Autopsy Prevalence of Intracranial Atherosclerosis in Patients With Fatal Stroke

Mikael Mazighi, MD, PhD; Julien Labreuche, Bst; Fernando Gongora-Rivera, MD; Charles Duyckaerts, MD; Jean-Jacques Hauw, MD; Pierre Amarenco, MD

Background and Purpose—The objective of this study was to determine the prevalence of intracranial plaques and stenoses and their causal role in patients with fatal stroke. Intracranial atherosclerosis is considered to be a rare condition with a severe prognosis. However, disease prevalence may be underestimated due to lack of appropriate diagnostic procedures.

Methods—We performed a systematic analysis of intra- and extracranial arteries, the aortic arch, and the heart in 339 consecutive autopsies of patients with stroke. Clinical history, risk factors, imaging data, and general autopsy reports were analyzed. Patients with brain hemorrhage (n=80) were used as control subjects.

Results—Intracranial plaques and stenoses occurred in 62.2% (95% CI, 56.3 to 68.1) and 43.2% (95% CI, 37.2 to 49.3) of patients with brain infarction, respectively, compared with 48.8% (P<0.05) and 17.5% (P<0.001) of patients with brain hemorrhage, respectively. In the 43% of patients with brain infarction with at least one intracranial plaque-inducing luminal stenosis graded >30%, the stenosis was considered to be causal in 5.8% of cases (n=15) because of superimposed clot on ulcerated plaques; 27% of these patients had stenoses graded 30% to 75%. In multivariate analyses, diabetes and male sex were significantly associated with intracranial plaques and stenosis. History of myocardial infarction was significantly associated with intracranial plaques and previous stroke was associated with intracranial stenosis.

Conclusions—Intracranial plaques and stenoses are highly prevalent in fatal stroke, and stenoses graded 30% to 75% may be causal. New arterial wall imaging techniques should be used to reevaluate the frequency and role of intracranial artery plaques in living patients with stroke. (Stroke. 2008;39:1142-1147.)

Key Words: intracranial atherosclerotic disease IAD plaque stenosis stroke

In pathological and angiographic studies, and in clinical trials evaluating surgery, extracranial disease is frequently identified as being causally related to downstream ischemic strokes. By comparison, intracranial atherosclerotic disease (IAD) is considered to be an infrequent cause of ischemic strokes. Evidence suggests that IAD occurs rarely in white populations but more frequently in Asian, black, and Hispanic populations. However, angiographic studies in patients with extracranial carotid atherosclerosis have shown that the prevalence of IAD can vary between 20% and 50%. Overall, IAD is considered to account for 5% to 10% of ischemic strokes and is associated with a risk of recurrent stroke as high as 15% per year. The severity of IAD warrants an accurate knowledge of the natural history of the disease and the development of diagnostic tools. Among the available imaging modalities, x-ray angiography only images the residual lumen of intracranial arteries, which may appear to be normal because of the Glagov phenomenon despite the presence of severe plaques. Magnetic resonance angiography, CT angiography, and transcranial Doppler ultrasonography may also fail to detect severe intracranial plaques. Only high-resolution MRI has proved capable of imaging the arterial wall and stenosis of intracranial arteries such as the M1 segment of the middle cerebral artery and basilar artery. Our aim was to determine the autopsy prevalence of intracranial plaques and stenoses in patients with fatal stroke.

Methods

This article is the first of a series that will focus on the anatomy of the intracranial atherosclerotic plaque. Patients with stroke were identified using the Multiple Atherosclerosis Site in Stroke autopsy database. Autopsies had been performed at La Salpêtrière Hospital in Paris, France, from November 1982 to February 1989, during which time the autopsy rate was 73%. The methods have been reported previously. Clinical history, risk factors, imaging data, and autopsy reports were available for our review. As reported previously, each autopsy report included a detailed anatomy of the extra-
and intracranial arteries with systematic drawings of the site of occlusion and the site and extent of atherosclerotic plaques or stenosis.\textsuperscript{23} Autopsies were excluded if clinical data (including heart weight) were incomplete or if detailed reports on cerebral arteries were missing.

We first identified the presence and location of atherosclerotic plaques in intracranial arteries. We then measured luminal stenosis on surface section of the arteries that each atherosclerotic plaque may have produced. Intracranial stenoses were graded blinded in clinical subtypes as percentages and then categorized as 0 (stenosis less than 30% including nonstenotic plaque), 1 (stenosis 30% to 75%), 2 (stenosis 75% to 99%), or 3 (occlusion) following the classification of the Raymond Escourroule Laboratory of Neuropathology since 1963. Intracranial plaque does include nonstenotic plaque and stenosis >30%. Microscopic sections of the main vascular lesions were also available for review, allowing distinction between embolic occlusion and occlusive thrombus superimposed on a ruptured plaque.\textsuperscript{23} Etiology was classified according to clinical data and pathological description. Stroke subtyping followed the GENIC classification\textsuperscript{26}: (1) atherosclerotic: ipsilateral internal carotid artery stenosis >30% or ipsilateral stenosis >50% in internal carotid siphon or middle cerebral artery (or any ipsilateral stenosis with ulcerated plaque and superimposed thrombus); (2) cardioembolic: cardiac source of embolism (recent myocardial infarction [MI], atrial fibrillation, intracardiac thrombus or tumor, valvulopathy, or endocarditis); (3) other cause: disseminated intravascular coagulation and other hematologic causes, inflammatory/infectious arterial disease (vasculitis), or intracranial or carotid dissection present; (4) coexisting causes: 2 or more possible etiologies as defined previously; and (5) unknown cause: no identifiable cause found. Patients with brain hemorrhage (BH) were used as a control group because they had been exposed to similar risk factors and were of a similar age at the time of their stroke.

Terminology Used
The term “atherosclerotic plaque” was used to describe the anatomic lesion of an artery produced by atherosclerotic disease. An atherosclerotic plaque may or may not induce an arterial stenosis with or without lumen narrowing. By using the term “intracranial plaque” we meant any anatomic plaque in the artery that included nonstenotic and stenotic plaques. By using the term “intracranial stenosis,” we meant any plaque that induced a stenosis of the arterial lumen >30%. Consequently, a plaque that induced a stenosis <30% was classified among the nonstenotic plaques.

Statistical Analysis
Data are presented as mean (SD) for continuous variables and percentage (number) for dichotomous variables. Patients with stroke included in the statistical analysis were compared with excluded patients with stroke with regard to demographics and vascular risk factors using Student t test for continuous variables and the \( \chi^2 \) test for dichotomous variables; Fisher exact test was used when the expected cell frequency was <5.

Comparisons of the prevalence of intracranial plaques and stenoses between the brain infarction (BI) and BH groups were adjusted on 3 prespecified confounding factors (age, sex, and heart weight, which reflects the presence of arterial hypertension) using logistic regression analysis; the adjusted ORs with their 95% CIs were calculated using patients with BH as the control group.

We compared demographics and vascular risk factors between patients with stroke with and without intracranial plaques using Student t test (for continuous variables) and the \( \chi^2 \) test (for proportions). Multivariable analyses were performed by including the 3 prespecified factors and other vascular risk factors associated with intracranial plaques in the univariable analysis. The same comparison and analyses were done for patients with and without intracranial stenosis.

We investigated the associations of intracranial atherosclerosis (plaques or stenoses) with coronary atherosclerosis, ulcerated plaques in the aorta (arch, abdominal, and thoracic), and lacunar state (unique and multiple) using the \( \chi^2 \) test. These associations were tested in a multiple logistic regression model that included the prespecified confounding factors and other vascular risk factors associated with intracranial atherosclerosis.

Statistical testing was done at the 2-tailed \( \alpha \) level of 0.05. Data were analyzed using the SAS package, release 9.1 (SAS Institute, Cary, NC).

Results
We excluded 42 of 381 (11%) consecutive autopsies of patients with stroke because of incomplete clinical data (including heart weight) or a missing detailed report on cerebral arteries (Figure 1). We included 259 patients with pathological evidence of BI and 80 patients with BH (including 10 patients with BI). There were no differences in age, heart weight, or the distribution of clinical risk factors between patients included and not included in the statistical analysis (data not shown), except for a higher frequency of men in patients included in analysis (56% versus 38%; \( P=0.03 \)).

Prevalence of Intracranial Atherosclerosis
The overall prevalence of intracranial plaques (ie, nonstenotic plaques and plaques inducing arterial stenosis) was 59.0%
(95% CI, 53.8 to 64.2) and the prevalence of intracranial stenosis (ie, only plaques producing intracranial stenosis) was 37.2% (95% CI, 32.0 to 42.3). Among the 259 patients with BI, the prevalence of intracranial plaques was 62.2% (95% CI, 56.3 to 68.1), and the prevalence of intracranial stenosis was 43.2% (95% CI, 37.2 to 49.3); these proportions were significantly higher than in patients with BH (Table 1). After controlling for age, gender, and heart weight, the difference in prevalence of intracranial plaques and stenoses between groups remained significant; the adjusted OR for the presence of intracranial plaques and stenosis in patients with BI relative to patients with BH were 1.70 (95% CI, 1.02 to 2.85) and 3.65 (95% CI, 1.94 to 6.88), respectively.

The prevalence of intracranial plaques and stenosis by BI subtype is also shown in Table 1. Among the 112 patients with BI with intracranial stenosis, 46 were classified into the atherothrombotic group because they had either extra- or intracranial stenosis that was considered likely to be causally related to the stroke. After macro- and microscopic examination of this subset of patients, 15 intracranial stenotic atherosclerotic plaques (3 of which were associated with extracranial stenosis) were considered to be causal because of superimposed clot on ulcerated plaques; 4 (26.7%) of these (including one associated with extracranial stenosis) were graded between 30% and 75%.

Table 2 shows the distribution of IAD according to arterial site involved and grade of stenosis. Middle cerebral artery and basilar artery appeared to be the predominant locations for stenosis >30%, in 18.3% and 15.9% of patients, respectively.

**Intracranial Atherosclerosis and Vascular Risk Factors**

Table 3 shows an analysis of the association between the presence or absence of intracranial plaques and various vascular risk factors, including cardiovascular history and prevalence of symptomatic and clinically silent MI (ie, discovered at autopsy). Patients with stroke with intracranial plaques were older were more frequently men who had macroscopic and microscopic evidence of previous MI. Diabetes was the only modifiable vascular risk factor associated with intracranial plaques. In patients with intracranial stenosis, a predominance of men (64.3% versus 51.6%; \( P < 0.05 \)) and diabetes (20.6% versus 10.3%; \( P < 0.01 \)) was also observed (supplemental Table I, available online at http://stroke.ahajournals.org). History of MI was associated with intracranial plaques (Table 3) but not with intracranial stenosis (37.1% versus 46.0%; \( P = 0.11 \)), whereas stroke history was associated with intracranial stenosis (27.0% versus 15.5%; \( P < 0.05 \)) and not with intracranial plaques (Table 3).

### Table 1. Prevalence of Intracranial Atherosclerosis in 339 Consecutive Autopsies of Patients With Cerebrovascular Diseases

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Patients With Intracranial Plaques,* Percent of Patients (n)</th>
<th>Patients With Intracranial Stenosis,† Percent of Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>339</td>
<td>59.0 (200)</td>
</tr>
<tr>
<td>Brain infarction</td>
<td>259</td>
<td>62.2 (161)</td>
</tr>
<tr>
<td>Atherothrombotic</td>
<td>62</td>
<td>87.1 (54)</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>94</td>
<td>46.8 (44)</td>
</tr>
<tr>
<td>Lacunar</td>
<td>23</td>
<td>60.9 (14)</td>
</tr>
<tr>
<td>Coexisting causes</td>
<td>38</td>
<td>81.6 (31)</td>
</tr>
<tr>
<td>Unknown cause</td>
<td>31</td>
<td>48.4 (15)</td>
</tr>
<tr>
<td>Dissection and other rare causes</td>
<td>11</td>
<td>27.3 (3)</td>
</tr>
<tr>
<td>Brain hemorrhage‡</td>
<td>80</td>
<td>48.8 (39)‡</td>
</tr>
</tbody>
</table>

*Plaques do include nonstenotic plaques and stenosis >30%.
†Stenosis does include only plaques that produced more than 30% stenosis of the arterial lumen.
‡Including 10 brain infarctions.
\( \text{§}P<0.05 \).
\( \text{¶}P<0.001 \) for comparison with patients with brain infarction.

### Table 2. Distribution of Intracranial Atherosclerotic Disease by Site and Severity

<table>
<thead>
<tr>
<th>Severity</th>
<th>Anterior Circulation, Percent of Patients (n)</th>
<th>Posterior Circulation, Percent of Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Infraclinoid Supraclinoid MCA</td>
<td>BA Vertebral Artery PCA</td>
</tr>
<tr>
<td>None</td>
<td>86.4 (293) 73.7 (250) 71.1 (241)</td>
<td>67.3 (228) 79.4 (269) 90.6 (307)</td>
</tr>
<tr>
<td>Nonstenotic plaque</td>
<td>6.2 (21) 17.4 (59) 10.6 (36)</td>
<td>16.8 (57) 13.0 (44) 2.4 (8)</td>
</tr>
<tr>
<td>Plaque with stenosis 30%</td>
<td>3.3 (11) 6.5 (22) 12.7 (43)</td>
<td>12.1 (41) 4.1 (14) 4.4 (15)</td>
</tr>
<tr>
<td>Plaque with stenosis 75%</td>
<td>4.1 (14) 2.4 (8) 5.6 (19)</td>
<td>3.8 (13) 3.5 (12) 2.6 (9)</td>
</tr>
</tbody>
</table>

MCA indicates middle cerebral artery; BA, basilar artery; PCA, posterior cerebral artery.
confirmed using modern imaging of the arterial wall of intracranial arteries,20,21 in series of patients with nonfatal stroke. Our findings parallel observations made in coronary arteries, which have similar lumen diameters as intracranial arteries.28

Another observation we have made is that IAD (plaques and stenoses) is highly prevalent in lacunar stroke either with a single lacune or with multilacunes. Multilacune is most likely to represent the true reflection of diffuse brain arteriolopathy of arteries <300 μm. In multivariable analysis, the observation of an association between lacunes and IAD, although of borderline significance, is similar to our previous observation that coronary atherosclerosis is as frequent in lacunar stroke as in atherothrombotic stroke,29 and is another indication that brain arteriolopathy and atherosclerosis may be 2 phenotypic expressions of the same disease, depending on the vascular bed involved; indeed, they also share the same risk factors. Further studies are needed to confirm these results.

The frequency of plaques and stenoses was similar in lacunar and BH, which often coexist.30,31 One could argue that patients with lacunar stroke have a very low death rate after their stroke and that the high frequency of intracranial plaques we found was related to the cause of their death. However, as reported previously,29 among 23 patients with lacunar stroke, only one died from MI; the others had sudden complications such as pulmonary embolism and aspiration pneumonia as the cause of their death. Nevertheless, we cannot dismiss this bias, and further confirmation in series of living patients are needed using appropriate neuroimaging of the intracranial arterial wall such as with high-resolution MRI.21

Our results bring new insights compared with early pathological studies, which supported the rarity of IAD.32–34 In a pathological study of 122 cases of middle cerebral artery ischemic stroke, Lhermitte et al34 reported that the underlying
mechanism for the BI was extracranial atherosclerosis of the carotid artery. In 1951, Fisher32 failed to document a single middle cerebral artery thrombosis in a necropsy series of 200 patients with stroke. In a necropsy study 10 years later, however, Moossy35 identified the presence of intracranial thrombi in 55% of 142 patients with recent BI; however, unlike the study of Fisher et al, the population was predominantly black. This racial disparity was considered to be the main explanatory factor for the increase in intracranial lesion incidence, and atherosclerosis as the cause for IAD was even debated.33 Beyond the abundant literature on intracranial lesions in Asian, black, and Hispanic populations,36–38 some groups have argued that the increased prevalence of IAD is not related to race–ethnicity but to a higher prevalence of vascular risk factors. Sacco et al3 emphasized this point in a population of 483 predominantly black and Hispanic patients with ischemic strokes, 8% of whom had IAD. After controlling for diabetes and hypercholesterolemia, the higher prevalence of these vascular risk factors in nonwhite patients explained the observed racial difference in IAD distribution. IAD may be underrecognized in white populations with diffuse atherosclerosis. In our series, the independent association between male sex and diabetes and either intracranial plaques or stenosis favors this hypothesis. It is worth noting that diabetes appeared to be positively related to the degree of stenosis (Figure 2), a relationship not described previously.

This study has the limitation of autopsy studies, especially recruitment biases. The results can therefore only be applied to fatal strokes because autopsy studies are not representative of the whole spectrum of strokes. We also cannot exclude the possibility that the retrospective review of vascular risk factors from the medical charts led to some bias and underestimation of the prevalence of vascular risk factors in this population.

Although the hospital death rate of patients with stroke at the time of accrual of this cohort was much higher than today (up to 40%), the cohort represents only a fraction of the patients with fatal and nonfatal strokes who were admitted to La Salpêtrière Hospital. Moreover, the patients who died were more likely to have had the most severe strokes, accounting for the high prevalence of cardioembolic strokes and low prevalence of lacunar strokes. Another concern is that this cohort was collected in the 1980s. However, although treatment and outcomes have evolved considerably since then, the pathophysiology, epidemiology, and associations between the various conditions are likely to remain unchanged. There is no reason to expect, therefore, that an association observed between intracranial atherosclerosis and BI in the 1980s would not hold true today. Today, because of the dramatic decline in postmortem studies, large autopsy studies are rare. For this reason, our extensive and thoroughly studied autopsy material is unique.

Table 5. Association of Intracranial Plaques With Coronary and Aortic Atherosclerosis and Lacunar Stroke or Multilacune

<table>
<thead>
<tr>
<th>Plaques* in Intracranial Arteries, Percent of Patients (n)</th>
<th>Absent (n=139)</th>
<th>Present (n=200)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary plaques</td>
<td>61.7 (82)</td>
<td>80.4 (152)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Coronary stenosis &gt;50%</td>
<td>30.8 (41)</td>
<td>42.3 (80)</td>
<td>0.04</td>
</tr>
<tr>
<td>Ulcerated plaques in aortic arch</td>
<td>20.1 (28)</td>
<td>25.5 (51)</td>
<td>0.25</td>
</tr>
<tr>
<td>Ulcerated plaques in abdominal or thoracic aorta</td>
<td>19.4 (27)</td>
<td>19.0 (38)</td>
<td>0.92</td>
</tr>
<tr>
<td>Lacunar stroke</td>
<td>22.3 (31)</td>
<td>34.5 (69)</td>
<td>0.02</td>
</tr>
<tr>
<td>Multilacune</td>
<td>11.5 (16)</td>
<td>21.5 (43)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Plaques do include nonstenotic plaques and plaques inducing luminal stenosis.

Conclusions
IAD may be underdiagnosed and responsible for a higher proportion of ischemic strokes than is currently accepted, particularly if stenosis 30% to 75% can be causal as suggested by some cases in this series. The use of accurate arterial wall imaging of intracranial arteries with, for example, high-
resolution MRI, should prompt a reappraisal of the frequency of IAD in nonfatal strokes. Our findings emphasize the importance of identifying IAD in patients with ischemic stroke and may impact on the management of intracranial lesions.

Acknowledgments

We thank Dr Sophie Rushton-Smith who provided editorial assistance in the preparation of this manuscript and was funded by SOS-ATTAQUE CEREBRALE Association. Statistical analysis was conducted by Julien Labreuche.

Source of Funding

This study was supported by a grant from SOS-ATTAQUE CEREBRALE Association.

Disclosures

None.

References

Autopsy Prevalence of Intracranial Atherosclerosis in Patients With Fatal Stroke
Mikael Mazighi, Julien Labreuche, Fernando Gongora-Rivera, Charles Duyckaerts, Jean-Jacques Hauw and Pierre Amarenco

Stroke. 2008;39:1142-1147; originally published online February 28, 2008;
doi: 10.1161/STROKEAHA.107.496513
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2008 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/39/4/1142

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org/subscriptions/