Association of Small-Vessel Disease With Dilatative Arteriopathy of the Brain
Neuropathologic Evidence

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Background and Purpose—Clinical and imaging studies have reported an independent and intriguing association between intracranial arterial dolichoectasia (IADE) and markers of small-vessel disease (SVD) such as lacune(s). We used a large brain-autopsy collection to investigate the relation between IADE and pathologically assessed cerebral SVD.

Methods—The entire arterial tree from the heart to the intracranial small intracerebral arteries was investigated in 381 consecutive autopsies from patients with stroke. Vascular risk factors, heart status (weight, coronary atherosclerosis, and myocardial infarction), prevalence and severity of atherosclerosis from heart to brain (aortic arch, carotid, vertebral, and intracranial arteries), dolichoectasia, cerebral SVD, and brain tissue lesions (lacune(s), état criblé) were evaluated. Analyses were adjusted for age, sex, and heart weight.

Results—Twenty-three (6%) of 381 patients had IADE, affecting mainly the basilar artery, with a median basilar artery diameter of 6 mm (range, 4 to 9 mm). Patients with IADE had a 2-fold increase in the prevalence of basilar artery plaques and ulcerated plaques in the aortic arch (both \(P=0.006\)), but there were no associations with coronary or cervical artery plaques. SVD was more frequent in IADE-positive than in IADE-negative patients (45% vs 18%; \(P=0.004\)). The adjusted odds ratio was 3.85 (95% confidence interval, 1.56 to 9.52). Cerebral amyloid angiopathy was not observed in IADE-positive patients.

Conclusions—Compared with stroke patients without IADE, those with IADE were more likely to have pathologic evidence of cerebral SVD and its consequences, independent of age, arterial hypertension, or diabetes mellitus. IADE and cerebral SVD may have unidentified biologic processes in common. (Stroke. 2007;38:1197-1202.)

Key Words: dolichoectasia ● autopsy ● atherosclerosis ● lipohyalinosis ● small-vessel disease ● multilacunes ● état criblé

Intracranial dilatative arteriopathy, also called intracranial arterial dolichoectasia (IADE), is defined as an increase in the length and diameter of the intracranial large arteries.\(^1,2\) IADE is found in 12% of patients with stroke and the pathophysiology is unknown.\(^3,4\) On autopsy, dolichoectatic arteries have an abnormally large external diameter with a thin arterial wall and sometimes bear an intraluminal thrombus or an atherosclerotic plaque.\(^5\) On microscopic examination, the main findings are in the media, with rarefaction of the elastic tissue and degeneration of the internal elastic lamina.\(^6,7\) Because they have risk factors in common, the relation between IADE and atherosclerosis is a matter of debate, atherosclerosis being either the cause or the consequence of dolichoectatic processes.\(^4,5,8\) In a large population of patients with brain infarction, we found no association between the prevalence and severity of carotid atherosclerosis on ultrasound examination and the presence of IADE on brain magnetic resonance imaging (MRI).\(^8\) No studies have investigated the relation between IADE and location of atherosclerosis from the heart to the brain, which could help us to understand the pathophysiology and may have practical implications, such as work-up and prevention in stroke patients with IADE.

Two studies have shown that stroke patients with IADE were more likely to have lacunar brain infarcts on brain imaging than stroke patients without IADE.\(^8,9\) We recently reported an independent association between IADE and MRI markers of small-vessel disease (SVD), such as multilacunes, leukoaraiosis, and dilatation of perivascular spaces (ie, état criblé).\(^3\) Although MRI scans show the consequences of cerebral SVD, they fail to show either the pathologic process underlying the signal changes or the nature of SVD. If
confirmed, simultaneous involvement of small intracerebral arteries and IADE could be due to a common pathologic cascade(s) or unknown risk factors.3–4

We carried out a case-control study to assess the pathology of the heart-to-brain arterial tree in patients with or without IADE, with a special focus on small intracerebral arteries. For this purpose, we used a large, brain-autopsy database because it included consecutive patients with stroke and a systematic evaluation of the brain and its arterial supply.

Subjects and Methods

The Multiple Atherosclerosis Site in Stroke (MASS) study is an autopsy database of patients who died with neurological diseases at La Salpêtrière Hospital in Paris between November 1982 and February 1989. The autopsy rate during this period was 73%.10

Among 886 autopsies, 381 were of patients with stroke, including 83 with brain hemorrhage, 288 with brain infarction, and 10 with both brain hemorrhage and infarction, and 505 were of patients with other neurological diseases.11

Autopsy Process

Autopsies were performed according to French legislation and the published guidelines of the Neuropathology Department of la Salpêtrière for brain examination and its arterial supply.12–16 Medical reports were available for each case. In brief, after dissection of the aorta and its cervical branches, the cervical spine with the base of the skull was removed en bloc and subsequently fixed for at least 1 month and decalcified. Sections were then cut to examine the extracranial arteries throughout their length. Similarly, the configuration of the circle of Willis was assed, and the arteries of the base of the brain were dissected along with their main branches. The arterial configuration and size and extent of arterial lesions were reported on a printed diagram according to a published classification.12–13

The brain was fixed in 10% formalin for at least 2 months. After sectioning of the midbrain at the level of the geniculate bodies, the brain was cut coronally at 1-cm intervals. The midbrain and cerebellum were cut perpendicular to the axis of the brain stem. On a printed diagram, brain lesions were drawn and samples identified. In each case, the sampling depended on the clinical data and pathologic examination. Basal ganglia and frontal white matter were sampled in most cases. Brain samples were always embedded in paraffin, whereas some other samples were embedded in celloidin. Microatheromas, with or without intramyocardial or intramyocardial extension and calcification, were defined as atherosclerotic plaque involving the proximal perforating arteries of small intracerebral arteries (200- to 800-µm diameter), was not specifically assessed in IADE-positive patients. The Figure). To ensure the validity of the IADE diagnosis and to characterize its severity, the formalin-fixed specimen were reexamined by measuring the diameter of the basilar artery in IADE-positive patients and in an equivalent number of IADE-negative patients who were matched for age, sex, and year of death.

Statistical Analysis

The statistical analysis was based on 381 autopsies of patients with stroke. Data are presented as mean (SD) for continuous variables and percentage (count) for dichotomous variables. Patients with stroke were divided into 2 groups according to the presence or absence of IADE. We compared clinical and autopsy characteristics between the IADE-positive and IADE-negative patients with Student’s t test for continuous factors and the χ2 test for dichotomous factors. Fisher’s exact test was used when the expected cell frequency was <5. Associations of IADE with atherosclerosis, lacunar infarct, multiculenes, and état criblé were adjusted for 3 prespecified confounding factors (age, sex, and heart weight, taken as a surrogate for the presence of arterial hypertension) by logistic-regression analysis. The adjusted odds ratios (ORs) were calculated with their 95% CIs. Statistical testing was done at the 2-tailed α level of 0.05. Data were analyzed with the SAS software package, release 9.1 (SAS Institute).

Results

Of the 381 patients with stroke included in the MASS study, IADE was identified in 23 (6%) individuals. The percentage of brain infarction and intracerebral hemorrhage was similar in the IADE-positive and IADE-negative groups. The median time between stroke and death was 8 days (interquartile range, 3 to 31 days) in IADE-positive patients versus 13 days (interquartile range, 5 to 34 days) in IADE-negative patients (Mann–Whitney U test, P=0.35). The median diameter of the basilar artery was 6 mm (range, 4 to 9 mm) in IADE-positive versus 3 mm (range, 2 to 5 mm) in IADE-negative patients (Wilcoxon rank test, P<0.0001).

Description of Patients With IADE

Among the 23 IADE-positive patients, 12 were men and the median age was 78 years. Fourteen patients had a brain infarction, including 5 (36%) in the territory of a dolichoectatic artery. One had locked-in syndrome with an occlusive thrombus of the dolichoectatic basilar artery. Six patients had an intracerebral hemorrhage and 2 had a subarachnoid hemorrhage, including 1 by rupture of the dolichoectatic basilar
artery. Among 6 patients who had a brainstem compression by the dolichoectatic basilar artery, 4 also had brain infarction, 1 had an intracerebral hemorrhage, and 1 had a subarachnoid hemorrhage. The dolichoectatic process affected the basilar artery in 20 patients, the vertebral arteries in 13 patients, the carotid arteries in 11 patients, and the middle cerebral arteries in 5 patients.

Clinical and Anatomic Vascular Risk Factors
As shown in Table 1, IADE-positive patients were older than IADE-negative patients ($P=0.02$). No significant differences in other clinical and anatomic factors were found between the 2 groups. However, except for arterial hypertension, IADE-positive patients had fewer clinical risk factors than IADE-negative patients but tended to have higher heart weights.

Atherosclerosis Involvement
One IADE-positive patient and 27 IADE-negative patients were excluded from this analysis because detailed diagrams of the anatomy and extent of atherosclerosis in the cerebral arteries were not available. Table 2 shows the prevalence of atherosclerotic lesions in IADE-positive and IADE-negative patients. Although plaques in any segment of the intracranial and extracranial arteries were slightly more frequent in IADE-positive than in IADE-negative patients, the difference was not statistically significant. However, when the analysis was stratified according to various segments of the cerebral arteries, IADE-positive patients had more plaques in the basilar artery ($P=0.006$). After adjustment for age, sex, and heart weight, the OR of IADE associated with the presence of plaques in the basilar artery was 2.83 (95% CI, 1.15 to 6.95). We also found a positive association between IADE and the presence of ulcerated plaques in the aortic arch, which remained significant after multivariable analysis (adjusted OR, 3.13; 95% CI, 1.26 to 7.78).

Brain Tissue and Small-Vessel Lesions
As shown in Table 3, IADE-positive patients had a higher frequency of lacunar infarction (48% vs 27%) and multilacunes (35% vs 16%) than IADE-negative patients. After adjustment for age, sex, and heart weight, multilacunes remained significantly associated with IADE (Table 3).

Interestingly, cerebral SVD, essentially hyalinosclerosis, was more frequent in IADE-positive than in IADE-negative patients (45% vs 18%) and remained significantly associated with IADE even after multivariable adjustment (adjusted OR, 3.85; 95% CI, 1.56 to 9.52; $P=0.004$). Exclusion of the 47 patients for whom SVD status was evaluated retrospectively for this study did not modify the strength of the association (adjusted OR, 4.23; 95% CI, 1.55 to 11.52; $P=0.01$). Isolated
fibrinoid necrosis was observed in neither IADE-positive nor IADE-negative patients. No case of cerebral amyloid angiopathy was detected on Congo red–stained sections in the IADE-positive group.

**Statistical Power Calculation**

We calculated the smallest difference (expressed as an OR) that our sample size allowed us to detect between IADE-positive and IADE-negative stroke patients at the 5% nominal significance level with 80% power and assuming an exposure frequency of 30% in IADE-negative stroke patients. On the basis of this calculation, without missing data, we could detect an OR of 3.3 with 23 IADE-positive and 358 IADE-negative stroke patients.

**Discussion**

In this autopsy study, we found that IADE-positive patients with fatal stroke were more likely than those without IADE to have a disorder of the arterial tree, including ulcerated plaques of the aortic arch, basilar plaques, and SVD. These associations were independent of known vascular risk factors such as age, sex, and heart weight (taken as a surrogate for arterial hypertension). No IADE-positive patient had diabetes mellitus in this series.

**Frequency of IADE**

In this series of patients with fatal stroke, we found a 6% prevalence of IADE, which is less than the 12% found in a previous MRI study of 510 distinct stroke patients in the GENIC study.8 This difference may be explained by differences in the diagnostic criteria used in the 2 studies. The strong association between IADE and lacunar infarction and the low case-fatality rate for lacunar infarcts make it less likely that these patients will die of their stroke. Therefore, our sample of 23 patients with IADE and fatal stroke should be regarded as cases different from those of the entire spectrum of IADE.

**IADE and Large-Artery Atherosclerosis**

The pathologic patterns of atherosclerosis and dolichoectasia are distinct. Atherosclerosis primarily involves the intima of TABLE 1. Clinical and Anatomic Vascular Risk Factors in Stroke Patients With and Without IADE

<table>
<thead>
<tr>
<th></th>
<th>IADE+ (n=23)</th>
<th>IADE− (n=358)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td><strong>Clinical factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y, mean±SD</td>
<td>78±11</td>
<td>72±12</td>
<td>0.02</td>
</tr>
<tr>
<td>Men, % (n)</td>
<td>52 (12/23)</td>
<td>55 (195/358)</td>
<td>0.83</td>
</tr>
<tr>
<td>Hypertension, % (n)</td>
<td>65 (15/23)</td>
<td>57 (199/352)</td>
<td>0.42</td>
</tr>
<tr>
<td>Diabetes, % (n)</td>
<td>0 (0/23)</td>
<td>51 (153/352)</td>
<td>0.06*</td>
</tr>
<tr>
<td>Smoking, % (n)</td>
<td>4.4 (1/23)</td>
<td>16 (55/352)</td>
<td>0.22*</td>
</tr>
<tr>
<td>Obesity, % (n)</td>
<td>4.4 (1/23)</td>
<td>9.9 (35/352)</td>
<td>0.71*</td>
</tr>
<tr>
<td>Dyslipidemia, % (n)</td>
<td>4.4 (1/23)</td>
<td>7.4 (26/352)</td>
<td>1.00*</td>
</tr>
<tr>
<td>Atrial fibrillation, % (n)</td>
<td>13 (3/23)</td>
<td>28 (87/352)</td>
<td>0.15</td>
</tr>
<tr>
<td>Cardiovascular history, % (n)</td>
<td>8.7 (2/23)</td>
<td>22 (79/352)</td>
<td>0.19*</td>
</tr>
<tr>
<td>Stroke history, % (n)</td>
<td>4.4 (1/23)</td>
<td>20 (71/355)</td>
<td>0.10*</td>
</tr>
<tr>
<td><strong>Autopsy factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart weight, g, mean±SD</td>
<td>458±114</td>
<td>417±102</td>
<td>0.06</td>
</tr>
<tr>
<td>Silent and nonsilent myocardial infarction, % (n)</td>
<td>44 (10/23)</td>
<td>39 (136/346)</td>
<td>0.69</td>
</tr>
<tr>
<td>Cardiac valvulopathy, % (n)</td>
<td>23 (5/22)</td>
<td>12 (40/342)</td>
<td>0.17*</td>
</tr>
</tbody>
</table>

Proportions and continuous variables were compared with the χ² (or Fisher’s exact*) test and Student’s t test, respectively.

<table>
<thead>
<tr>
<th></th>
<th>IADE+ (n=22)</th>
<th>IADE− (n=331)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic plaques in the cerebral arteries</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any segment of cerebral arteries</td>
<td>91 (20/22)</td>
<td>77 (256/331)</td>
<td>0.18*</td>
</tr>
<tr>
<td>Any segment of intracranial arteries</td>
<td>68 (15/22)</td>
<td>58 (192/331)</td>
<td>0.35</td>
</tr>
<tr>
<td>Siphon and termination of ICA or MCA</td>
<td>50 (11/22)</td>
<td>45 (150/331)</td>
<td>0.67</td>
</tr>
<tr>
<td>V4 segments of vertebral artery</td>
<td>19 (4/21)</td>
<td>20 (67/329)</td>
<td>1.00</td>
</tr>
<tr>
<td>Basilar artery</td>
<td>59 (13/22)</td>
<td>31 (102/330)</td>
<td>0.006 (0.02†)</td>
</tr>
<tr>
<td>Posterior cerebral artery</td>
<td>23 (5/22)</td>
<td>8.8 (29/331)</td>
<td>0.05* (0.05†)</td>
</tr>
<tr>
<td>Any segment of extracranial arteries</td>
<td>73 (16/22)</td>
<td>67 (223/331)</td>
<td>0.60</td>
</tr>
<tr>
<td>ICA origin and CCA</td>
<td>64 (14/22)</td>
<td>62 (204/331)</td>
<td>0.85</td>
</tr>
<tr>
<td>Origin and V2 segments of vertebral artery</td>
<td>27 (6/22)</td>
<td>23 (76/331)</td>
<td>0.64</td>
</tr>
<tr>
<td>Subclavian arteries</td>
<td>36 (8/22)</td>
<td>18 (61/331)</td>
<td>0.05 (0.08†)</td>
</tr>
<tr>
<td>Coronary artery plaques</td>
<td>91 (20/22)</td>
<td>71 (219/308)</td>
<td>0.05 (0.20†)</td>
</tr>
<tr>
<td>Coronary artery stenosis</td>
<td>55 (12/22)</td>
<td>36 (111/308)</td>
<td>0.08 (0.27†)</td>
</tr>
<tr>
<td>Ulcerated plaques in aortic arch</td>
<td>50 (11/22)</td>
<td>22 (70/325)</td>
<td>0.006 (0.011†)</td>
</tr>
<tr>
<td>Ulcerated plaques in the abdominal or thoracic aorta</td>
<td>36 (8/22)</td>
<td>18 (59/331)</td>
<td>0.05* (0.10†)</td>
</tr>
<tr>
<td>Abdominal or thoracic aortic aneurysm</td>
<td>9.1 (2/22)</td>
<td>4.2 (14/331)</td>
<td>0.26*</td>
</tr>
</tbody>
</table>

ICA indicates internal carotid artery; MCA, middle cerebral artery; and CCA, common carotid artery. P values were computed with the χ² or Fisher’s exact* test.

†P values were calculated by logistic regression, adjusted for age, sex, and heart weight.

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TABLE 3. Association Between IADE and Parenchymal Abnormalities Related to SVD

<table>
<thead>
<tr>
<th></th>
<th>IADE+ (n=23)</th>
<th>IADE− (n=358)</th>
<th>P</th>
<th>OR† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small vessel disease,*</td>
<td>45 (10/23)</td>
<td>18 (61/338)</td>
<td>0.004†</td>
<td>3.85 (1.56–9.52)</td>
</tr>
<tr>
<td>Lacunar infarction, %</td>
<td>48 (11/23)</td>
<td>27 (97/358)</td>
<td>0.03</td>
<td>2.42 (0.99–5.89)</td>
</tr>
<tr>
<td>Multilacunes, %</td>
<td>35 (8/23)</td>
<td>16 (58/358)</td>
<td>0.04†</td>
<td>2.85 (1.11–7.32)</td>
</tr>
<tr>
<td>État criblé, %</td>
<td>23 (5/22)</td>
<td>13 (44/347)</td>
<td>0.19†</td>
<td>1.78 (0.62–5.17)</td>
</tr>
</tbody>
</table>

*Sclerosis, hyalinosis, or lipohyalinosis of small arteries <300 μm and arterioles.

†ORs were calculated by logistic regression, adjusted for age, sex, and heart weight.

P values were computed with the χ² or Fisher’s exact test.

IADE and SVD

The present study is the first to assess the pathology of small intracerebral arteries in IADE patients with stroke. We confirm the strong, independent association between IADE and multilacunes that we reported previously in the GENIC study,3 and we further show that the underlying changes in the deep, small arteries are so-called “small-vessel disease” (sclerosis and hyalinosis in arteries <300 μm). Neither isolated fibrinoid necrosis nor amyloid angiopathy was seen. As mentioned in the Methods section, microatheroma of the proximal perforating arteries (200- to 800-μm diameter) was not specifically investigated in this study. This lesion has been described by Fisher et al.30 in patients with lacunar infarction. We cannot assess any relation between IADE and microatheroma.

Interestingly, in IADE-positive patients, SVD was nearly 4 times more frequent than in IADE-negative patients, independent of age, sex, and heart weight. In contrast, diabetes mellitus, reported to be associated with multilacunes,21,22 was not observed in IADE-positive patients. Because both IADE and small-vessel arteriopathy affect the media of the artery, the involvement of matrix metalloproteinase (MMP) metabolism could be hypothesized. Other ectatic arterial disorders have been associated with the MMP pathway: abdominal aortic aneurysm growth and rupture have been linked to MMP-9 blood levels and genetic polymorphism,23–25 and ectasia of the coronary artery has been associated with MMP-3 polymorphism.26 In a brain-autopsy study, cells that contained MMP-3 (macrophages and microglia) were more often present around hyalinosclerotic, small perforating arteries and areas of severe white matter damage corresponding to leukoaraiosis.27 In a previous autopsy study, abdominal aortic aneurysm was found in one third of patients with IADE,8 and concurrent ectasia of coronary and basilar arteries has been reported in 4 patients.28 MMP dysfunction could bridge IADE and SVD.

Study Limitations

This study suffered from the limitations of all post mortem studies. Hence, our results apply only to patients with fatal strokes. Although the hospital death rate of patients with stroke at the time of accrual of this cohort (1982–1989) was much higher than it is today, this cohort represents only a fraction of patients with a fatal stroke who were admitted to La Salpêtrière Hospital. At that time, the stroke case fatality was 30% to 40%; since then, it has decreased dramatically with the development of Stroke Unit facilities. This recruitment bias (ie, inclusion of fatal stroke) may explain the relatively low percentage of aortic aneurysm (9%) in the IADE-positive group because patients who had a ruptured aortic aneurysm were unlikely to die in neurological departments.

After retrieval of SVD status for 47 patients, we had missing data on the presence of SVD in 4% of IADE-positive patients and in 6% of IADE-negative patients. Although this difference was not significant, the analysis of cerebral SVD could have been biased. However, IADE and in most cases, SVD status were assessed before the discovery in 1998 of the association between lacunar infarcts and IADE.9 The missing data on SVD status that we have recently retrieved were assessed blindly of IADE status, and their inclusion did not modify the results.

Another limitation of our study is the lack of statistical power to detect weak associations, as shown by the a posteriori power calculation. Owing to the multiple testing performed, we cannot exclude the possibility that some findings could be due to the play of chance; however, the consistency of the results with previous studies argues against a chance finding. For these reasons, the present results should be replicated in further studies.

In conclusion, intracranial arterial dolichoectasia was associated with cerebral SVD, mainly hyalinosclerosis, independent of age, arterial hypertension, and diabetes mellitus. This finding suggests that these media-involving arteriopathies have biological processes in common.

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Disclosures
None.

References
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