Clinical and magnetic resonance observations in cerebral small-vessel disease
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T2-weighted MRI-hyperintense lesions in the pons in patients with atherosclerosis

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Abstract

Background and purpose
Pontine hyperintense lesions (PHL) on T2-weighted MRI have been recognized recently. Histopathological findings resemble periventricular white matter lesions, and a vascular etiology has been suggested. We studied the frequency and the associated factors of PHL in patients with symptomatic atherosclerosis.

Methods
Two independent observers assessed brain MRI’s in a prospective cohort of patients with symptomatic atherosclerosis. Only patients in whom both observers scored PHL on T2- and proton density-weighted spin-echo images, but not on T1-weighted spin-echo images, were considered to have the lesion.

Results
We studied 229 patients: 31% presenting with ischemic stroke, 31% with myocardial infarction and 38% with peripheral arterial disease. Both observers scored PHL in 23% of all patients. Patients with PHL are significantly older and have more lacunar infarcts and periventricular white matter lesions, compared with patients without PHL. There are more women, more hypercholesterolemic and diabetic patients and on MRI more cortical infarcts (not statistically significant). After logistic regression the presence of white matter lesions (odds ratio (OR) 2.7, 95% confidence interval (CI) 1.4-5.3) and lacunar infarcts (OR 2.0, 95% CI 1.01-4.0) remain independently associated with PHL. PHL is more common in patients with ischemic strokes (39%) than in patients with myocardial infarctions (11%) or peripheral arterial disease (19%) (p < 0.004).

Conclusions
We found that PHL on T2- and proton density-weighted images of MRI are often found in patients with symptomatic atherosclerosis. The association with periventricular white matter lesions and lacunar infarcts suggests that PHL is a form of small-vessel disease, with possibly the same pathophysiology. The clinical symptoms and consequences of PHL are however not yet clear.
In 1995 Pullicino et al. reported 16 cases with “ischemic rarefaction” of the pons in a series of 85 patients examined with an MRI. They studied two cases histopathologically. The pontine areas that were hyperintense on T2-weighted (T2W) MRI showed white matter pallor with reactive astrocytosis, mostly in the central parts of the pons, with arteriosclerotic changes in the small arteries. The authors also saw lacunar infarcts in and around these areas. The histopathological findings are similar to those found in periventricular leukoaraiosis (LA) as seen on CT-scans or white matter lesions (WML) as seen on MRI. Patients with pontine rarefaction more often suffered from hypertension and diabetes mellitus, as compared with patients without these lesions, but differences were not statistically significant. The clinical relevance of these pontine rarefaction is not clear.

The findings in the two cases of Pullicino et al. suggest a vascular etiology. We therefore expected to find pontine hyperintense lesions (PHL) on T2W MRI more frequently in a population of atherosclerotic patients. We examined the frequency of PHL in a cohort of atherosclerotic patients and studied its association with vascular risk factors and other manifestations of vascular brain disease.

Patients and Methods

Patients with symptoms of atherosclerosis were recruited prospectively from January 1992 to February 1996 in two teaching hospitals with both regional and secondary referral function. We collected patients with recent ischemic stroke, myocardial infarction or peripheral arterial disease, since these diseases are the most important clinical manifestations of atherosclerosis. Recent ischemic stroke was defined as an acute focal neurological deficit persisting at least one week. Hemorrhage was ruled out by a CT-scan. The type of stroke was determined according to the criteria of Bamford et al. Severity was graded on a clinical scale: mild stroke: symptoms or signs that did not cause impairment in activities of daily living (ADL); moderately severe stroke: paresis of arm or leg that caused moderate impairment in ADL, or dysphasia with residual verbal communication;
severe stroke: paresis of arm or leg or both, that caused severe impairment of ADL, or a severe communication disorder. Myocardial infarction was defined as characteristic angina pectoris for more than 20 minutes and laboratory- or ECG-findings characteristic for myocardial infarction. Peripheral arterial disease was defined as intermittent claudication with characteristic leg pain on walking that disappeared in rest or a history of intermittent claudication treated with vascular surgery. Patients with dementia were excluded. The study was approved by the medical ethics committees in both hospitals. All patients gave their informed consent. We recorded smoking status and medical history. Hypertension was defined as a diastolic blood pressure of $\geq 95$ mmHg on repeated prior measurements or a current treatment for hypertension. Hypercholesterolaemia was defined as a total plasma cholesterol level of $\geq 7$ mmol/l or a current treatment for hypercholesterolaemia.

MRI was performed with a Siemens Magnetom 63 SP/4000 (1.5 Tesla). Transversal T1-weighted (T1W), T2W and proton density-weighted (PDW) spin echo images were made. Two investigators (VIHK,BV) independently assessed the MRI scans without knowledge of clinical or laboratory data.

We defined PHL as confluent hyperintense areas on T2W, PDW, or both images, without distinct borders, but with normal or slightly hypointense corresponding signals on T1W images. Lacunar infarcts were defined as well-demarcated hyperintense lesions on T2W images with corresponding demarcated hypointense lesions of less than 2 cm diameter on T1W images. With these definitions the agreement for the presence or absence of PHL between the two observers was good (kappa = 0.63). We considered patients to have PHL only if both observers agreed on its presence. In all other cases PHL was judged absent.

We assessed hemispheric white matter lesions (WML) on the T2W and PDW images. WML was graded according to an adapted version of the scoring-system of Fazekas et al. Periventricular hyperintensities limited to small caps and pencil-thin linings were considered normal.
Statistical analysis

The presence or absence of PHL was related to other clinical and MRI characteristics. Frequency differences were analyzed with the Chi-squared test with the Yates' correction for small sample sizes. Continuous data were analyzed with the Student’s t-test or the Mann-Whitney U-test, when appropriate. Since we made multiple comparisons, a p-value of ≤ 0.005 (0.05/10) was considered significant. This analysis was also done in the different vascular subgroups. Lastly, we compared patients with PHL only to patients with neither WML nor PHL.

We examined the association between PHL and a number of variables with multivariate analysis using a logistic regression model. The presence or absence of PHL was assigned as dependent variable and the other data of interest as independent variables using a stepwise forward selection strategy. For this analysis age was dichotomised according to the median (65 year). Patients with missing values were excluded from the analysis. A second logistic regression analysis was done in patients without supratentorial WML to compare patients with PHL only to patients with neither WML nor PHL.

Results

We analyzed 229 patients in this study (table 1). Thirty-one percent had an ischemic stroke, 31% a myocardial infarction and 38% peripheral arterial disease. The mean age was 61.8 (sd 11.7). Most patients were male (68%). Forty-one percent had hypertension and a majority were smokers (86%). Approximately half have hypercholesterolaemia and 12% was diabetic. On the MRI many patients showed WML (39%) and lacunar infarcts (46%), while only a minority had cortical infarcts (12%).

Of the patients with ischemic stroke, 60% had symptoms of a (sub)cortical infarct and 40% of a lacunar infarct. Most of them (76%) had a moderately severe stroke and a minority a mild (17%) or a severe (7%) stroke. All stroke patients had hemispheric infarcts, except for three with brainstem signs. Among the stroke patients 15% had a history of TIA or
Table 1. Characteristics of 229 patients with and without pontine T2W-hyperintense lesions.

<table>
<thead>
<tr>
<th></th>
<th>All patients</th>
<th>Pontine T2W-hyperintense lesions +</th>
<th>Pontine T2W-hyperintense lesions -</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>229</td>
<td>52</td>
<td>177</td>
<td></td>
</tr>
<tr>
<td>age, yr†</td>
<td>61.8 (11.7)</td>
<td>66.8 (9.1)</td>
<td>60.3 (12.0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>male, %</td>
<td>67.7</td>
<td>57.7</td>
<td>70.6</td>
<td>ns</td>
</tr>
<tr>
<td>hypertension, %</td>
<td>40.6</td>
<td>42.3</td>
<td>40.1</td>
<td>ns</td>
</tr>
<tr>
<td>cardiac disease, %</td>
<td>31.0</td>
<td>30.8</td>
<td>31.1</td>
<td>ns</td>
</tr>
<tr>
<td>smoking, %</td>
<td>85.6</td>
<td>76.9</td>
<td>88.1</td>
<td>ns</td>
</tr>
<tr>
<td>hypercholesterolaemia, %</td>
<td>48.2</td>
<td>52.9</td>
<td>46.8</td>
<td>ns</td>
</tr>
<tr>
<td>diabetes mellitus, %</td>
<td>11.8</td>
<td>13.5</td>
<td>11.3</td>
<td>ns</td>
</tr>
<tr>
<td>WML, %†</td>
<td>39.2</td>
<td>61.5</td>
<td>32.8</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>lacunar infarcts, %</td>
<td>45.9</td>
<td>65.4</td>
<td>40.1</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>cortical infarcts, %</td>
<td>11.8</td>
<td>19.2</td>
<td>9.6</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Chi-square test, except for age: Student's t-test †mean (sd) ‡(supratentorial) white matter lesions

Fig. 1. MRI scan shows pontine hyperintense lesions (PHL) on T2W images (right) without marked hypointense corresponding signals on T1W images (left).

minor stroke, while among the myocardial infarction and peripheral arterial patients 6% and 5% had such a history, respectively. Conversely, 9% and 11% of the stroke patients had a history of myocardial infarction or a peripheral arterial disease, respectively.

In 52 cases (23%) both observers independently agreed on the presence
of PHL (figures 1 and 2). In 16 patients there was disagreement. These patients were added to the control group. The three patients with brainstem signs all had PHL and also a lacunar infarct in a different location: two about 10 mm caudally and one only unilaterally, while the PHL was seen bilaterally. Thirty-two (14%) patients had both PHL and supratentorial WML. Thus, 20 patients (9%) had PHL without evidence of WML. Hundred-nineteen (52%) patients had neither WML nor PHL. Fifty-eight (25%) patients had WML only.

Patients with PHL were significantly older and more often had lacunar infarcts and WML than patients without PHL (table 1). There were more women, more hypercholesterolaemic and diabetic patients, but less smokers (not statistically significant). The frequencies of hypertension and cardiac disease were similar in patients with and without PHL. Cortical infarcts were seen more frequently in patients with PHL, but this was not statistically significant. The presence of PHL was significantly correlated with the severity of WML ($p < 0.001$, Mann-Whitney U-test).

After logistic regression only the presence of WML (odds ratio (OR) 2.7, 95% confidence interval (CI) 1.4-5.3) and lacunar infarcts (OR 2.0, 95% CI 1.01-4.0) remained independently associated with PHL.
To clarify the differences between the symptomatic groups we analyzed the frequencies of the vascular risk factors and the MRI-findings within the subgroups (table 2). PHL was more frequent in patients with ischemic strokes (39%) than in patients with myocardial infarctions (11%) or peripheral arterial disease (19%) \((p < 0.004, \text{Chi-square test})\). In all subgroups patients with PHL were older, but this was statistically significant only in those with peripheral arterial disease. The only other factor significantly associated with PHL was the presence of WML in patients with ischemic stroke. The other factors did not differ significantly within the subgroups, but there were more lacunar infarcts in patients with PHL within the stroke and myocardial infarction groups.

We analyzed the patients with PHL only (without supratentorial WML) and contrasted them to patients with neither WML nor PHL. In a univariate analysis only age was significantly correlated with PHL \((p < 0.001, \text{Student's t-test})\). The presence of lacunar infarcts was weakly correlated with PHL \((p = 0.02, \text{Chi-square test})\). In a logistic regression analysis age is the only factor independently associated with isolated PHL \((\text{OR 3.4, 95\%CI 1.3-9.1}))\).
Discussion

In a population of patients with different manifestations of atherosclerosis we found a substantial proportion of patients with PHL (23%). We used a strict definition of PHL to be as specific as possible. With our definition of PHL a good interobserver agreement was achieved. The observed proportion of PHL is comparable with an earlier study. To our knowledge the first report on hyperintense MRI-lesions of the pons was published in 1993 by Watanabe et al. (in Japanese).

Hyperintense pontine lesions on T2W MRI may be caused by multiple sclerosis, neoplasms, central pontine myelinolysis, infarcts and Wallerian degeneration. It is highly unlikely, that one of these conditions caused PHL in our patients. They neither had a history of multiple sclerosis, nor cancer, nor severe alcoholism, nor electrolyte disturbances. Pontine infarcts would leave corresponding sharply demarcated, hypointense signals on the T1W images. This was only seen (in a different location than the PHL) in three patients with clinical signs of brainstem infarct. We found no evidence for Wallerian degeneration, such as lesions that are more rostrally located in the pyramidal tract or other long tracts.

Pullicino et al. suggested that PHL is a variant of WML. In two of their patients the histopathological features of PHL resembled those of WML. They suggest that PHL is caused by hypoperfusion. The central part of the pons may be particularly vulnerable for effects of hypoperfusion. As shown in a recent study, this area corresponds with a vascular borderzone, supplied by the anteromedial, the lateral and the posterior groups of small penetrating arteries arising from the basilar and superior cerebellar arteries. A similar borderzone exists in the periventricular areas between the vascular territories of the long penetrating pial arteries and the lenticulostriate arteries. WML is probably caused by arteriolosclerosis of small arteries and arterioles of the brain. Hyaline deposits and intimal atheroma formation may narrow the orifices of the penetrating arteries and the lumen of small arteries. This so-called small-vessel disease is likely to impair the microcirculation. When a substantial part of the small arteries becomes affected, the tissue in the borderzones of these arteries may
become compromised, leading to demyelination.\textsuperscript{8} Arteriolosclerosis, expressed by increased wall thickness of the arterioles, is strongly associated with WML.\textsuperscript{3} Occlusion of a single small artery results in a lacunar infarct.\textsuperscript{8} This type of infarct occurs frequently in patients with WML.\textsuperscript{14}

We postulate that arteriolosclerosis in the small arterioles of the pons leads to PHL in the central pontine areas by the same mechanism as in WML. Two findings support this hypothesis. Firstly, in our patients WML is associated with PHL and the severity of WML correlates with the presence of PHL. This may point to a common pathophysiological mechanism, namely small-vessel disease. Secondly, lacunar infarcts are also associated with PHL. As mentioned above, this type of infarct is probably also caused by a small-vessel disease. In addition Pullicino et al. provided pathological evidence for this hypothesis, when they mentioned “typical” arteriosclerotic hypertensive changes of the small arteries in the pons, although they did not describe these changes in detail.\textsuperscript{1}

Several case-control studies show that the strongest risk factor for WML is age.\textsuperscript{15} In our patients with PHL (without supratentorial WML) age is the only factor independently associated with PHL. Hypertension is also associated with WML and is likely to be important in its pathogenesis.\textsuperscript{15-17} A prior history of stroke, myocardial infarction and diabetes mellitus has variably been reported in patients with WML.\textsuperscript{15,16,18-21} We found more hypercholesterolaemia and diabetes mellitus in patients with PHL, but this was not statistically significant. Pullicino et al. found higher frequencies of hypertension and diabetes mellitus in patients with PHL, but this was also not statistically significant.\textsuperscript{1}

Within the symptomatic subgroups the only factors associated with PHL were age (in patients with peripheral arterial disease) and WML (in patients with stroke) (table 2). The higher frequencies of WML and lacunar infarcts (although the latter is not statistically significant) within the stroke group could explain the higher prevalence of PHL in our stroke patients. For that matter we found a larger proportion of patients with lacunar
infarcts than in other series of stroke patients,\(^4\) probably due to the fact that a number of patients with large infarcts could not give consent, were not able to undergo an MRI or died before MRI could be performed.

To summarize, we found that patients with different clinical manifestations of atherosclerosis often have pontine hyperintense lesions on MRI T2W- and PDW-images. The association with periventricular white matter lesions and lacunar infarcts suggests that pontine hyperintense lesions are a form of small-vessel disease with possibly the same pathophysiology. This is supported by histopathological findings in a previous study on this subject.\(^1\) The clinical significance of PHL, if any, is not clear. Some authors speculate that these patients may have neurological symptoms,\(^1,6\) but this remains to be demonstrated in clinical studies.

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