusion—In this South American cohort, recent respiratory tract infections were significantly associated with atherothrombotic stroke, suggesting that prompt identification and treatment of individuals with or at risk for these infections may mitigate the burden from this type of stroke. (Stroke. 2009;40:1986-1990.)

Key Words: infection ■ inflammation ■ ischemic ■ risk factors ■ stroke

Mounting evidence has linked infections to atherosclerosis.1,2 Case–control and cohort studies have found that infections, especially of the respiratory tract and odontogenic tissues,3 are associated with ischemic vascular events, especially coronary disease.4 Ischemic stroke is a heterogeneous mixture of different stroke subtypes caused by atherosclerotic as well as nonatherosclerotic mechanisms, and although atherosclerotic stroke is pathogenetically related to coronary atherosclerosis, data on infection in cerebrovascular disease are limited.5 Nonetheless, in basic experimental studies, proinflammatory alterations, including leukocyte activation with subsequent accumulation of inflammatory cells (mainly monocytes/macrophages) inside the vascular wall, are present in early stages of atherosclerotic disease. In later stages, their activation can lead to plaque rupture and thrombus formation, thereby increasing the risk of stroke.6–8 Also, inflammatory markers (eg, leukocytes, fibrinogen, C-reactive protein) have been associated with endothelial dysfunction.9 However, although a few prior studies from the United States and Europe have demonstrated that up to 35% of patients with ischemic stroke have a history of infection within the preceding month,10,11 its role as an independent stroke risk factor is not well established. Furthermore, there are no published data on the nature of this potential relationship beyond the aforesen-
tional continents, and confirmatory studies are certainly needed. In this study, we conducted a case–control study to investigate this relationship in a South American population.

**Materials and Methods**

**Study Subjects**

Stroke cases and control subjects belonged to a prepayment health system provided by the healthcare system of the Hospital Italiano of Buenos Aires, Argentina. Stroke cases were admitted to the neurological department with diagnosis of ischemic stroke due to atherothrombotic mechanism and were prospectively included in the PROGrama inTEgral GEneral de Accidente Cerebrovascular (PROTEGE-ACV) program. The main objective of this multidisciplinary program is to optimize secondary prevention for patients with stroke. Hospital Italiano is a third-level university hospital located in Buenos Aires city covering a population of approximately 140 000 people. Our patients are mainly of Spanish, Italian, and Asian ethnic origin. We have no African American or indigenous patients.

Eligible cases included all consecutive patients with ischemic stroke with atherothrombotic pathogenesis admitted between December 2006 and October 2007. Age- and sex-matched control subjects were selected from the same medical health system population. Calendar time was taken into consideration to avoid seasonal variation bias. More than 3 nonstroke control subjects were selected for each case using a statistical program. In the review of the clinical records for the control population, we excluded only individuals with recent myocardial infarction and stroke (<1 year for both).

To prevent bias in the quality of the information between cases and control subjects, both populations were evaluated for history of infection and vascular risk factor profile based on a review of outpatient clinical records. Data obtained during a visit within 1 month after the stroke were used only to classify the cases according to the Trial Of Org 10172 In Acute Stroke Treatment (TOAST) algorithm for stroke subtype (large artery atherosclerosis, cardioembolic, lacunar, and other determined and undetermined etiology). Patients with large artery atherosclerosis were defined by the presence of either occurrence or stenosis >50% of a brain-supplying artery corresponding to the vascular territory of stroke, as documented by ultrasound or angiography. Small vessel occlusion was diagnosed in patients with one of the traditional lacunar syndromes of pure motor stroke, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis, or dysarthria–clumsy hand syndrome. Neuroimaging in patients with lacunar stroke showed either an absence of lesions or a deep ischemic infarction <15 mm in size in a territory consistent with the clinical syndrome. Strokes of undetermined origin were those in which etiology could not be determined or when more than one potential mechanism was present at the moment of stroke. Transient ischemic attack was defined as a focal neurological deficit lasting <1 hour with normal neuroimaging.

After the workup with neuroimaging, laboratory tests, electrocardiogram, vascular Doppler, and echocardiogram, we excluded cardioembolic stroke. The presence of nonatherosclerotic vascular disease, hypercoagulability states, history of HIV positivity, pregnancy, vasculitis, intracerebral hematoma, and tumor were also excluded. Finally, patients with recent myocardial infarctions were not included in the analysis, because this condition has been associated with preceding infective sources in epidemiological studies (Figure 1).

**Definitions**

**Vascular Risk Factors**

Hypertensive was defined as systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg. The diagnosis was based on a medical history of hypertension, current treatment, and direct measurements performed on 3 different occasions during the study.

**Diabetic** was defined as a history of diabetes or fasting glucose >6.93 mmol/L, abnormal oral glucose tolerance test, or current treatment.

**Dyslipidemic** was defined as a history of dyslipidemia or low-density lipoprotein cholesterol ≥3.36 mmol/L, high-density lipoprotein ≤1.03 mmol/L in males and ≤1.29 mmol/L in females, or current treatment.

Smoking was categorized according to tobacco consumption status in the previous year as current, former, or nonsmoker.

Coronary heart disease was defined as a history of myocardial infarction, angina pectoris, or previous coronary revascularization procedures.

**Infection Event**

Respiratory tract infection was defined by the presence of pyrexia, auscultatory abnormalities, or productive cough, all with or without positive hemocultures. To define pneumonia, we required corresponding chest x-ray abnormalities.

Urinary tract infection was defined as dysuria, urinary frequency, and/or urgency with a positive urine culture.

Abdominal infection (gastrointestinal tract or abdominal cavity) was considered when any episode of abdominal pain, fever, diarrhea, and/or vomiting required antibiotic therapy or surgery.

Infections occurring during the 3 months before the stroke were included in the analysis so as to provide a reasonable probability of interactions with the cerebral ischemic event. Prevalence in the previous year of all and specific infections were evaluated in cases and control subjects. Mean values of white blood cell count, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol were also determined.

Cases and control subjects were of the same socioeconomic distribution corresponding to segments C2 and C3 of the Argentine classification. These segments are composed of working and retired patients from the metropolitan area with both complete and incomplete high school and university education working in the public or service sectors or self-employed with 50% homeowners and/or car owners and with a middle class income or comparable pension. The hospital’s monthly prepay health plan covers this segment of the population exclusively. All of these patients had a family physician with access to a primary prevention program for the following chronic diseases: hypertension, diabetes, and dyslipidemia. The patients also had free vaccination for influenza and pneumonia according to international criteria.

**Data Analysis and Statistics**

Data are given as mean±SD for continuous variables, proportions, and OR estimates and 95% CIs. Statistical analysis was performed with χ² analysis and t test, as appropriate. Baseline demographic and vascular risk factor profiles were compared between cases and control subjects. A conditional logistic regression model containing major vascular risk factors and history of respiratory infection as the primary predictor was computed. Statistical analysis was performed using a commercially available STATA software (Version 7.0,
One hundred five cases of ischemic stroke and 354 control subjects matched by age (mean age, 73.2 ± 12.3 years, respectively), sex, and major vascular risk factors were studied (Table 1). We found a significant difference between cases and control subjects regarding history of smoking and dyslipidemia.

History of all types of infection during 1 year was more frequent in cases than in control subjects and showed a statistically significant difference (29% versus 13%; OR, 2.6; CI, 95% 1.4 to 4.5; P=0.0004; Table 2). In the conditional regression model, history of respiratory infection was adjusted for the other major vascular risk factors with an OR of 4.9 (2.3 to 10.2; P<0.001; Table 3). Nineteen percent of cases had a history of infection in the 3 months before stroke. Community-acquired respiratory tract infections were the most prevalent type of infection during the 3 months before an atherothrombotic ischemic event with a statistically significant association when compared with control subjects during the same period (17% versus 4%; OR, 5; 95% CI, 2.2 to 11.3; P=0.00001; Figure 2). White blood cell count was significantly higher in cases than in control subjects (7602 ± 2029 versus 7121 ± 1947, P=0.01). Total cholesterol and high-density lipoprotein cholesterol showed no difference between the 2 groups; however, low-density lipoprotein cholesterol was higher in cases (2.7 ± 0.8 versus 2.5 ± 0.7 mmol/L, P=0.0006; Table 4). There were no statistically significant differences between cases before stroke and control subjects in the rate of aspirin use (50% versus 57%) and statin use (40% versus 37%).

### Discussion

Several observations have suggested that infection may be a trigger for acute ischemic stroke, probably related to the prothrombotic effect of the inflammatory response. However, the diagnosis of infection in these studies was based on patient interviews that may have been influenced by recall bias or by serum markers possibly elevated as a consequence of the event. A recent large study based on a primary care database provided more compelling evidence linking respiratory infections to risk for acute vascular events, including stroke.

Our data agree with the hypothesis of an association between stroke and respiratory tract infection. However, because many clinical conditions that predispose to infection also increase the risk of stroke (eg, diabetes), special care had to be taken when selecting control subjects. The history of infection and vascular risk factor profile were evaluated by a retrospective review of the electronic medical record, thereby avoiding bias for in- and outpatient evaluation between cases and control subjects. Control subjects and cases belonged to the same medical facility and were assigned primary care physicians. Access to chronic medication, to the health system prevention program, and patient socioeconomic status were similar previous to stroke. Although we did not specifically evaluate the socioeconomic standing of our patients, both cases and control subjects belonged to the same socioeconomic segment of our society. In a previous study, Ngoh et al found that socioeconomic deprivation had only a modest effect on the association between chronic atypical respiratory infectious burden and elderly patients with stroke/transient ischemic attack.

Several theories link infectious/inflammatory syndromes with an increased risk of stroke, probably due to the different

### Table 1. Demographic Variables and Risk Factors

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n=105)</th>
<th>Control Subjects (n=354)</th>
<th>Statistical Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>73.2 ± 12</td>
<td>72.9 ± 12</td>
<td>0.81</td>
</tr>
<tr>
<td>Male sex</td>
<td>58.1%</td>
<td>55.9%</td>
<td>0.39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>82.6% (86)</td>
<td>80% (284)</td>
<td>0.32</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>63.4% (66)</td>
<td>51% (180)</td>
<td>0.01</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11.4% (12)</td>
<td>8% (30)</td>
<td>0.22</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>15% (16)</td>
<td>11% (40)</td>
<td>0.17</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>54% (57)</td>
<td>80% (284)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Former</td>
<td>31% (32)</td>
<td>9% (30)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

Significance: P<0.05.

### Table 2. Infections in the Previous Year

<table>
<thead>
<tr>
<th>Type of Infections</th>
<th>Cases (n=105)</th>
<th>Control Subjects (n=354)</th>
<th>Statistical Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>All types of infection</td>
<td>29% (30)</td>
<td>13% (47)</td>
<td>OR, 2.6; 95% CI, 1.4–4.5 (P=0.0004)</td>
</tr>
<tr>
<td>Respiratory infection</td>
<td>19% (20)</td>
<td>6% (20)</td>
<td>OR, 3.9; 95% CI, 1.9–8 (P&lt;0.0001)</td>
</tr>
<tr>
<td>Urinary infection</td>
<td>7% (7)</td>
<td>7% (25)</td>
<td>OR, 0.94; 95% CI, 0.3–2.3 (P=0.54)</td>
</tr>
<tr>
<td>Abdominal infection</td>
<td>2% (3)</td>
<td>1% (2)</td>
<td>OR, 5.1; 95% CI, 0.5–62.4 (P=0.08)</td>
</tr>
</tbody>
</table>

Significance: P<0.05.
mechanisms involving prothrombotic state, changes in lipid metabolism and platelet aggregation, alterations in endothelial function, plaque instability, and rupture. After adjusting for major vascular risk factors, prevalence of acute respiratory infection in the year previous to stroke and current smoking were independent stroke risk factors in our multivariable regression model; respiratory infection remained a risk factor for stroke independently of the smoking status.

Active smoking increases the risk of respiratory infection through the alteration of the defense mechanisms of the bronchial epithelia, which may explain the difference found in our study. Additionally, a history of heavy smoking is associated with the development of chronic pulmonary disease, which may predispose to a greater risk of respiratory infection. We believe that this may have occurred in our population.

In our study, patients with stroke had higher levels of low-density lipoprotein cholesterol and white blood cell count than control subjects. Although it would be interesting to consider the differential white cell count and platelet count, these data were unfortunately not available. Nonetheless, our results still support the pathophysiological hypothesis that links the infection process with the atherothrombotic event. According to our study, the variations in lipid profiles and white blood cell count than control subjects. Although it would be interesting to consider the differential white cell count and platelet count, these data were unfortunately not available. Nonetheless, our results still support the pathophysiological hypothesis that links the infection process with the atherothrombotic event. According to our study, the variations in lipid profiles and white blood cell count were not explained by the differences in the use of primary prevention antithrombotic agents and statins between cases and control subjects. Prospective trials have studied the association between high leukocyte levels and stroke; however, there are none that assess this association in white Latin American patients. Because atherosclerosis is an inflammatory disease, macrophages and T lymphocytes are cardinal components of human atheromas, even at the earliest stages of the disease process. Leukocytes may be associated with stroke risk through a variety of mechanisms; they may induce acute thrombotic events by participating in plaque rupture, and they may also serve as a biomarker of vascular risk beyond the traditional vascular risk factors. Although our study provides evidence that there is an increase in leukocyte count in patients with stroke as compared with similar risk profile control subjects, the evidence is limited because this is a case–control study and inflammatory biomarkers were not measured.

We assumed that our study contained the inherent limitations common to all case–control studies and tried to reduce bias by matching populations by sex, age, and major vascular risk factors to reduce the difference between cases and control subjects as per previous reports in the literature. We used the established definition for the diagnosis of different infection subtypes, which was used for cases and control subjects on the basis of the electronic clinical records (as opposed to direct interview), with the aim of reducing recall and information bias that might otherwise have existed if the data for cases had been gathered during admission to the hospital. Only the classification of stroke subtype was performed by direct assessment within 1 month after the stroke.

To our knowledge, the relatively few published articles regarding the association between ischemic stroke and infection have come from American and European populations, so ours would be the first case–control study confirming this association in South America.

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**Disclosures**

None.

**References**


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