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Silent intracerebral microhemorrhages in patients with ischemic stroke

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Chapter 5

Abstract

We compared the frequencies of signs of old intracerebral hemorrhages on brain MRI’s in 66 patients with ischemic stroke, 69 with myocardial infarction and 86 with peripheral arterial disease (total 221 patients). MRI’s were independently assessed by two investigators without knowledge of clinical or laboratory data. In 31 patients (14%) we found local cerebral hemosiderin deposits. In 24 patients they were clinically silent. Hemosiderin deposits were significantly more frequent in patients with ischemic stroke (26%) than in patients with myocardial infarction (4%) or peripheral arterial disease (13%) (p=0.002). Hemosiderin deposits were associated with cerebral white matter lesions (odds ratio 5.3, 95%CI 2.5-12.4). The odds ratio’s were higher in patients with severe cerebral white matter lesions. Our findings support the hypothesis that cerebral vessels of patients with ischemic stroke are more prone to rupture than those of patients with other manifestations of atherosclerotic disease, which may explain the higher incidence of intracerebral hemorrhages when these patients are treated with oral anticoagulants. The microhemorrhages were associated with cerebral white matter lesions, which suggests that they are another manifestation of cerebral small-vessel disease.
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Introduction

The risk of intracerebral hemorrhage after secondary prophylactic treatment with oral anticoagulants seems larger in patients anti-coagulated after a non-disabling ischemic stroke than after a myocardial infarction. In one recent study of anticoagulants after ischemic stroke the incidence of intracerebral hemorrhage was 36 per 1000 patient-years, against 1 to 10 per 1000 patient-years in patients anticoagulated after myocardial infarcts. In patients with peripheral arterial disease the incidence of intracerebral hemorrhage was smaller too (4 per 1000 patient-years), as reported in a study of secondary prophylaxis with oral anticoagulants. These observations suggest that the cerebral vessels of patients with ischemic stroke are more prone to rupture than those of patients with myocardial infarction or peripheral arterial disease.

In pathological studies signs of small old intracerebral hemorrhages have been found in patients with hypertension as collections of hemosiderin adjacent to arterioles and to the micro-aneurysmata of Charcot-Bouchard. These deposits are associated with small-vessel disease of the brain. Cerebral small-vessel disease is a distinct cerebrovascular disorder with lipohyalinosis of the small arterioles associated with small deep (lacunar) infarcts and cerebral white matter lesions.

Hemosiderin can easily be detected in the brain by magnetic resonance imaging (MRI). It remains detectable for years after a hemorrhage as a local signal loss on T2-weighted spin-echo images and, more pronounced, on T2-weighted gradient echo images, especially with high field magnets (1.5 Tesla). We compared the frequency of small old intracerebral hemorrhages on MRI in patients with ischemic stroke, myocardial infarction, or peripheral arterial disease, and examined the association with vascular risk factors, lacunar infarcts and cerebral white matter lesions.
Patients and Methods

Patients with a recent ischemic stroke, myocardial infarction or peripheral arterial disease were examined prospectively from January 1992 to February 1996 in two teaching hospitals. Ischemic stroke was defined as an acute focal neurologic deficit persisting at least one week. A symptomatic intracerebral hemorrhage or hemorrhagic infarct was ruled out by a CT-scan. The type of stroke was assessed according to the criteria of Bamford et al. Myocardial infarction was defined as angina pectoris for more than 20 minutes and with laboratory- or ECG-findings consistent with myocardial infarction. Peripheral arterial disease was defined as intermittent claudication with characteristic leg pain or a history of intermittent claudication treated with vascular surgery. Patients with dementia, patients with anemia and patients using oral anticoagulants were excluded. We recorded smoking status and medical history. Hypertension was defined as a diastolic blood pressure of 95 mmHg or higher on repeated prior measurements or a current treatment for hypertension. Hypercholesterolemia was defined as a total plasma cholesterol level of 7 mmol/l or higher or a current treatment for hypercholesterolemia. The study was approved by the medical ethics committees. All patients gave informed consent to participate.

MRI was performed with a 1.5 Tesla Siemens Magnetom 63 SP/4000 (Siemens AG, Erlangen, Germany). Five millimeter transversal images were obtained with a T1-weighted (T1W-SE), a combined proton density-weighted (PDW-SE) and a T2-weighted (T2W-SE) spin echo sequence. The same series of images were made with a T2W-gradient echo FLASH 2D sequence. Two investigators (VIHK, BV) independently assessed the MRI scans without knowledge of clinical or laboratory data. Patients with a cerebral vascular malformation were excluded.

Hemosiderin deposit was defined as a local hypointense signal on a T2W-SE image, more pronounced on the T2W-gradient echo images, with corresponding normal or slightly hypointense signals on the T1W-SE image. Flow-void artifacts and symmetrical signal loss in the basal ganglia were ruled out, to avoid inclusion of blood vessels or basal ganglia ferric iron deposits. The agreement between the investigators was good.
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(agreement 87%, kappa = 0.6). In a second session we discussed the doubtful cases. Only cases in which consensus was reached, were considered to have local hemosiderin deposits. We checked the corresponding areas on the CT-scans and ruled out cerebral calcifications. 

The MRI-lesions were categorized as follows: hemorrhagic lacunes were defined as lacunar lesions smaller than 2 cm with central or peripheral hemosiderin deposits (figure 1), lobar hemorrhages as the presence of hemosiderin deposits in the cortical areas combined with local atrophy, and microbleeds as point lesions with hemosiderin deposits (figure 2). Lacunar infarcts were defined as well-demarcated areas of both hyperintense lesions on T2W-SE images and corresponding hypointense lesions on T1W-SE images without signs of hemosiderin deposits. We assessed cerebral hemispheric white matter lesions on the T2W-SE and PDW-SE images, using an adapted version of the scoring-system of Fazekas et al. Hyperintensities limited to small caps and thin linings along the ventricles were considered normal.

Figure 1. Hemorrhagic lacune in the brain: hemosiderin deposit is visible on a T2W-gradient echo MRI-scan as a black ring around a cyst-like lesion in the left putamen.

Figure 2. Microbleeds in the brain: multiple small hemosiderin deposits are visible on a T2W-gradient echo MRI-scan as black dots in the thalamus on both sides.
Statistical analysis

The presence of local hemosiderin deposits was related to patient characteristics. Frequency differences were analyzed with the Chi-square test with the Yates’ correction for small sample sizes. We also performed a multivariate analysis of the association between hemosiderin deposits and possibly related factors using a logistic regression analysis with a stepwise forward selection strategy. All factors with a \( p \leq 0.20 \) in the univariate analysis were entered in the model. The associations were expressed as odds ratios (calculated as the anti-logarithm of the regression coefficients of the logistic regression model) with 95% confidence intervals. Patients with missing values were excluded.

Results

We studied 66 patients with an ischemic stroke, 69 with a myocardial infarction and 86 with peripheral arterial disease, a total 221 patients (table 1). The mean age was 62.0 years. Most patients were male (69%) and smokers (86%). A substantial part had hypertension (41%), half had hypercholesterolemia (49%) and 12% had diabetes. On MRI many patients showed white matter lesions (41%) and lacunar infarcts (47%). Four percent of the patients with ischemic stroke and 7% of the other patients had a history of a prior transient neurological deficit, assumed to be a transient ischemic attack (TIA) or minor stroke. Mean interval between index stroke and MRI was 6.0 months (sd 3.2). No new symptomatic strokes occurred between the index stroke and the time of the MRI.

Local hemosiderin deposits were found in 31 of the 221 patients (14%). Among stroke patients 17 of 66 (26%) had hemosiderin deposits, against 3 of 69 (4%) patients with myocardial infarction and 11 of 86 (13%) patients with peripheral arterial disease (Chi-square test, \( p = 0.002 \)). The hemosiderin deposits consisted of 18 hemorrhagic lacunes, 4 small lobar hemorrhages and 9 microbleeds. The hemorrhagic lacunes and microbleeds (total 27) were located in the basal ganglia in 16 patients, in the subcortical white matter in 7 patients, in the pons in 2 patients and in the cerebellar hemispheres in 2 patients. There were no differences in location
of the hemosiderin deposits (basal ganglia versus subcortical white matter) between younger and older patients (Chi-square test, p = 0.6) and hypertensive or non-hypertensive subjects (Chi-square test, p = 0.8).

All 17 patients with an ischemic stroke, who turned out to have hemosiderin deposits, had a CT-scan. Fourteen patients were scanned within 14 days and 3 patients on day 19, 20 and 27. No hemorrhages or calcifications were seen. In all patients with a prior neurological deficit a CT-scan was made at that time. These scans did not show any hemorrhages. The hemosiderin deposits in 12 of the 17 stroke patients were located in the clinically unaffected hemisphere. From the 14 other patients with hemosiderin deposits, 12 never had a TIA or stroke. This implies that in 24 patients (77%) the hemosiderin deposits could not be attributed to any clinical event.

In the univariate analysis age and the presence of cerebral white matter lesions and lacunar infarcts were significantly associated with hemosiderin deposits (p = 0.004, < 0.0001 and 0.003 respectively, table 2). Patients with hemosiderin deposits were more often female, hypertensive, and non-smokers (p = 0.07, 0.03 and 0.009 respectively, table 2). After multivariate logistic regression analysis cerebral white matter lesions remained the only factor independently associated with the presence of hemosiderin deposits (odds ratio (OR) 5.3, 95% confidence interval (95% CI) 2.5 - 12.4).

We also examined the relation between the severity of the cerebral white matter lesions and the frequency of the hemosiderin deposits. Compared
Table 2. Characteristics of patients with and without local hemosiderin deposits.

<table>
<thead>
<tr>
<th></th>
<th>Hemosiderin deposits (n=31)</th>
<th>No hemosiderin deposits (n=190)</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>mean (SD) age, yr</td>
<td>67.1 (10.0)</td>
<td>61.0 (11.7)</td>
<td>0.004( ^* )</td>
</tr>
<tr>
<td>male, %</td>
<td>55</td>
<td>71</td>
<td>0.07</td>
</tr>
<tr>
<td>hypertension, %</td>
<td>58</td>
<td>38</td>
<td>0.03</td>
</tr>
<tr>
<td>smoking, %</td>
<td>71</td>
<td>88</td>
<td>0.009</td>
</tr>
<tr>
<td>hypercholesterolemia, %</td>
<td>57</td>
<td>47</td>
<td>0.3</td>
</tr>
<tr>
<td>diabetes mellitus, %</td>
<td>16</td>
<td>11</td>
<td>0.6</td>
</tr>
<tr>
<td>cerebral WML*, %</td>
<td>74</td>
<td>35</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>lacunar infarcts, %</td>
<td>71</td>
<td>43</td>
<td>0.003</td>
</tr>
<tr>
<td>cortical infarcts, %</td>
<td>16</td>
<td>11</td>
<td>0.4</td>
</tr>
<tr>
<td>cerebral atrophy, %</td>
<td>16</td>
<td>6</td>
<td>0.12</td>
</tr>
</tbody>
</table>

\( ^* \) Chi-square test \( ^1 \) Students t-test \( ^1 \) white matter lesions

to patients with normal white matter, patients with mild cerebral white matter lesions (less than half of the white matter involved) had an odds ratio for having hemosiderin deposits of 5.0 (95%CI 1.7-14.9), patients with moderate cerebral white matter lesions (about half of the white matter involved) 6.2 (95%CI 1.8-21.4), and patients with severe cerebral white matter lesions (more than half of the white matter involved) 9.4 (95%CI 1.9-40.4).

Discussion

In this study we found intracerebral local hemosiderin deposits on MRI in 14% of patients with different atherosclerotic diseases. Most lesions were clinically silent. Patients with ischemic strokes significantly more often had cerebral hemosiderin deposits than patients with myocardial infarction or peripheral arterial disease. The most important factor associated with hemosiderin deposits was cerebral white matter lesions.

Although we do not have pathologic confirmation, there is ample evidence in the literature that the lesions we described on the T2W-gradient echo and T2W-SE MRI are indeed deposits of hemosiderin.\(^{15,20,24}\) The degradation products of blood (like hemosiderin) remain visible on MRI after many years.\(^{14,15,20,21,25}\) Old silent punctate microbleeds and
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hemorrhagic lacunes on MRI have been reported in patients presenting with an acute intracerebral hemorrhage. In postmortem studies, deposits of hemosiderin were described in patients with small-vessel disease due to hypertension and in patients who died from an intracerebral hemorrhage.

Most of the hemosiderin deposits could not be attributed to a past or recent clinical event. Only a minority of the lesions were compatible with the symptoms in the stroke patients. However, CT-scans of these patients did not show cerebral hemorrhage in the acute phase. There are several possible explanations. First, the infarcts could have become hemorrhagic later and were not seen on an early CT-scan. However, in 12 patients there was no history of TIA or stroke at all. Second, small intracerebral hemorrhages can be missed on CT, since they resolve rapidly and become isodense within three weeks. In our stroke patients most CT-scans were made within two weeks. It is unlikely that an intracerebral hemorrhage would have been missed within this period. Third, in patients with severe anemia intracerebral hemorrhage can be isodense on CT in the acute phase, because the density is related to the hemoglobin level. However, patients with anemia were excluded from our study.

The cerebral hemosiderin deposits were associated with higher age and the presence of white matter lesions and lacunar infarcts. The severity of the white matter lesions was correlated with the frequency of the hemosiderin deposits. These findings suggest a link to a disease of the small cerebral arterioles. An association between intracerebral hemorrhage and small-vessel disease has been found in pathological studies. The simultaneous occurrence of ischemic lacunar infarcts and intracerebral hemorrhage has been described in postmortem studies of patients with small-vessel disease due to hypertension. Hypertension leads to lipo-hyalinosis of the small arterioles, but also to micro-aneurysmata (of Charcot-Bouchard) or medial degeneration of the vessel wall, which may tear and cause small localized bleeding or a symptomatic intracerebral hemorrhage. Several authors have described hemorrhagic lacunes, that may result from such tears, or from secondary hemorrhage after an ischemic lacunar infarct, or even from bleeding into a lacune. In this study we can not determine which mechanism is responsible for the hemosiderin deposits. Another
explanation for our findings may be amyloid angiopathy, a small vessel
disease presenting with lobar hemorrhages with the co-existence of small
infarcts and white matter lesions, often in elderly, non-hypertensive
patients. One of our patients was 73 years and normotensive, and had
hemosiderin deposits in the peripheral subcortical white matter. In the
entire group however, we could not demonstrate that peripheral location
of the hemosiderin deposits was more frequent in elderly patients without
hypertension. Therefore, although amyloid angiopathy may be the cause
of the micro-hemorrhages in some of our patients, we believe that
hypertensive small-vessel disease is the underlying pathology in most
cases.

Postmortem studies in hypertensive patients showed that small
spontaneous hemorrhages are often self limiting. Hemostatic mechanisms
are apparently sufficient to stop such bleeds, probably because they occur
in low-pressure vessels. When these patients are given anticoagulants,
these small bleedings may enlarge to symptomatic or even lethal intra-
cerebral hemorrhages. Our findings offer a potential explanation for the
higher incidence of intracerebral hemorrhages after anticoagulant treatment
in stroke patients as compared with patients with myocardial infarction or
peripheral arterial disease.

In conclusion, in patients with different manifestations of atherosclerosis
we found MRI-evidence of old small intracerebral hemorrhages, that were
clinically silent. In patients with an ischemic stroke they are significantly
more frequent than in patients presenting with a myocardial infarction or
peripheral arterial disease. The lesions are associated with cerebral white
matter lesions, which supports the idea that they may be another
manifestation of cerebral small-vessel disease. Silent microhemorrhages
may be a risk factor for developing symptomatic intracerebral hemorrhage
in patients receiving oral anticoagulation.

(for other examples of MRI's: see Appendix B)
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References


